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20924

DP/ID/SER.A/1713
9 January 1995
ORIGINAL: ENGLISH

DEVELOPMENT OF THE PHARMACEUTICAL INDUSTRY IN THAILAND

DP/THA/88/018

THE KINGDOM OF THAILAND

Technical report: Air handling and air conditioning systems in the pharmaceutical industry*

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 John Clark, expert in air-handling and air-conditioning of pharmaceutical industry

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Vienna

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* This document has not been edited.

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ABSTRACT

A technical mission to Thailand was undertaken by the Unido Technical Expert to support the Project 'Development of the Pharmaceutical Industry in Thailand' (UNDP/UNIDO DP/THA/88/018). The principal aim of the mission was to provide technical assistance and training on the design, operation and maintenance of air handling and air conditioning systems in pharmaceutical facilities. The subjects of the training activities were professionals and senior personnel involved in the manufacturing of pharmaceutical products in Thailand. In addition, the technical expert assisted in presenting a training seminar to a visiting delegation from a similar WHO/UNIDO project in Syria.

1 PROJECT BACKGROUND

In April 1991 the Royal Thai Government in conjunction with UNDP/UNIDO, set up the Pharmaceutical Technology Service Centre (PTSC), at the Faculty of Pharmacy at Chulalongkorn University in Bangkok. The objectives of the Centre were to assist in the development of the Thai pharmaceutical industry, and to promote communication between academia, industry, regulatory agencies, and government.

The Service Centre objectives included the aim of improving local GMP (good manufacturing practices) levels, in order to meet international quality standards. The Centre enables Thai pharmaceutical companies to introduce GMP's into production plants, through training of personnel at all management levels. The training is carried out at seminars and workshops on GMP and pharmaceutical technology, and the training sessions are showing considerable success in educating local manufacturers.

Another PTSC aim is to maintain effective Quality Assurance practices in the industry. This is being achieved by the preparation and implementation of detailed written Standard Operating Procedures (SOP's) and guidelines on GMP.

2 THE TECHNICAL MISSION

On 1st September 1994 a Technical Mission was undertaken to Thailand to support the project UNDP/UNIDO DP/THA/88/018 'Development of the pharmaceutical industry in Thailand'.

The mission's objective was to give technical support to the Pharmaceutical Technology Service Centre by providing training and technical advice to local industrialists, and also by reviewing documentation relating to air handling systems and clean rooms available at the Centre. The terms of reference for the technical mission are given in Appendix 1, and the technical experts' brief encompassed several activities, executed as follows:

i) Review Technical Documentation.

Within the PTSC no technical documentation exists specifically related to air handling, air conditioning or clean room installations. During the course of the mission, copies of several standard reference documents were provided for the use of the Centre, in particular U.S. Federal Standard 209E, and B.S. 5295. Recommendations were made to the Director that the Centre form closer links with the Faculty of Engineering at the university, as many relevant works of reference are available in their library, and much of the necessary engineering expertise exists within that Faculty of the University.

ii) Training Local Experts

On arrival at the PTSC, and after some discussion with the CTA and director, the intention was to deliver a number of workshops to industry principals in Thailand, and also a seminar to a larger audience, which should precipitate further discussions. In reality, factory managers and operators were reluctant to discuss their expansion plans, product development ideas and existing factory shortcomings with the perceived competition in an open forum. The result was that very poor attendance was initially indicated at planned workshops. To overcome this, factories were visited at the

invitation of the owners to provide individual specific comment on proposed factory developments and advice on the operation, testing and maintenance of air handling and clean systems. The discussions with factory principals and their local consultants and architects covered factory layouts, dust extract, load estimation, humidity high and low control, air filtration, clean room testing and validation and many other topics. Reports concerning each factory visit are attached, Appendix 2. A total of 11 visits were made to manufacturing plants ranging from a small tabletting operation, to the 100 acre Government Pharmaceutical Organisation site.

The large seminar, held for one day in an hotel conference room, proceeded successfully and was attended by approximately 90 pharmaceutical industry principals, managers, pharmacists and engineers. The seminar centred around the specific applications of air conditioning in pharmaceutical manufacturing facilities, hence more general topics were addressed, relating to the whole audience without comment on individuals plans or facilities. One area of particular concern to Thai industry is the control of relative humidity, and this topic occupied the seminar for some time with considerable discussion involving all participants. The seminar projector slides are attached for reference, Appendix 3.

iii) SOP Preparation

The preparation of any standard SOP relating to air conditioning/air handling in pharmaceutical facilities proved to be very difficult. Each air handling installation is custom-built to suit the particular factory and application, and can comprise many different components. To overcome this, 'generic' SOP's were prepared which could relate to more than one installation. The intention is to issue these SOP's to serve as a model for future development of manuals for particular installations. Samples of SOP's prepared are given in Appendix 4.

iv) Assist Training Programmes

In addition to the training offered to local industry, the Centre is also able to offer training facilities to other organisations. During the technical mission, a party of managers and administrators from Syria attended the Centre for training in GMP and related management disciplines, and to visit established factories in Thailand. The air handling expert took part in some of the training seminars, assisting the national experts and the CTA.

3 THE PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE

The PTSC is an autonomous institution physically located within the Faculty of Pharmaceutical Sciences at Chulalongkorn University in Bangkok. The Centre has a part-time executive director who reports to the board of directors. The staff consists of one administrative assistant and two technical personnel. The Centre is supported by a Chief Technical Advisor from UNIDO, with assistance from short-term UNIDO experts and a pool of national experts from universities and industry.

The Centre's facilities comprise principally a laboratory with analytical instruments for the testing of pharmaceutical products. There is a small library containing information on GMP, QA, validation and other publications relevant to their activities.

Since its beginning in 1991, the Centre has carried out many training activities and promoted improvements throughout the pharmaceutical industry in the region. Informal discussions with local industrialists indicate that the Centre's expertise and help are generally welcomed, and a real desire exists for the Centre to increase its range of services to assist local industry. The contribution made by UNIDO to the Centre has allowed it to develop as an independent and respected authority.

To date, the activities of the Centre have focused upon the quality testing of products, preparation of SOP's, and GMP education. All activities have taken place within the context of the pharmaceutical requirements, with little reference to other disciplines such as engineering or industrial management.

4 RECOMMENDATIONS FOR THE FUTURE

The PTSC has developed to date under the auspices of UNIDO, the TPMA, the FDA and Chulalongkorn University. The atmosphere at the Centre is very much that of an academic institution, advising and assisting when requested to do so by outside agencies, but not actively promoting its services. The Centre at present concentrates on product testing and delivering training to industry, usually in the form of workshops and seminars, to pharmacists and chemists involved in manufacturing and quality control.

Discussions with local manufacturing principals indicate a current need for a consultancy service which can advise on all aspects of pharmaceutical production. As the Thai industry develops, the need will increase for a training service, and technical assistance on implementation of all aspects of GMP.

The Centre now needs to develop a strategy for further development, so that the reputation acquired is maintained, and the Centre remains a centre of excellence in the region. Some areas of potential development are as follows:-

Personnel: The key to success of future initiatives is wholly dependent upon the human resources available to the Centre. In particular, for the Centre's activities to be expanded, the need for a full time manager and co-ordinator is paramount. Specialists can be imported as required, but to achieve continuity of effort, and maintain contact with the local industry to anticipate and cater for their needs, a continuous effort is necessary.

Marketing: A prime objective of the Board and Director must be to market the Centre's facilities and capabilities to all parts of industry. The pharmaceutical industry will continue to be the principal area of activity, but the pharmaceutical, cosmetic, food, veterinary etc. industries all have similar needs. In addition, the provision of

suitable facilities for manufacturing does need input from engineering, construction, electronics, etc. all of which disciplines need to be made aware of the opportunities, otherwise the necessary techniques will not be available to the pharmaceutical and allied industries to develop the manufacturing facilities in the future.

Collaboration: The Centre can continue to remain the co-ordinating Centre for the core activities but to make sure the industry is suitably served, collaboration with other organisations should be encouraged. As an example, the Centre could compile a database of contractors with qualified operators capable of testing clean rooms and DOP testing HEPA filters. Similarly, testing could be carried out for the Centre, using the resources of the Faculty of Engineering, and sharing the fees.

Financial: With the development of a marketing strategy, allied to collaborative arrangements, additional income can be generated. However, this is necessarily a longer term prospect, so financial support either from industry, government or other grant will be necessary in the short term.

Consultancy: As well as the training activities, the Centre is ideally placed to provide a consultancy service to manufacturers, advising on implementation of GMP and related topics such as factory layout, product and personnel flow, validation requirements, etc.

ANNEX I

UNIDO JOB DESCRIPTION

Z.Csizer
10 January 1994

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

JOB DESCRIPTION

DP/THA/88/018/11-04

Post title	Expert in air-handling and air-conditioning of pharmaceutical industry
Duration	2 months
Date required	1 February 1994
Duty station	Bangkok
Purpose of project	To develop the pharmaceutical industry in Thailand with specific reference to the modern airhandling and airconditioning methods in the aseptic and sterile areas of pharmaceutical manufacturing facilities.

Duties

The expert in pharmaceutical air handling and aircobnditioning will in cooperation with the international and national experts be expected to carry out the following duties:

1. Review and validate all technical documentation available in the Pharmaceutical Technology Service Center (PTSC) on the air-handling and air-conditioning in the aseptic and sterile areas of the pharmaceutical manufacturing facilities.

2. Train local experts in drawing layouts and calculating required capacities of air-conditioning, refrigeration, airfiltering, compression, dehumidifying, pumps, etc. for proper sizing and meeting the needed requirements in different manufacturing areas of pharmaceutical industry.

3. Prepare all relevant SOPs, operating manuals, maintenance manuals and other cGMP related basic documentation for aseptic and sterile air handling and airconditioning in the pharmaceutical industry.

4. Assist in preparation of training materials on the above and participate in the delivery of training programmes.

5. Prepare a mission report on the above with specific recommendations on outstanding matters.

Qualifications Mechanical engineer or process engineer with extensive experience in designing and constructing pharmaceutical manufacturing facilities. Specific experience in pharmaceutical air handling and airconditioning is needed. Personal working experience in developing countries would be necessary.

Language English

Background information

To promote pharmaceuticals of high quality, UNIDO has developed a concept for providing support to the national drug regulatory and quality control authorities. To realize this concept a Pharmaceutical Technology Service Centre (referred to as Centre) was established with UNDP/UNIDO assistance at the Faculty of Pharmaceutical Sciences of Chulalongkorn University, Bangkok, Thailand, in close cooperation with the Federation of Thai Industry (FTI), the Pharmaceutical Industry Club (PIC), the Thai Pharmaceutical Manufacturing Association (TPMA), and Department of Technical and Economic Cooperation (DTEC) and the Food and Drug Administration (FDA) of the Ministry of Public Health.

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

A. Training of personnel at all levels in the pharmaceutical industry in current good manufacturing practices (CGMP) and quality assurance.

B. Monitoring compliance with requirements of CGMP and auditing/self auditing. A few most frequent occurring examples of non-compliance are as follows:

1. Inadequate layout due to incorrectly designed material, product and personnel flows.

2. Cross contamination due to the above.

3. Unmonitored environmental conditions such as atmospheric pressure, airborne particle count, temperature, humidity, etc. particularly in aseptic area.

4. Inadequate stability of the products.

C. Provision of services required by the pharmaceutical industry as follows:

1. Advice on planning and designing new manufacturing facilities with optimized layout.

2. Establishment of criteria for the construction of clean rooms and production of rooms of special/toxic substances, such as penicillin, steroids, etc.

3. Selection of the right construction materials for the interior portion of the manufacturing plant or laboratory (i.e. insulations, water or vapour barriers, interior finishing and coating, etc.)

4. Designing model types for production service facilities and equipment required.

5. Assistance in selection of manufacturing equipment.

6. Establishment of appropriate standard operating procedures and sound/effective preventive maintenance programmes for equipment, facilities and building(s).

7. Identify, order or design and fabricate calibration equipment required for validation of instruments and machinery.

8. Designing a portable waste water plant and other pollution control equipment adapted to the capacity of the pharmaceutical production plant.

D. Introduce the basic GMP documentation in the pharmaceutical industry as standard operating procedures (SOPs), batch production records (BPRs), test records (TRs), etc.

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

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

ANNEX II

FACTORY VISIT REPORTS

FACTORY VISIT REPORTS

	DATE OF VISIT	SITE OF VISIT
1.	6 September 1994	Biolab Co. Ltd
2.	7 September 1994	LBS Co. Ltd
3.	9 September 1994	Polipharm Co. Ltd.
4.	12 September 1994	General Drugs House Co. Ltd
5.	14 September 1994	F.E. Zeullig (Bangkok) Ltd
6.	20 September 1994	Berlin Pharmaceutical Industry Co. Ltd
7.	27 September 1994	Suphong Pharmaceutical Laboratories (at PTSC)
8.	28 September 1994	Biolab Co. Ltd - 2nd visit
9.	29 September 1994	Polipharm Co. Ltd.- 2nd visit
10.	4 October 1994	Golden Cup Pharmaceutical Co. Ltd.
11.	18 October 1994	Medicap Ltd
12.	26 October 1994	Government Pharmaceutical Organisation, Bangkok

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Bangkok

JC/ 15 Sept 1994

Report of visit to manufacturing facility

Site of Visit: Biolab Co. Ltd
625 Bangpoo Industrial Estate
Soi 7 A, Muang
Samutprakarn 10280 Thailand

Personnel:		
	Mr. J. Clark	UNIDO Air Handling expert
	Mr. J. Beelen	UNIDO CTA to PTSC
	Dr. Rachod Thakolsri	Deputy Managing Director, Biolab Co. Ltd.
	Dr. Sompong Panichpol	Director of R & D/ QA Biolab Co. Ltd.

Date of visit: 6 September 1994

Purpose of visit:

To observe the methods and operating conditions of a Thai pharmaceutical manufacturing establishment, with particular reference to air handling systems operation hardware and software.

To discuss with local industry principals the application of air systems technology in particular in order to promote and develop the implementation of Good Manufacturing Practice.

Activities:

This was an initial courtesy visit to Biolab to discuss the air handling and dust control systems as installed in the factory. The first part of the meeting took place in the Biolab conference room, drawings of the factory were tabled in order to demonstrate the installed systems.

An extended discussion took place concerning humidity control, how dust can be controlled, reheaters on fan coil units and related topics. JC was requested to return at a later date to carry out a more detailed survey into the air handling systems, in order to make recommendations for the improvement of dust control in particular.

After discussions concerning future developments were concluded, JC, JB and SC walked around the factory in order to observe the condition of the existing building, the air conditioning and air handling systems currently in use, and the general operating environment within the factory.

Polipharm ar just completing the first stage of their factory development, which consists of providing new toilet and changing facilities within the existing building. These are generally well constructed, but the tiled finish included conventional grouting between tiles, making a rough surfaced crevice which is very difficult to clean.

Access to the changing room is via a corridor and, after changing, personnel must use the same corridor to walk to the production areas.

Through a double door into the main central corridor, all activities could be observed through windows without entering the process rooms.

First impressions were of labour intensive, mainly manual sytems, with only a few semi-automatic machines for tablet compressing etc.

The false ceiling throughout the ground floor factory area was in poor condition. The ceiling was a lay-in grid type, with poorly fitted panels, badly replaced lighting diffusers, what appearred to be cobwebs hanging in some places, and generally a very poor standard of finish.

Partition constuction was painted timber, in some areas this was flaking, and door transfer grilles were also loosing the paint finish.

Small propeller fans direct to atmosphere were the only form of extract or ventilation in the tabletting booths, and other areas. Very few of these were switched on.
At the end of the factory, a worker was washing out product bins over an open drain and in the open air. He was not wearing any overall or gloves.

After the visit, away from the factory, JC, JB and SC discussed at length the relationship between temperature, relative humidity, moisture content and cooling duty of air conditioning equipment. JC began to appreciate the attitude of entrepreneurial Thai industry to plant investment, SC requiring to air condition the factory using package units commonly available, JC saying they do not comply with GMP, clean production or packaging requirements.

Conclusions:

This was the first experience for JC of meeting the Thai industrialists. The meeting was very instructive, and of immense value in assessing the most useful content of the seminar and workshops.

No installation or maintenance records exist for any of the fans etc. in the building.

Further discussions will take place regarding specific systems when the preliminary layouts are further developed, and the building arrangements and phasing decided.

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Bangkok

JC/ 15 Sept 1994

Report of visit to manufacturing facility

Site of Visit: LBS Co. Ltd
Thailand.

Personnel:		
	Mr. Lee	President, LBS Co.Ltd
	Ms. Orani	Plant Manager, LBS Co. Ltd
	Mr. J. Clark	UNIDO Air Handling expert
	Mr. J. Beelen	UNIDO CTA to PTSC

Date of visit: 7 September 1994

Purpose of visit:

To observe the methods and operating conditions of a Thai pharmaceutical manufacturing establishment, with particular reference to air handling systems operation hardware and software.

To discuss with local industry principals the application of air systems technology in the particular in order to promote and develope the implementation of Good Manufacturing Practice.

Activities:

LBS is a manufacturer of oral and injectable pharmaceuticals. The activities include sterile liquid and powder filling, vials ampoules and bottles, tabletting, capsule filling. The sterile suite is on the third floor, between what is to be the hormone area and the penicillin area.

First impressions compared favourbly with other facilities visited, but in fact on closer inspection the operating methods equipment and records are similarly poor.

Sterile Suite

We first visited the sterile suite. The entrance comprises an airlock corridor from the general corridor to the changing room. This corridor is poorly ventilated, with aluminium extrusion partition system, lots of crevices, ledges, leaks.

The changing room was very small, with an openable window to the outside with daylight visible through a crack around the window frame. Ventilation to this change area is again poor, and the supply HEPA and ceiling extract grille are close together. No stepover bench or hand washing facility. Lockers containing test equipment, old overalls, paper. One locker up on castors, very dirty beneath, discarded shoe. We entered the area after having some difficulty obtaining overalls to fit, with gloves and masks. Access into the ceiling void above is from the change area, via an access panel. No interlocked doors anywhere, very easy to open both changing room doors together.

The airlock leads straight into the internal clean corridor, which has differential pressure manometers indicating the difference between corridor and production areas. (0.02"w.g. to 'kitchen' (preparation area), 0.015"w.g. to ampoule filling room, 0.016"w.g. to vial filling room). Small temperature/humidity gauge provided by LBS indicated 30°C 70% r.h. in corridor. The manometers were not labelled. A capping machine is sited in this corridor, with trays of vials. Also bins are left here. Nothing appears to be labelled, no room names or numbers.

Looking along the corridor to the ampoule filling room, to the right is a depyrogenating oven installed through the wall of the sterile area. The sealing around this oven is very poor, light is again visible through cracks. The oven exhaust passes through the ceiling, gap around the hole, cracked paint on the pipe. Behind the oven front panel electrical wiring is exposed. The woman emptying the oven of trays of vials is using very frayed and worn asbestos gloves, placing trays of 'sterile' vials on an open bench next to the oven-no laminar flow protection or special provision.

Conditions in the ampoule filling room are 38°C 35% r.h. Exposed hoses are draped across the floor, pipework is too close to the all to allow cleaning behind. One ampoule filler is

enclosed within a laminar flow canopy in poor condition with a dirty plastic curtain, this is extended backwards, which will produce turbulent airflow. The canopy has mild steel legs rusty in places, paint flaking off in others, 0.52"w.g. canopy manometer indicates. The room has tiled walls, one tile missing near a pipework hole through the wall, horizontal ledges everywhere.

Pass-through hatches between areas are installed, but these have no independent air supply or exhaust, no interlocked doors. A pass-through hatch is provided between the 'kitchen' area and the outside (black) corridor. All canopies are painted steel. The ceiling is a stainless steel plenum secured with PK screws, gaps are evident between panels. Valves on one of the ampoule filling machines are corroded and rusty.

Throughout the suite air change rates feel very low, this will have to be checked. 'Washable' filters on the inlet to HEPA canopies are filthy, not been looked at for a long time. Everywhere granolithic floor with no coving.

Vial filling room turning right as you enter at end on left. Same story, dirty prefilters on laminar flow canopy, 2 dehumidifiers in this room.

Outside of the sterile suite, the vial washing is between the sterile and penicillin areas with the inlet side of the oven. Washed vials are transferred with bare hands into trays for washing. A laminar flow canopy over the ampoule washer was not in use, they turned it on for me, & it vibrated very badly, probably due to dirty & blocked filters.

JC climbed into the ceiling void above the sterile area to have a closer look at the plant and equipment there. The void was generally very dusty, and several areas of duct insulation had fallen off the duct. No airflow balancing dampers could be seen, which may account for the lack of airflow and pressure in some areas. The ceiling was constructed of plywood and timber battens, with no easy route to examine or clean ductwork.

Penicillin Area

This has fan coil units and high level dust extract canopies in each room, the canopies are circular, conical and on 4" dia. ducts. The fan coil unit filters are covered in white dust, probably product and obviously not been cleaned for some time.

Manual filling of vials was being carried out in one room in a large glove box, which was connected by 100mm flexible ducts to a large box on the floor, probably a dehumidifier with a HEPA filter. Unfortunately the operators had propped open a door of the glovebox to speed up movement of trays of vials, thus rendering the dehumidification ineffective.

Looking above the ceiling the dust extract system rises to above, to the roof plant described below, the air discharge from the dust collector unit then drops down again to supply air into the inner corridor. A small additionnal fresh air makeup plant, comprising fan and HEPA filter is sited in the ceiling void, to pressurise the outer corridor and airlock.

Hormone area

This is to the left of the sterile area,when approaching from the main access stair. The first room is the vial washing area, and had a small pile of broken glass on the floor, which was swept up while we were there. HEPA'd air supply to this room. Oven to one side, very dusty on top, with again exposed electrics.

Supply air HEPA filters are provided in the hormone area entrance corridor, and the rooms off it. Also installed are split type air conditioning units, with dirty inlet filters. The blender area has three extract canopies, again at high level. Small changing area to production rooms. Another small change space, unventilated to the right off the corridor. The outer rooms of the hormone area have no supply or exhaust ventilation. Recirculating fan-coil units, no fresh air supplies.

Ground floor

Mixing room has a temperature problem. There is one central supply grille, 6 no. extract canopies, 4 further square outlets approximately 300 x 300, I am informed these are extract, but to me they look more like supply. Part of the problem is lack of air movement in this room. Surface dust is apparent.Vacuum cleaner store in here.

Coating room adjacent comparatively comfortable. Extracts from the coating equipment to outside. Split fan coil units with dust loaded filters.

Capsule filling room. Reportedly product leak on machine, but a dust extract system is still necessary to remove the surface dust apparent everywhere.

Compression booths for tabletting machines, supply to each booth, dust extract from above each machine, supply and extract in corridor.

4th Floor and plant area

The fourth floor is at present used for offices and label printing. The area is air conditioned using split systems as elsewhere. The air handling and dust extract plants are located at this level on the balcony area. A visual examination of these plants would suggest that they have not received any maintenance attention for some time. The sterile area plant has a Centralair (of Thailand) air cooled condensing unit, model CTU77, serial no. 770112. The other plant condensing unit, presumably the hormone area plant, is a Thai manufactured Carrier 38GR type.

After the plant walkabout, a lengthy discussion ensued concerning the most effective way to upgrade the factory to comply with GMP requireements. All options were explored, including building a new sterile building on another site, and using this plant for packaging and non-sterile manufacture.

Conclusions:

The factory air handling and air conditioning systems as existing do not appear to have been maintained adequately, and no documentation is available to indicate the original design intent. As commented above, the dust extract systems extract from high level at low velocity, therefore stand little chance of catching any dust.

The ground floor mixing room urgently requires attention, to reduce the high temperatures. It became apparent that the operatives understanding of GMP was small, more training in this respect is necessary, although that is outside the scope of this report.

As a beginning, all the Laminar Flow units should be carefully removed from the sterile area, thoroughly cleaned, prefilters replaced, HEPA filters replaced, put back into position and DOP tested in situ.

All fan coil unit filters must be removed carefully, and cleaned outside the building, before being examined for damage, replaced if necessary and refitted.

The Sterile Area plant should be given a full service, all belts and pulleys checked for tension and wear, the refrigerant gas pressures checked and gas topped up if necessary. The prefilter in the air handling plant should be replaced, and a filter manometer fitted to give an indication of the filter condition without stopping the plant. To ensure the correct air change rates and room pressures, the duct system needs to be rebalanced, cutting in additionnal duct dampers if necessary to achieve the required pressure regime. Finally, all HEPA filters should be DOP tested to confirm their integrity, any filter failing the test to be replaced and retested.

A planned maintenance program should be instigated, to cover all air handling, air conditioning ventilation and dust extract plant in order to ensure that the new operating conditions of the system can be guaranteed for the remainder of the life of the plant.

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Bangkok

JC/ 16 Sept 1994

Report of visit to manufacturing facility

Site of Visit: General Drugs House Co. Ltd
2-4 Lard Prao Road
Bangkapi
Bangkok

Personnel:		
	Dr. Sureerat Pracharktam	General Drugs House Co. Ltd.
	Mr. Vichai Chaiamnuay	Managing Director General Drugs House Co. Ltd.
	Ms. Sriwan Siritheeramongkon	Clean Room Specialist Global Tech Co. Ltd.
	Mr. J. Clark	UNIDO Air Handling expert

Date of visit: 12 September 1994

Purpose of visit:

JC was invited to visit the factory by Dr. Sureerat, for two purposes:

1) They are experiencing some difficulty in achieving the required relative humidity in their penicillin filling area, and
2) They have an unacceptably high failure rate of liquid fills due to particulate contamination, apparent from visual inspection of the vials.

JC also wished to continue the more general function of observing the methods and operating conditions of Thai pharmaceutical manufacturing and air handling systems design.

Activities:

JC was introduced to Mr. Vichai Chaiamnuay, Managing Director of General Drugs House Co. Ltd.,and to Ms. Sriwan Siritheeramongkon, the Clean Room Specialist from Global Tech Co. Ltd. Ms. Sriwan Siritheeramongkon was the design engineer for the air handling systems in the building.

A drawing showing the layout of the systems was tabled, and a discussion ensued concerning the reasons for particulate contamination in the liquid filling room. The design incorporated low level extract, from a single point, from the powder filling room and HEPA filters on both supply and extract. The two filling rooms are on separate systems, but the mixing room, also a dusty area, is on the same plant as the liquid filling room. Neither room is provided with an airlock, the doors are directly opposite each other across a corridor approximately 1.5m wide.

Although the pressure gradients as indicated on the drawing are correct to contain contamination, it was pointed out that if a door is open the pressure difference is lost, and if both room doors are open together the possibility of cross-contamination exists. The particulate contamination in the liquid appears (by visual inspection only) to be a fibre, and if this is the case is probably not product. Further investigations will be carried out by Mr. Vichai's staff.

The discussion then progressed to relative humidity problems, in particular in the Cephalosporin filling area, where a relative humidity of 30% at 24°C (moisture content .0057 Kg/Kg) is required. A Munters dehumidifier has been installed to achieve this, but at present the system as installed gives 22°C at 35%. This, from the psychrometric chart, equates to a moisture content of .0058 Kg/Kg, so the required condition is probably achievable by simply raising the room temperature control. In all other areas no humidity controls are provided, the systems relying on temperature sensors only to modulate the cooling capacity.

JC then looked at the air conditioning plant installed, obviously the main problem at the time of installation was space. The air handling equipment is sited on the perimeter balcony of the first floor, on a specially constructed steel platform. The Munters dehumidifier is positioned next to the Cephalosporin area air handling unit. Within the limits of the space available, the installation has been installed reasonably well, my main reservation being that the electrical wiring and manometer tubing are unsupported and thus vulnerable to damage. The chilled water circulates at 7°C flow temperature, low enough to dehumidify air at 24°C, with the correct control system.

Conclusions:

The relative humidity problem in the cephalosporin area can probably be solved by simply increasing the dry-bulb temperature in the room to 24°C, and then using an independent instrument to check the relative humidity achieved. To control the r.h. in other areas would require the addition of sensors and controllers to the plant, to allow the cooling coils to overcool and then reheat for temperature control.

Particulate contamination of the liquid filling operation may not be dust from the powder filling room, particularly if the contamination is a fibre. I suggest that the first action is to ensure that all overalls, caps, boots etc. are lint free and any paper or similar material excluded from the filling room. Next, keep the filling room doors closed at all times, do not open the liquid filling room and powder filling doors at the same time. If these measures do not stop the problem, it may be necessary to carry out a more detailed survey of the systems, to include a filter test and internal examination of the ductwork, cleaning all surfaces downstream of HEPA filters and laminar flow HEPA filters.

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Bangkok

JC/ 15 Sept 1994

Report of visit to manufacturing facility

Site of Visit:	F.E. Zeullig (Bangkok) Ltd. Pharmaceutical Laboratories 1899 Phaholyothin 39 Jatuchak Bangkok 10900	
Personnel:	Ms. Pacharee Setthasawad	Technical Plant Manager, F.E. Zeullig (Bangkok) Ltd.
	Mr. Surin Siripanich	Engineering and Maintenance Manager, F.E. Zeullig (Bangkok) Ltd.
	Mr. Prepond Banditayanond	UNIDO National Expert, Refrigeration and Humidity
	Mr. J. Clark	UNIDO Air Handling expert
Date of visit:	14 September 1994	

Purpose of visit:
JC was invited to visit the factory by Ms. Pacharee,to commnt on their existing air handling systems, and advise on humididty control systems.

JC also wished to continue the more general function of observing the methods and operating conditions of Thai pharmaceutical manufacturing and air handling systems design.

Report:
F.E. Zeullig (Bangkok) Ltd. is the largest factory yet visited by JC, carrying out contract manufacture for several multi-nationals. JC was first conducted to the meeting room by Ms. Pacharee to meet Mr. Surin. Mr.Prepond had already arrived. An extensive discussion then ensued concerning the existing air handling system and the merits of the clean air units it is proposed to install (see attached drawing). These clean air units are essentially a split type air conditioning unit with uprated fan and HEPA filter, and temperature and humidity controls with DX cooling and electric reheat. It is proposed to install one in each of the tabletting booths. to provide class 10,000 conditions. JC recommended low level return air from the tablet areas.

The general air handling system to this area of the factory comprises air supply from air handling units to the corridors, and extract from rooms. JC expressed reservations with this arrangement as particles are carried into prodution rooms from the corridor with the ventilation.

We then walked around the factory to observe the operation of the systems. First impressions are the supply and return air grilles and diffusers are small, are the air change rates adequate. JC commented that standard split type air conditioning units are not considered suitable for use in clean areas. The filters are too coarse to be of benefit and no humidity control is usual.

At lunchtime Mr. Prepond left for another meeting, and after lunch we discussed the advantages and disadvantages of Munters dehumidifiers for humidity control. JC agreed to work out a comparison between DX cooling and Munters based upon a notional 3m x 3m x 2.8m room with 20 air changes per hour and 15Pa positive pressure.

Conclusions:
As stated above, a check should be carried out as to air change rates in all areas. To remove the likelihood of contamination between rooms, modifying the duct system to provide individual supplies into each room should be considered.

A comparison of performance of DX cooling and Munters unit for dehumidification is attached.

Comparison of Energy Use to Maintain an Air Condition of 25°C 40% Relative Humidity in a Room 3.0m x 3.0 x 2.8m

a) Dehumidifying With Cold Coil.

Assumptions:

External air 38°C 80%

For pressurisation & dust extract 50% fresh air

20 air changes per hour supply air volume

Internal room heat gains 500w sensible, 0w latent.

From psychrometric chart:

a] External air 38°C, 80% r.h., 29.5g/Kg,

b] Room air 25°C, 40% r.h., 8.1g/Kg, 45.5 KJ/Kg

c] Mixed air (on-coil) 30°C, 18.8g/Kg, 78 KJ/Kg

To maintain room at 40% r.h, supply air must be reduced to 8.1 g/Kg moisture content by overcooling down to 8.1g/Kg, and then reheating to control room dry-bulb temperature. Chilled water temperature critical in determining off-coil condition, we require 8.1 g/Kg at saturation line, so assume coil dew point of 9°C, achievable with a chilled water flow temperature of 7°C flow 12°C return.

d] Therefore 'off-coil condition 10.8°C, 8.1 g/Kg, 31.5 g/Kg.

Supply air temperature to room = Room temperature - $\frac{\text{Room heat gain}}{\text{Air mass flow x specific heat}}$

$$= \frac{25-500}{0.14 \times 1.1 \times 1000} = 22.24^{\circ}C$$

Cooling requirement = Enthalpy difference c] to d] x air mass flow

= (78-31.5)0.14/0.85 = **7.66Kw**

Room must be maintained at 25°C when all equipment off & no internal heat gain, so reheat to 25°C, not supply temperature

Reheat duty = Mass flow x specific heat x (temp b]- temp.c])

= 0.14/0.85 x 1.1 x (25-10.8) = **2.57 Kw**

b) <u>Dehumidifying With Munters Rotary Wheel Chemical Absorbtion Dehumidifier</u>

All conditions to be as above i.e. room at 25°C, 40% r.h.

As before, mixed air on to Munters 30°C, 18.8 g/Kg

20°C rise assumed through Munters, so air leaving wheel at 50°C, 8.1 g/Kg, 71.5 KJ/Kg

Cool to 22.24°C from 50°C = (50-22.24) x 0.14 x 1.1/0.85 = 5.03Kw

Plus reactivation heat for Munters, say to 65°C on reactivation air = 50% process air

= .07 x 30 x 1.1/0.85

= 2.72 Kw

Summary:	Cooling Kw	ReheatKw	Reactivation Kw
Cooling dehumidification	7.66 Kw	2.57Kw	---
Munters dehumidification	5.03 Kw	---	2.72 Kw

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Bangkok

JC/ 21 Sept 199

Report of visit to manufacturing facility

Site of Visit: Berlin Pharmaceutical Industry Co. Ltd.
63 Romklao Road
Bangkok 10520
Thailand

Personnel:

Dr, Termchai	
Ms. Lalana Setasuban	Pharmacist
Mr. J. Clark	UNIDO Air Handling expert

Date of visit: 20 September 1994

Purpose of visit:

JC was invited to visit the factory by Dr. Termchai to commnt on their existing air handling systems, and advise on humididty control problems they have.

JC also wished to continue the more general function of observing the methods and operating conditions of Thai pharmaceutical manufacturing and air handling systems design.

Report:

JC was first asked to explain the theory of air handling systems with particular reference to control of differential pressures between rooms, relative humidity control, dust extract systems and refrigeration. Berlin do not have any sterile facility, so the requirements of U.S.Fed. Std. 209E were not considered. I in fact gave a preview of the full seminar, which was very useful as it allowed me to see which parts need elaboration, and where more detailed explanations are needed for non-engineers.

After the general discussion, we went through the factory existing air conditioning system drawings in detail, with particular reference to relative humidity and differential pressures.

An external air-cooled water chiller supplies cooling through a pumped and insulated chilled water cicuit at 7°C flow 12°C return to a total of 8 air handling units and 10 fan coil units.

The two large air handling plants, AHU7 and AHU8 are located in a plantroom at the rear of the building, all other air conditioning equipment is in the roof space.

Air handling units AHU7 and AHU8 are ducted together to form a single control zone for packaging and central non critical areas of the building. Air is supplied to rooms via insulated ductwork and ceiling diffusers, and returned from a single central grille in the corridor. Rooms are thus pressurised with airflow out into the corridor. The remainder of the air handling units are smaller, designed to serve one or two rooms only, each small unit having a separate fresh air inlet from outside. Small fans are provided to remove exhaust air from the rooms.

I was asked to particularly to advise on how to achieve better humidity control in the tabletting and powder filling areas. At the meeting I endeavoured to show a comparison between Munters dehumidification and cold coil dehumidification, but this became complicated, and confused rather than clarified the issue. I agreed to write to Dr.Termchai with this and explanatory notes.

The meeting then walked around the factory, to show JC the systems.

Outside the building the chilled water make-up tank ball valve is leaking badly and requires replacing.

AHU7 and AHU8 are rather rusty due to condensation, which could carry particles into the buildig as their is no filter after the fans.

Dust extract nozzles are not close to the dust generating tablet press, vial fillers etc. although they are designed to be.

No duct dampers are on the supply ductwork from the small air handling units.

The film coating machine dedicated air handling unit inlet filter is very dirty.

Conclusions and Recommendations:

A comparison of performance of DX cooling and Munters unit for dehumidification is attached.

Replace ball valve on chilled water make-up tank.

Clean and paint the air handling units internally and externally, preferably replace them.

Locate the dust extract nozzles close to the machines they serve.

Add duct dampers to air ducts to balance the air, and rebalance all systems to achieve the required air pressures

Replace film coating machine air filters.

The systems generally are adequate for the purpose, and appear to be maintained in good order. To achieve the control of humidity sought for some areas it will be necessary to install additionnal cooling, and air handling equipment, as outlined below.

Air Conditioning to Low Humidity Areas - Berlin Pharmaceutical Industry Company Ltd.

Powder Filling Room - 6.8m x 3.4m x 2.8m

i) control at 25°C,40%r.h., from psychrometric chart 8.1 g/Kg moisture content, 45.5 KJ/Kg enthalpy

ii) control at 25°C,25%r.h., from psychrometric chart 5.0 g/Kg moisture content, 37.7 KJ/Kg enthalpy

Existing air handling unit - from schedule 1000CFM = 26 air changes per hour

Record drawing - 700CFM supplied to room, = 18.4 air changes per hour

External Maximum air @ 35°C,80%r.h. Reading from psychrometric chart this is 29.5 g/Kg moisture content. Chilled water temperature 7°C flow, 12°C return. This will give a coil dew point of 9°C.

For a new system, assume air supply rateof 1000CFM = 0.47m^3/s.

From psychrometric chart,

'on-coil' mixed air 30°C,18.8 g/Kg,78 KJ/Kg

Drawing a straight line from the on-coil air condition to the coil dew point, and looking at the required 'off-coil'moisture content of 8.1 g/Kg, the off-coil condition will be 10.8 °C, 8.1 g/Kg,31.5 KJ/Kg, 0.85m^3/Kg

Therefore the cooling required = specific enthalpy difference x mass flow

= (78-31.5) x 0.47/0.85

= 25.7 Kw cooling

but with no internal heat gains to the room, a room temperature of 10.8 °C would result, thus reheating needed to 25°C.

Reheater output = (45.5 - 31.5) x 0.47/0.85 = 7.74 Kw

As an alternative, Munters chemical dehumidification can be used.

Moisture removal required = 18.8 g/Kg to 8.1 g/Kg
= (18.8-8.1)0.47/0.85
= 5.916g/second = 21.3 Kg/Hour.

Assuming a leaving process air temperature from the Munters of 40°C,

cooling duty = (40-25)0.47 x 1.1/.85
= 9.12Kw.

At lower humidity, Munters must be used,

Moisture removal required = 18.8 g/Kg to 5.0 g/Kg
= (18.8-5.0)0.47/0.85
= 7.631g/second = 27.5 Kg/Hour.

Again, assuming a leaving process air temperature from the Munters of 40°C,

cooling duty = (40-25)0.47 x 1.1/.85
= 9.12Kw.

Capsule Filling

To be maintained at 25°C, 40% r.h.

Existing air handling unit - from schedule 1200CFM = 0.57 m^3/s

Record drawing 900CFM supply to room, 450CFM fresh air, i.e. 50% fresh air so take psychrometric conditions as before, & maximum airflow.

Therefore cooling required = (78-31.5) x 0.57/.85 = 31.2 Kw

Reheater Output required = (45.5 - 31.5) x 0.57/0.85 = 9.39Kw

Tabletting Booths

To be maintained at 25°C, 40% r.h.%, 5 No. booths & corridor

Existing air handling unit from schedule 1200CFM 33,400Btu/hr cooling. From drawing, supply to each booth 100CFM, with individual fan exhausting 80CFM from each booth.

No separate fresh air supply shown to this area, to make up exhaust, thus with doors closed booths are positive to corridor, corridor negative to atmosphere.

Assume 5 x 80 CFM = 400CFM make-up fresh air comes from adjacent areas at up to 80%r.h. at 25°C. Thus fresh air ratio 400/1200 = 0.33

From psychrometric chart, 'on-coil' conditior then becomes 25°C, 10.7g/Kg, 52.6KJ/Kg & straight line to coil dew point of 9°C gives an off coil condition of 13.5°C, 8.1 g/Kg. (34.0 KJ/Kg).

Therefore cooling required = (52.6-34) x 0.57/.85 = 12.47 Kw

Reheater Output required = (45.5 - 34.0) x 0.57/0.85 = 7.71 Kw

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
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Bangkok

JC/ 3 October 1994

Report of discussion with factory principals

Site of Visit: At PTSC

Personnel:		
	Mr. J. Clark	UNIDO Air Handling expert
	Dr. Prachueb Sirivongrungson	Softpack Co. Ltd
	Ms. Pavadee Jivavichakun	General Manager, Suphong Pharmaceutical Laboratories

Date of visit: 27 September 1994

Purpose Of Visit:

Dr. Prachueb and Ms.Pavadee both wanted to discuss control of humidity in their factory, also dust extract and control of dust. JC repeated his run through the psychrometric chart and explained cooling coil processes to them, they understood very quickly the mechanics of dehumidification.

Dust extract, room pressures, crack leakage and pressure control were all touched on during our meeting, which lasted only two hours. They were particularly interested in the 'reverse laminar flow' dispensing booth idea.

Conclusions:

Dr. Prachueb and Ms.Pavadee were very interested, and expressed an interest in using the services of the Centre in the future, for further factory developements.

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JC/ 3 October 1994

Report of visit to manufacturing facility

Site of Visit: Biolab Co. Ltd
625 Bangpoo Industrial Estate
Soi 7 A, Muang
Samutprakarn 10280 Thailand

Personnel:

Mr. J. Clark	UNIDO Air Handling expert
Dr. Rachod Thakolsri	Deputy Managing Director, Biolab Co. Ltd.
Dr. Sompong Panichpol	Director of R & D/ QA Biolab Co. Ltd.

Date of visit: 28 September 1994

Purpose of visit:

1) To continue the discussions of JC first visit to Biolab Ltd.
2) To conduct a more detailed survey of the existing installed systems, and make recommendations for their improvement.
3) To advise on HEPA filter test procedures, air flow balancing & commissioning procedures.

Report:

Three maintenance and engineering staff were also in attendance at the meeting, although they were not introduced by name.

Mr. Rachod first established an agenda for the day, as follows:

A) CLEAN ROOM AREAS

1) JC to explain how HEPA filters are tested in situ, and to indicate on the record drawings any additions to the systems necesary to DOP test the installation.
2) Biolab are thinking of installing a temperature, humidity and pressure control system. JC to advise on type of system, sensor positions etc.

B) NON-STERILE AREA

1) Dust collector systems to be surveyed and recommendations made for improvements.

2) Validation of performance of dust collection systems.

3) Controls.

A) CLEAN ROOM AREAS

JC first explained the principles behind DOP testing of HEPA filters i.e. to challenge the filter with a 'dust' (smoke) of known particle size distribution and density, to ascertain the filter effectiveness. We then looked at the drawings of the systems, to identify the best position to introduce the smoke into each system. JC would send a copy of a test protocol for Mr. Rachod information.

Part of the test procedure is to measure the filter face velocity and pressure drop. The maintenance staff were not aware of any pressure tappings on the filter housings, JC would investigate with them later in the day.

The control system Biolab intend to install is a monitoring system, to record the temperature, humidity and pressure in the laminar flow area. JC suggested that continuous monitoring of the conditions is not necessary, just continuous sensing, and log the data every 15 or 30 minutes. The system should be programmed so that any abnormal condition is logged, when it occurs, with the date and time of the occurence, and all parameters continuously logged from that time, until the equipment is reset, or a non- critical parameter could automatically reset.

B) NON-STERILE AREAS

After lunch JC and the engineers walked around the factory, in particular to look at the sterile area plant, and the dust collection systems.

The Biolab engineers use a Velometer to measure the airflow at the discharge diffusers, using the grille nozzle to take a velocity reading. This could be one reason why they are recording such high air change rates, as 'jetting' through the diffuser vanes will give a very high reading, not related to the real air volume. JC advised they construct a hood of cardboard or similar to shroud the diffuser and give a velocity perpendicular to a known

duct area. A better way would be to take a pitot traverse across the duct, but as is usual with installations like this, there are no straight lengths of duct suitable for the purpose.

While in the sterile area, JC recommended that the sensor probes be installed below the laminar flow canopy, by the return air inlet. JC advised that Biolab use smoke streaming to visualise the airflow patterns under the laminar flow canopy, to make sure of sterile conditions at the point of fill.

We then went up to look at the sterile area plant. The HEPA filter housings in the lower ceiling void were extremely difficult to get to, crawling precariously across ceiling support frameworks, across trailing cables, and other debris. I strongly suggested they fix the cables securely, and provide some form of access equipment for the area. The HEPA housings do not have pressure tappings, so these must be fitted.

The air handling plants have differential pressure Magnahelic gauges fitted, but none of these reads as the drawings say they should. None of the engineers could remember when the filters were last changed, so I suggested they be inspected, and replaced where necessary. In particular the prefilter may have collapsed. The HEPA filters on the exhausts were in a poor state, approximately a 10mm hole in one could be seen.

The dust extract equipment is intended to take air from the room, filter out the dust, and return air to the room. The duct inlets are nowhere near the point of dust generation though. I suggested that at the very least a flexible duct to this position would improve things. Several rooms are served from the same plant, so cross contamination is quite likely. I recommended individual small dust collectors, if the intention is to continue returning air back to the tabletting rooms.

In the cream mixing area a cooling coil and condensing unit could be added to the existing ventilation system.

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
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Bangkok

JC/ 3 October 1994

Report of visit to manufacturing facility

Site of Visit: Polipharm Co. Ltd.
109 Mu 12, Bangna-Trad Road
Bangpleeyai
Samutprakarn
Thailand.

Personnel:		
	Mr. Suchart Chookruvong	Plant Manager, Polipharm Co. Ltd
	Mr. Sumsak	Polipharm Co. Ltd.
	Mr. Vichai Jittawait	OPEC Ltd., Consulting Engineers
	Mr. Anan Pakastain	OPEC Ltd.
	Mr. Teeraded Jaretoun	OPEC Ltd.
	Mr. J. Beelen	UNIDO CTA to PTSC
	Mr. J. Clark	UNIDO Air Handling expert

Date of visit: 29 September 1994

Purpose of visit:

This was the second visit to Polipharm, intended to discuss in detail the proposed factory extension, with Mr. Suchart and his engineers. In particular, advice was required relating to air handling and air conditioning systems.

Report:

On arrival at Polipharm, JC & JB were introduced to Mr. Sumsak, a pharmacist working with Mr. Suchart on the planning of the proposed factory developement. We were then conducted through to a larger meeting room, and introduced to the gentlemen from OPEC, the consulting engineers working on the project for Mr. Suchart.

Mr. Vichai tabled a revised layout for the new factory, and a general discussion followed about product and personnel flows and several minor changes made.

The various rooms were then identified from a numbered schedule tabled by Mr. Vichai, and cleanliness class, temperature and humidity parameters established for each room. Mr. Vichai redorded the details, to be put on a new drawing of the factory.

Services required in each area were then established, and recorded for inclusion on the revised drawing. JC was then asked for an opinion as to how the humidity and pressure in each room could best be controlled, with particular regard to the tabletting and film coating areas. A lengthy discussion then ensued regarding heat recovery, chilled water systems, air filtration standard, and provision for future expansion. The method of supporting air handling plant, ductwork and filters was discussed, particularly with regard to maintenance access, and testing of he installation.

Finally, materials and methods of construction were discussed, in particular mechanical protection of the structure, and finishes.

Conclusions:

Some considerable time had been spent preparing the latest layout, and thus very few changes were made to the overall scheme. The discussions were constructive and given the limited time available necessarily of a somewhat general nature, but still of value. Mr. Vichai is to revise the drawings to include revisions made, and a further meeting has been provisionally arranged for Monday 10 October for a final review before detail design is begun.

[N.B. Due to a confusion over dates and transport arrangements, JC did not attend the meeting on 10 October].

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
Faculty of Pharmaceutical Sciences
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Bangkok

JC/ 5 October 1994

Report of visit to manufacturing facility

Site of Visit: Golden Cup Pharmaceutical Co. Ltd.
289 Jaransanitwongse Road
Bangkok 10600
Thailand

Personnel:

Dr. Nilsuwan Leelarasamee	R & D, Golden Cup Ltd.
Mr. J. Clark	UNIDO Air Handling expert

Date of visit: 4 October 1994

Purpose of visit:

JC was invited to visit the factory by Dr. Nilsuwan to comment on their existing air handling systems, and advise on dust control problems they have.

JC also wished to continue the more general function of observing the methods and operating conditions of Thai pharmaceutical manufacturing and air handling systems design.

Report:

JC was first shown around the factory, in order to comment upon the recently completed improvements.

In general, the new plant is air conditioned by fan coil units in the ceiling void. In the tabletting area, air is supplied to each tabletting machine booth, then passes via a transfer grille and filter to the corridor, and back to the fan coil unit through a single return air grille. A central dust extract system is installed with a 1 1/2 in. hose to each tabletting machine.

The balm production floor is not yet developed, ventilation being by opening windows, with no mechanical assistance. A problem here is the smell of menthol, eucalyptus etc. which is very strong and pervades the whole area. JC was asked for a solution to the problem. The

warm balm is manually dispensed into small metal containers and bottles using a teapot, then cooled to set using a floor-standing fan.

JC then shown the Eye Drops 'Sterile' area. No airlocks, no external ventilation or pressure control, wood doors, exposed wiring, no coving, only a single old laminar flow canopy, under which the eye drop solution is manually filled. JC told better than class 100 is achieved under the canopy, and the product is tested regularly for contamination by particulates, and always passes.

The factory is currently undergoing a major upgrade, the tabletting area being the only completed improvements to date. As with most other factories visited, maintenance of equipment is minimal, with no appreciation of airflows or pressure regimes. All cooling is by DX fan coil unit, horizontally mounted above the ceiling. Lay-in grid ceiling, with exposed T bars.

JC then taken to meeting room and asked for his opinions of the new developement. I first said that the airflow in the tablet booths was wrong and would cause cross-contamination of the products. A more effective air filter must be fitted to each fan-coil ststem, uprating the fan if necessary. The airflow is from each booth into a common area, carrying dust. The dust extract system provides only one small outlet per booth, not very effective.

Difficult to comment without causing offense, as the whole factory has been designed with very little regard for pressure regimes or efficient air filtration.

JC was then asked for a solution to the odour control problem. Dr. Nilsuwan said they had tried electrostatic filters, but not effective. I said the only real solution was fresh air ventilation. Suggested they put the balm filling operations under a canopy, all together, and exhaust from there.

More general ideas of dust and fume control were then discussed, with clean room construction methods and 'double wall' low level extract, corner extract ducts etc.

The 'sterile area' needs to be completely rebuilt, employing suitable materials, air handling and pressure control.

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
Faculty of Pharmaceutical Sciences
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Bangkok

JC/ 3 October 1994

Report of visit to manufacturing facility

Site of Visit: Medicap Ltd
384 Soi 6,
Pattana 3 Road,
Bangpoo Industrial Estate
Samutprakarn 10280,
Thailand.

Personnel:		
	Mr. Vivek Dhawan	Managing Director, Medicap Ltd.
	Mr. Neel Kant Saxena	Engineering Manager
	Mr. Apichai Chancharusiri	Manufacturing Manager
	Mr. C.R. Achuthananda	Materials Manager
	Mr. Pornchai Wongpayak	QA/QC Manager
	Mr. J. Clark	UNIDO Air Handling Expert

Date of visit: 18 October 1994

Purpose of visit:

To review proposed new factory extension and refurbishment relative to Australian TGA requirements for production of pharmaceutical products, listed products and food supplements. To advise on air handling systems to achieve class 10,000 clean room standards in production areas.

Report:

Mr Viveck first described the Medicap operations and products, which are all soft gelatin capsules, liquid filled, for oral dosing. Medicap output is currently 20% ethical products, 20% cosmetics, and 60% food supplements. The purpose of the expansion is to increase production by 100%, and improve quality to permit expansion into other markets. Mr. Neel then tabled a drawing showing the proposed development, both the existing building improvements, and the extension.

JC then walked round the factory with Mr. Neel, to observe first-hand the building construction and production processes. Several key points were made during this walkabout, in particular:

Control of dust during powder dispensing is a problem at present

Oil mist from capsule filling machines blocks HEPA filters

Capsule drying close r.h. control required.

Future hormone production area to be incorporated .

Discussion then centred on details of air handling and refrigeration systems, prevention of cross contamination and control of room pressure gradients.

Mr. Vivek stressed his concern that they maintain quality with their expansion through inclusion of GMP and good engineering, while at the same time not wishing to over-engineer the facility and make the expansion uneconomic.

JC agreed to put together an outline proposal for GRC to advise and assist the design of the factory, commissioning and validation.

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Bangkok

JC/ 21 Sept 1994

Report of visit to manufacturing facility

Site of Visit:	Government Pharmaceutical Organisation Bangkok	
Personnel:	Singhathep Thepkanjana	Project Manager, Chula Unisearch
	Paitoon Tungkaserawong	Assistant Manager, Chula Unisearch
	Managing .Director	G.P.O.
	Distribution Director	G.P.O.
Date of visit:	26 October 1994	

Purpose of visit:

JC visited the factory with Chula Unisearch, preparatory to the compiling of a technical proposal for a feasibility study for improvements to the GPO

JC also wished to continue the more general function of observing the methods and operating conditions of Thai pharmaceutical manufacturing and air handling systems design.

Report:

The first part of the morning was spent in a meeting with the GPO MD, mainly conducted in Thai, concerning possible commercial uses of the existing site, I am told.

We then walked round the factory, observing existing operations and organisation.

The ground floor liquid filling was the first area visited, they are filling normal cough mixture type suspension in non-sterile warehouse conditions. Manual filling, manual screw capping. Short sleeved overalls & hats. Manual labelling. 3 automatic lines, 5 semi-automatic. Budget to buy one further fully automatic line this year. Lay-in grid false ceiling, vent duct from adjacent lightwell. Stainless steel pipework at high level delivers product from upstairs

through valves to distribution manifold to each line. 5 pipes feed from above, and after use they are only flushed with demin. water for cleaning. Room 25m x 15m approx.

Through plastic strip curtain to corridor. Lift to 4th floor, sterile products. Lobby area, office, with ampoule cleaning taking place. Dextrose, glocose filling, vitamin B injections, all ampoules. Area does not meet any sterile guidelines, transfer grilles into corridor, high level exhaust, meant to be class 10,000. Filters DOP tested every year. AHU off at present, area to be formalin gassed before restarting, but no retesting of filters or room pressures. Still room unclassified H/L supply & exhaust. Each room 2 no. 600 x 1200 HEPA filter supply, H/L extract. Aseptic area class 100 within sterile suite, laminar flow canopy visible. Finish epoxy paint on aluminium frame partitioning, pressure relief flaps between rooms recessed light fittings. Opening windows to access corridor, open. Some Dwyer manometers, unlabelled. Area looking grubby & in need of refit. TS autoclaves in non-sterile area. Aseptic autoclave double door type, under laminar flow. System not running at present, technician working inside in street clothes.

Moving along corridor, packaging & inspection, non-sterile, split fan-coil unit.

Ceiling throughout area lay-in grid, class 10000 & 100 hard plaster s/s grilles. Return air extruded aluminium grilles. No coving at walls or floors, grano floors.

Down to third floor, tablet production. Various products. Tablet booths are all individual, H/L supply air, exhaust transfers out to central corridor. 20 m/c, Kilian, Manesty, DCE minimaster at each m/c, in room, one or two modern m/c. All areas kept clean & tidy, apart from pile of rubbish in corner.

Back to lift lobby area, across to coating section.

27+ coating pans, 48" s/s, supply & exhaust vent to each. Film coaters not seen.

Solution production, cremes & ointments. Solvent smell. Hand packing. Tube filling m/c COMADIS, Italy. Three similar all filling at about 3 per 5 secs.

Corridor to formulation and preparation. 2 vessels, jacketed with top mixers. 3rd vessel with top & bottom mixer, on gimbals & bearings, top mixer variable gearbox drive, vessel heated and cooled. No mechanical ventilation to this room. Stick-on coving, ledges everywhere.

Old manual mixing pans, damaged insulation, at end tube filler. Bins wax & powder manual stirrer air in central, out through transfer grilles to common corridor.

Back to lift lobby, across to liquids preparation. above filling room below.

Met manager of area. wet area, minimal ventilation. 35 storage tanks, average size 3000l. Downstairs to offices, met Mr. Vichai, said just ask if anything needed.

In the main entrance a very useful overall model of site was on display, which gave a better appreciation of the problems involved in relocating a manufacturing facility on this scale. At present the site accommodates 47 buildings in a 40 rai (100 acre) area. Tablett production 3.8 x 10^9 last year.

Conclusion:

This was very much a preliminary visit and quick walk round, but it is obvious that in the building visited, much of the production equipment is obsolete and must be replaced. The mechanical services are basic, the sterile area does not comply to any standard. The operation is labour intensive, close discussions must be had with the GPO principals to determine the extent of the new investment, and level of automated technology adviseable.

ANNEX III

SEMINAR OVERHEAD PROJECTOR SLIDES AND HANDOUTS

A ONE DAY SEMINAR FOR MANAGERS
AND TECHNOLOGISTS IN THE
THAI PHARMACEUTICAL INDUSTRY

AIR CONDITIONING
IN THE
PHARMACEUTICAL INDUSTRY

PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Bangkok

JC/ October1994

PROGRAM

1) INTRODUCTION

2) WHAT IS AIR CONDITIONING

3) WHY DO WE NEED IT

4) PROPERTIES OF AIR AND WATER VAPOUR (PSYCHROMETRICS)

5) A/C SYSTEM COMPONENTS

6) TYPES OF A/C SYSTEM

7) ROOM AIR DISTRIBUTION

8) DUST CONTROL SYSTEMS

9) VALIDATION OF AIR CONDITIONING SYSTEMS

10) MAINTENANCE

WHAT IS AIR CONDITIONING?

IT IS CONTROL OF THE ATMOSPHERE WITHIN AN ENCLOSED SPACE.

AIR CONDITIONING CAN CONTROL:-

AIR TEMPERATURE

AIR RELATIVE HUMIDITY

AIR PRESSURE

DUST (AIRBORNE PARTICULATES)

AIR VELOCITY AND DISTRIBUTION

ODOURS AND VAPOURS

WHY DO WE NEED AIR CONDITIONING?

PHARMACEUTICAL MANUFACTURING

PRODUCT PURITY AND STERILITY

PRODUCT STABILITY

OPERATOR PROTECTION

OPERATOR COMFORT

DOSE CONTROL

GMP CONSIDERATIONS

PSYCHROMETRIC CHART

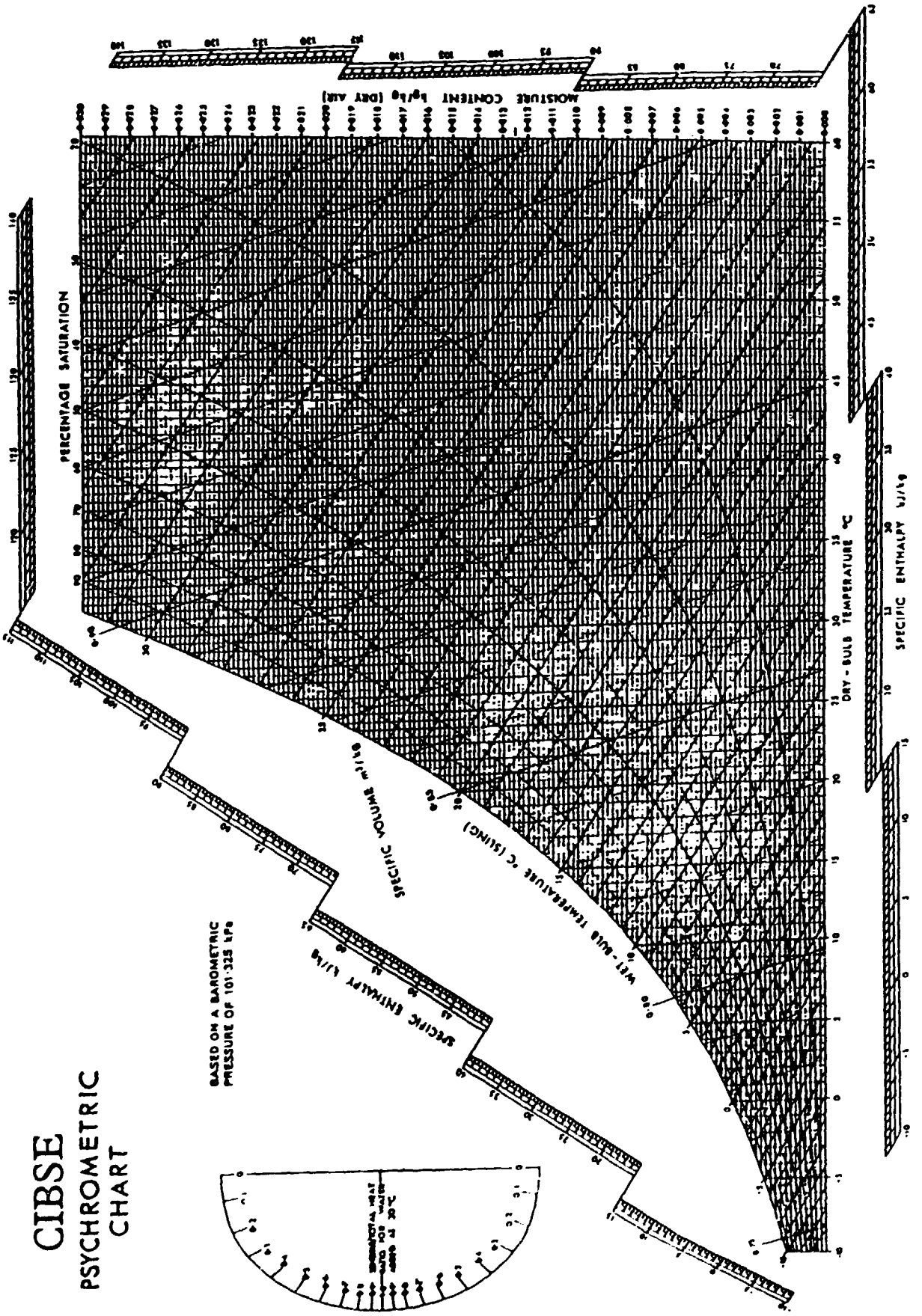


Fig. C1.2. CIBSE Psychrometric Chart (−10°C to 60°C)

Pads of 50 charts (A3 size) are available from the CIBSE, Delta House, 222 Balham High Road, London SW12 9BS

PROPERTIES OF AIR AND WATER VAPOUR

PSYCHROMETRIC PROPERTIES OF AIR:

TEMPERATURE

RELATIVE HUMIDITY

SPECIFIC VOLUME

MOISTURE CONTENT

SPECIFIC ENTHALPY

PSYCHROMETRC TABLES

AIR CONDITIONING SYSTEM COMPONENTS

HEATING COIL	LTHW/Steam/Electric/Gas
COOLING COIL	DX/Chilled Water
FAN	Centrifugal/ Axial/ Mixed flow
FAN DRIVES	Direct/ Belt/ Variabie speed
AIR FILTERS	Panel/Bag/HEPA/Filter position
HUMIDIFIER	Steam/Pan/Spinning disc
DEHUMIDIFIER	Cold coil/Dessicant wheel(Munters)
DUCTWORK	Materials/Construction methods/Pressure Classifications/Pressuretesting
AIR VOLUME CONTROLS	(valve or damper) single blade /multiblade /iris /neoprene/manual /automatic system powered/ motorised
AIR TERMINAL DEVICES	Grilles/diffusers/HEPA Filters/Panel ceiling/False floor
REFRIGERATION SYSTEMS	Refrigerants/Vapour Compression Cycle /Absorbtion /Chilled Water/Ethylene Glycol

TYPES OF A/C SYSTEM:

PACKAGE UNITS:

SINGLE PACKAGE

SPLIT UNIT

CLOSE CONTROL SPLIT UNIT

CUSTOM BUILT SYSTEMS:

AIR HANDLING UNIT

ROOM AIR DISTRIBUTION:

CLEAN ROOMS

CONVENTIONAL FLOW

LAMINAR FLOW

CRC

CONTROLLED ENVIRONMENT TO BS 5295: PART 1: 1989

B.S. Class	Approx Old Class	MAX. PARTICLES/M³ (≥ STATED SIZE) 0.3µm	0.5µm	5µm	10µm	25µm	4	5	6
C		100	35	0	NS	NS	M1.5 (1)	10	D
D		1000	350	0	NS	NS	M2.5(10)	10	D
E	(1)	10,000	3500	0	NS	NS	M3.5(100)	10	W
F	(1)	NS	3500	0	NS	NS	M3.5(100)	25	W
G		100,000	35,000	200	0	NS	M4.5(1K)	25	M
H		NS	35,000	200	0	NS	M4.5(1K)	25	M
J	(2)	NS	350,000	2000	450	0	M5.5(10K)	25	M
K	(3)	NS	3,500,000	20,000	4500	500	M6.5(100K)	50	Q
L	(4)	NS	NS	200,000	45,000	5000		50	Q
M		NS	NS	NS	450,000	50,000		50	Q

1. ALWAYS REFER TO COMPLETE STANDARD FOR FULL DETAILS
2. ALL FIGS. ROUNDED DOWN EXCEPT CLASS C/0.5µm.
3. NS–NO SPECIFIED LIMIT
4. APPX. FED. STD. 209E AT 0.5µm SIZE (NOT PRECISE COMPARISON)
5. MAX. AREA PER SAMPLING POSITION (M^2)
6. PARTICLE SAMPLING FREQUENCY - DAILY/ WEEKLY/MONTHLY/QUARTERLY.
7. $1M^3 \triangleq 35.71FT^3$

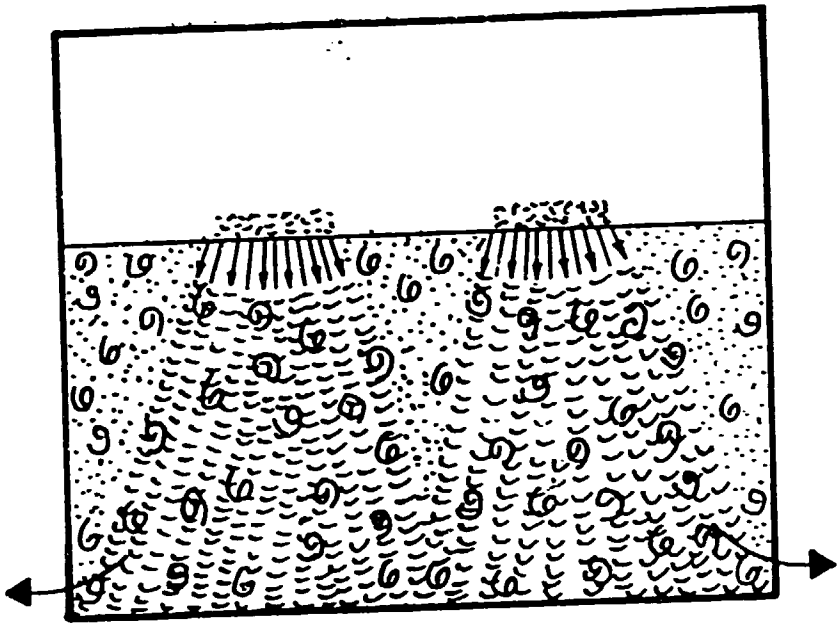
CRC

CONTROLLED ENVIRONMENT TO U.S. FEDERAL STANDARD 209E
(95% UPPER CONFIDENCE LIMIT AS SECTION 6.4)

F.S. CLASS * S.I.	ENGLISH	MAX. PARTICLES/M³ ★ (≥ STATED SIZE) 0.1µm	0.2µm	0.3µm	0.5µm	5µm	APPROX.★★ B.S. 5295 1989 CLASS
M1		350	75.7	30.9	10	–	
M1.5	1	1,240	265	106	35.3	–	C
M2		3,500	757	309	100	–	
M2.5	10	12,400	2,650	1,060	353	–	D
M3		35,000	7,570	3,090	1,000	–	
M3.5	100	–	26,500	10,600	3,530	–	E (F)
M4		–	75,700	30,900	10,000	–	
M4.5	1,000	–	–	–	35,300	247	H (G)
M5		–	–	–	100,000	618	
M5.5	10,000	–	–	–	353,000	2,470	J
M6		–	–	–	1,000,000	6,180	
M6.5	100,000	–	–	–	3,530,000	24,700	K
M7		–	–	–	10,000,000	61,800	

1. ALWAYS REFER TO COMPLETE STANDARD FOR FULL DETAILS.
2. ALL CLASSES - OPTION TO SPECIFY ONE OR MORE PARTICLE SIZES.
3. IT IS IMPORTANT TO APPLY STATISTICAL ANALYSIS AS DESCRIBED IN SECTION 6.4 OF THE F.S. WHEN DETERMINING RESULTS.
4. PARTICLES/FT^3 ARE NOT SHOWN ABOVE BUT ARE SHOWN IN THE COMPLETE STANDARD.
5. ALTERNATIVE PARTICLE SIZES AND CLASSES MAY BE BE DEFINED WITHIN CERTAIN LIMITS -SEE COMPLETE STANDARD.
6. ★ S.I. CLASSES AND UNITS ARE PREFERRED.
7. ★★ NOT A PRECISE COMPARISON.
8. $1M^3 \triangleq 35.71\ FT^3$.

CONVENTIONAL (TURBULENT) FLOW AIR DISTRIBUTION



DOWNFLOW LAMINAR (UNIDIRECTIONAL) AIR DISTRIBUTION

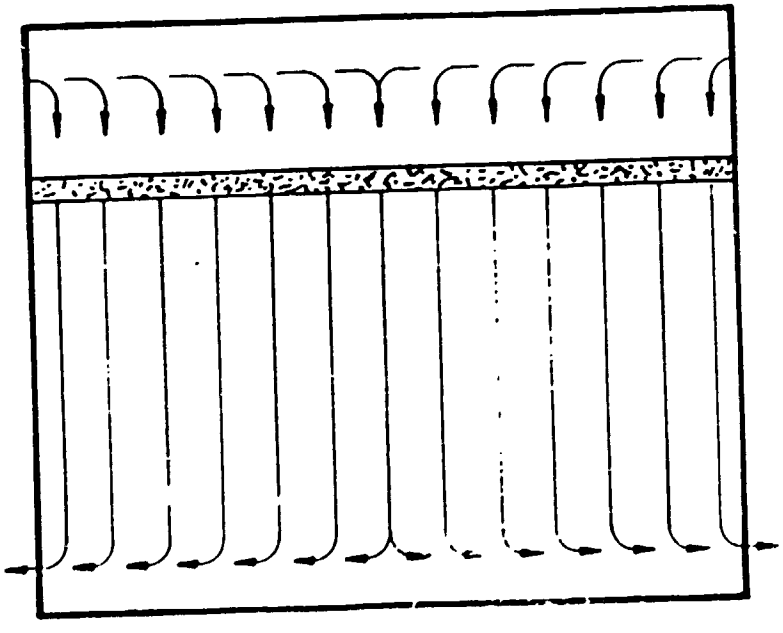
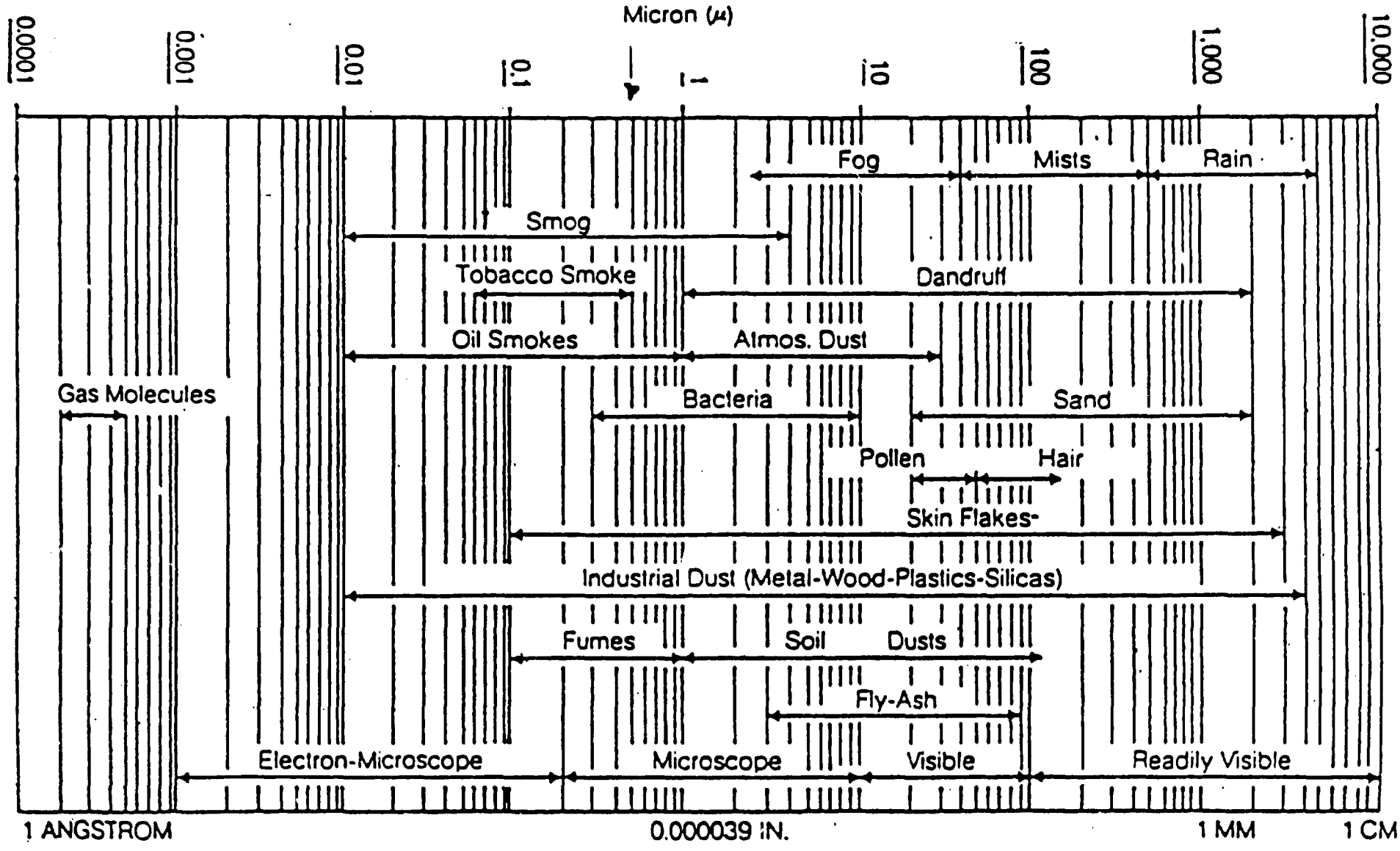
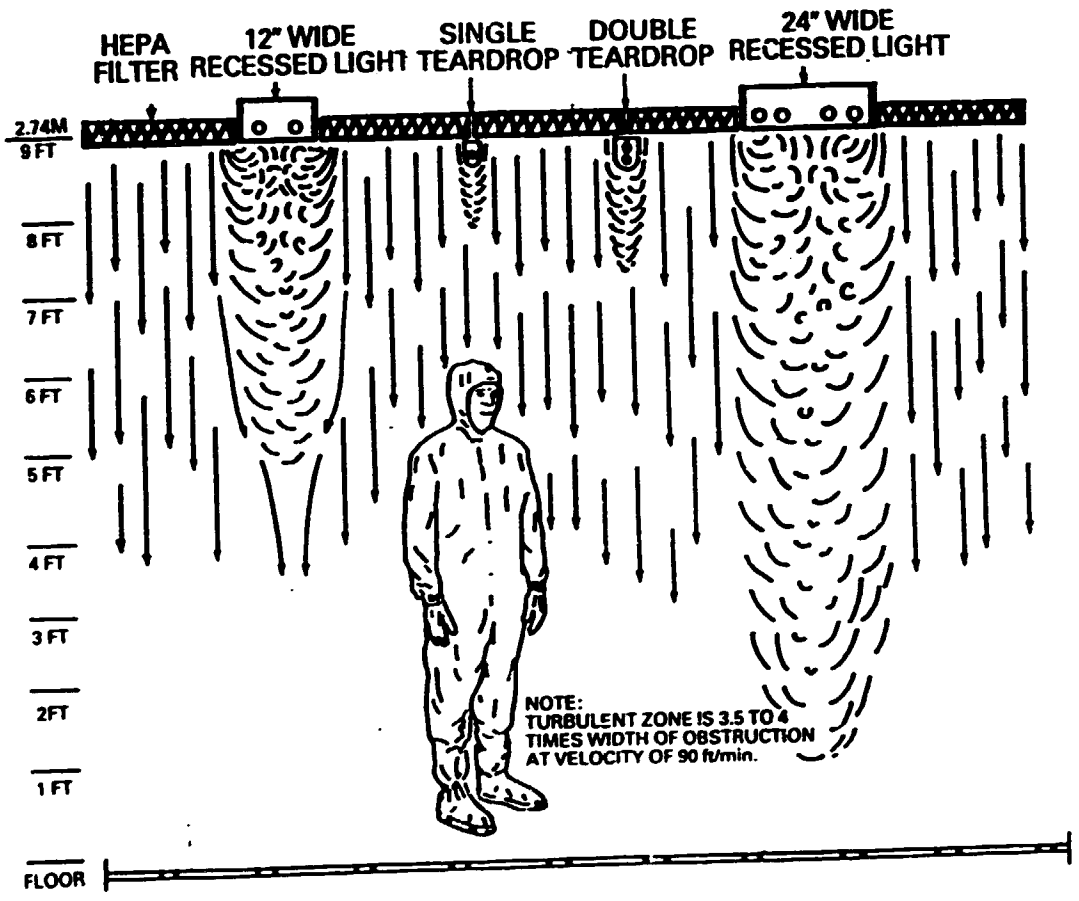


FIGURE 2: PARTICLE SIZE RANGES FOR COMMON CLEAN ROOM REQUIREMENTS





—Obstruction induced turbulence in a laminar flow clean room (Source: American Air Filters).

FIGURE 1: PERSONNEL CONTAMINATION EFFECTS ON CLEAN ROOMS

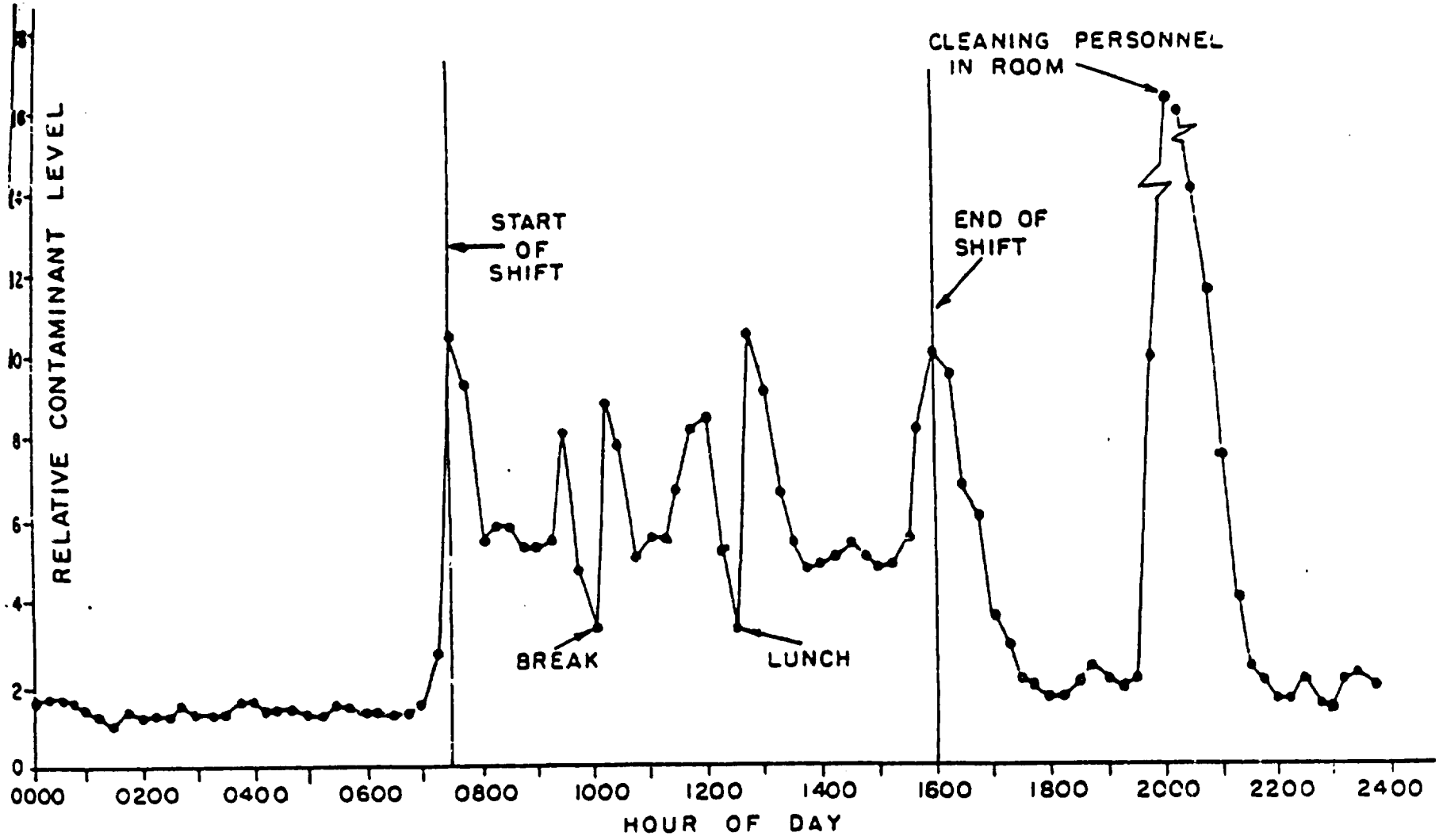


FIGURE 6-1. Typical clean room contaminant levels. The relation between activity and cleanliness is clearly shown by this plot. Increased activity increases contamination. *U. S. Air Force Technical Order* [illegible]

DUST CONTROL SYSTEMS

PHARMACEUTICAL OPERATIONS PRODUCING DUST

'DUST' FROM A PROCESS IS WASTED PRODUCT

TWO CONTROL METHODS:-

1. CONTAINMENT

2. COLLECTION AND REMOVAL

DESIGN OF DUST COLLECTION SYSTEMS:

1. TERMINAL DEVICES (HOODS, SLOTS ETC.)

2. DUCT SYSTEM

3. DUST COLLECTOR

VALIDATION

DEFINITIONS:

1) VALIDATION IS ATTAINING DOCUMENTATION OF SUFFICIENT EVIDENCE TO GIVE REASONABLE ASSURANCETHAT THE PROCESS UNDER CONSIDERATION DOES, AND WILL DO, WHAT IT PURPORTS TO DO.

2) PROCESS VALIDATION IS THE SCIENTIFIC STUDY OF A PROCESS TO:-
   a) PROVE THAT IT IS UNDER CONTROL, i.e. DOES WHAT IT IS SUPPOSED TO DO.
   b) DETERMINE THE PROCESS VARIABLES, AND ACCEPTABLE LIMITS FOR THE VARIABLES, AND SET UP IN-PROCESS CONTROLS.

I/Q (Installation Qualification) - verifying that the installed equipment has been manufactured and installed as designed.

O/Q (Operational Qualification) - setting equipment to work, and setting up plant and controls so that the system operates to achieve the design intent.

P/Q (Performance Qualification)- confirmation that the system will perform as commissioned under all validated operating conditions.

MAINTENANCE OF AIR CONDITIONING SYSTEMS

VERY IMPORTANT to ensure continued production in accordance with the terms of the validation, the operation of the environmental control system must remain consistent.

Part of the OQ must be to confirm that an SOP in the form of full operating and maintenance instructions have been prepared approved by your engineers, and formally handed to your maintenance staff.

ANNEX IV

SAMPLE STANDARD OPERATING PROCEDURES:

25-0001 OPERATION AND MAINTENANCE OF A PACKAGED AIR CONDITIONING UNIT.

25-0002 PREPARATION OF MAINTENANCE PROCEDURES FOR AIR HANDLING SYSTEMS IN PHARMACEUTICAL APPLICAIONS.

25-0003 SPECIFYING ENVIRONMENTAL CONDITIONS IN PHARMACEUTICAL MANUFACTURING PLANTS.

25-0004 PROCEDURE FOR THE LEAK TESTING OF HEPA FILTERS IN CLEAN ROOM INSTALLATIONS.

STANDARD OPERATING PROCEDURE

TITLE	SOP # 25-0001/ 1.....
OPERATION AND MAINTENANCE OF A PACKAGED AIR CONDITIONING UNIT	Effective Date from .... to ....
	Page 1 of 4

1) PURPOSE

To establish a procedure to ensure the correct operation and maintenance of air handling plant in the production environment,including full records and history of the equipment such that any progressive deterioration in performance can be identified and corrected.

2) SCOPE

This document contains guidelines for the operation and maintenance only. It is not intended to be implemented before full validation and handover to the owner of the air handling equipment. The operating parameters of the equipment must be based upon the validation documentation.

3) RESPONSIBILITY

The Production Manager is to ensure that this procedure is being implemented by the maintenance staff before commencing production. The engineering manager is directly responsible for carrying out this procedure.

4) DESCRIPTION OF INSTALLATION

The system comprises two principal sections, the inside room fan coil unit, and the external refrigerant condensing unit.

The room fan coil unit consists of a steel casing containing the room air circulating fan, the cooling coil with associated drain pan and refrigerant expansion valve, electric heating coil, air filter and room thermostat.

The external condensing unit consists of a weatherproofed steel housing containing the refrigerant compressor, refrigerant condensing coil, condensing coil cooling fan, compressor starter and electrical controls, high and low pressure switches, and refrigerant gas charging valves

The two sections are connected by refrigerant pipework and control and power wiring. The refrigerant pipework is run in copper tube,the smaller diameter pipe is the hot liquid line from the condenser to

STANDARD OPERATING PROCEDURE

TITLE	SOP # 25-0001/ 1.....			
	Effective Date from	D	M	Y ....
OPERATION AND MAINTENANCE OF A PACKAGED AIR CONDITIONING UNIT	to	....	....	....
	Page 2	of 4		

the expansion valve, the larger diameter insulated pipe is the cold gas line from the cooling coil (evaporator) to the compressor.

The system is powered by a three phase electrical supply, which is connected to the external condensing unit. Single phase power to the internal fan coil unit is run from the control box in the external unit to the connection terminals in the fan coil section.

5) DOCUMENTATION

The Building Manager is to prepare a log book for the purpose of recording all activities relating to this equipment. This logbook is to be kept for reference with the manual and data recorded during validation of the equipment.

6) EQUIPMENT START-UP

To restart the equipment after a shut-down for maintenance:

1) Check that all electrical safety covers have been replaced.
2) Check that all external equipment casings are properly secured.
3) Check that the room side air filter is correctly fitted.
4) Check that the room fan speed control is in the 'OFF' position
5) Turn on the main electrical isolator adjacent to the condensing unit
6) Turn the room side fan speed control to the required position
7) Check that the room thermostat is at the correct setting to maintain the required temperature
8) Check the refrigerant sight glass is flooded, i.e. there is sufficient refrigerant in the system for correct operation.
9) After the equipment has run for 1 hour,take measurements of room conditions as described in the validation procedure, compare the data with the validation performance data. If the operating conditions are not in accordance with the validated requirements, switch off the plant and investigate for malfunctions in accordance with the manufacturers operating manual.

7) MAINTENANCE PROCEDURES

All maintenance is to be carried out with the equipment electrically isolated.

Prepared By:	Reviewed By:	Approved By:	Authorized By:
Date:	Date:	Date:	Date:
Positon:	Positon:	Positon:	Positon:

STANDARD OPERATING PROCEDURE

TITLE	SOP # 25-0001/ 1.....			
	Effective Date from	D	M	Y ....
OPERATION AND MAINTENANCE OF A PACKAGED AIR CONDITIONING UNIT	to	....	....	....
	Page 3	of	4	

Should these instructions in any way conflict with the manufacturers recommendations, refer to the engineering manager for guidance.

EVERY DAY

Record the room conditions and external conditions in the logbook

Check that theoperator controls are at the correct settings, reset if necessary.

EVERY WEEK

Inspect the air filter. If an exessive build-up of dust occurs, clean outside the room and investigate the cause.

Check the refrigerant sight glass. If the glass shows excessive gas, check pipework for damge and leaks.

EVERY MONTH

Remove casing and remove the room air filter from the equiipment. Remove from the room and clean. If the filter becomes damaged, replace.

Ensure drain pan condensate drain is sealed by flushing with water, to fill trap.

EVERY THREE MONTHS

When carrying out the filter clean, vacuum clean the inside of the casing and the surface of the cooling coil.

Attach a pressure gauge to the refrigerant charging valves, record refrigerant pressures. Check against validation documentation

Clean cooling coil drain pan to prevent the build-up of any contaminant.

8) BREAKDOWNS

If the equipment ceases to function:

1) Check that the isolator adjacent to the condensing unit is not turned off.
2) Check that the main fuse or circuit breaker has not fused or tripped. If the safety device has been activated, check the equipment for electrical fault in accordance with the manufacturers instructions.

Prepared By:	Reviewed By:	Approved By:	Authorized By:
Date:	Date:	Date:	Date:
Positon:	Positon:	Positon:	Positon:

3) Check that the refrigerant high or low pressure switches have not stopped the equipment If the safety device has been activated, check the equipment for refrigeration circuit fault in accordance with the manufacturers instructions.
4) Check the room thermostat for correct operation. Replace if defective.

9) SPARES LIST

A spares list was requested with the order for the installation,and is kept with the manufacturers literature for this equipment. This must be examined and any item not already held in stock must be evaluated, as to the effect on production if a breakdown of this component occurs. All spares held must be catalogued and clearly labelled and stored in a central location, not in the production area.

Prepared By:	Reviewed By:	Approved By:	Authorized By:
Date:	Date:	Date:	Date:
Positon:	Positon:	Positon:	Positon:

STANDARD OPERATING PROCEDURE

TITLE	SOP # 25-0003/ 1.....			
	Effective Date from	D	M	Y ....
SPECIFYING ENVIRONMENTAL CONDITIONS IN PHARMACEUTICAL MANUFACTURING PLANTS.	to	....	....	....
	Page 1	of	4	

1) PURPOSE

To ouline the steps to take to ensure that specifiers of factory facilities communicate the HVAC requirements effectively.

2) SCOPE

This procedure applies to all factories, clean rooms, sterile areas, packaging halls, laboratories, warehouses or other construction intended for use in accordance with GMP guidelines. .It is intended to be used by purchasers and specifiers of pharmaceutical installations and provides a check list of design, construction and commissioning requirements which might or might not be relevant. Detailed recommendations are not given concerning the level or control of contamination but allows for them to be agreed by the interested parties.

3) RESPONSIBILITY

The purchaser is responsible for ensuring that all information outlined below is made available to the supplier if necesary in consultation with the user and/or supplier.

4) GENERAL GUIDELINES

Prepare a 'General Arrangement' drawing of the facility, showing production equipment, machinery, vessels, ovens, autoclaves etc.

Show on the G.A. drawing peripheral areas such as product and personnel airlocks.

Conduct a survey of the facility to identify where air handling equipment can be located, inside and outside of the building.

Discuss with production departments and maintenance departments essential requirements of the system, and additionnal desirable but not essential qualities to be considered, such as provision for future expansion, etc.

Prepared By:	Reviewed By:	Approved By:	Authorized By:
Date:	Date:	Date:	Date:
Positon:	Positon:	Positon:	Positon:

STANDARD OPERATING PROCEDURE

TITLE	SOP # 25-0003/ 1.....			
	Effective	D	M	Y
SPECIFYING ENVIRONMENTAL CONDITIONS IN PHARMACEUTICAL MANUFACTURING PLANTS.	Date from	....	....	....
	to	....	....	....
	Page 2	of	4	

Compile a design brief describing system requirements in detail, based on the elements listed in this SOP.

Review design brief with production and maintenance managers.

5) INFORMATION TO BE INCLUDED IN THE DESIGN BRIEF

a) Standards, referenced by originating source, number, date and title, to which the facility is to be constructed. e.g. U.S. Federal Standard 209E, September 1992, 'Airborne Particulate Cleanliness Classes in Clean Rooms and Clean Zones'.
b) The required class or classes relevant to this installation. If part or all of the facility is to be unclassified, this must be stated.
c) The purpose for which each space is to be used, the operations to be carried out, and any constraint imposed by the operating criteria.
d) The General Arrangement layout.
e) All critical dimensions, including those relating to available space for plant, and production space.
f) Special ventilation services required, e.g. dust extract, fume cupboards etc.
g) Responsibility for witnessing and performing commissioning tests and procedures.
h) Specify environmental parameters: Temperature ^{o}C+/-^{o}C,
Relative Humidity %+/-%
Ventilation and Air Change Rate,
Room Pressure Pa (indicate whether relative to adjacent room or atmosphere)
j) Requirement for determining environmental cleanliness at sampling positions additionnal to those required by the standards specified in items a) and b).
k) Requirement for periodic or continuous monitoring and associted alarms if required.
l) Special filtration requirements, e.g. laminar flow area above outlet from steriiising oven

Prepared By:	Reviewed By:	Approved By:	Authorized By:
Date:	Date:	Date:	Date:
Positon:	Positon:	Positon:	Positon:

STANDARD OPERATING PROCEDURE

TITLE	SOP # 25-0003/ 1.....			
	Effective Date from	D	M	Y ....
SPECIFYING ENVIRONMENTAL CONDITIONS IN PHARMACEUTICAL MANUFACTURING PLANTS.	to	....	....	
	Page 3	of	4	

6) DETAILED INSTRUCTIONS

a) Standards can be national, international, of foreign origin, or an internal company standard. .The purchaser and specifier must ensure that the supplier is aware of the source of the standard so that he may obtain a copy for reference.

b) Class must be indicated for each room, including the occupancy state, e.g. as built, at rest or operational. .The purchaser should fully understand the implications the selection of occupancy state will have for the supplier in designing, constucting and testing the clean room.

c) The purpose for which each space is to be used, e.g. changing room, quarantine, autoclave loading, finished goods store. Any constraints imposed by operating requirements, e.g. hazard due to solvent, explosive or toxic vapours, room to be gas sterilised, etc.

d) The General Arrangement should include all available information regarding equipment positions, power supply, room heeights, materials of construction and where possible mechanical and electrical services to be provided by others nd coordinated with the HVAC services.

e) The dimensions of all openings,doors, pass-through hatches, conveyor transits, windows should be made known to the supplier as soon as possible. In the case of openings which are to be determined by installed equipment, sufficient information must be given to the supplier for him to be able to make an assessment of the effect on room conditions caused by the opening.

f) The data must include whether special ventilation services run continuously or intermittently, constant or variable volume.

g) The purchaser may require the supplier to include in his estimate for the services of an independent testing and commissioning specialist. The purchaser must specify to the supplier the extent of testing to be carried out, with clearly stated acceptance criteria.

h) An example of additionnal continuous monitoring which could be required is the particle counts to be taken adjacent to filling needles on a sterile injectable vial or ampoule filling machine.

j) Any monitoring limits or alarm limits specified must be established before the detailed design of the air handling system, so as to be within the capabilities of that system.

k) The purchaser must specify control points and tolerances for internal temperature, relative humidity, room pressures for each zone or room. The purchaser must advise the supplier of any heat & moisture generated in the room, the location of heat & moisture sources, and the nature of any dynamic variation.

Prepared By:	Reviewed By:	Approved By:	Authorized By:
Date:	Date:	Date:	Date:
Positon:	Positon:	Positon:	Positon:

STANDARD OPERATING PROCEDURE

TITLE	SOP # 25-0003/ 1.....			
	Effective Date from	D	M	Y ....
SPECIFYING ENVIRONMENTAL CONDITIONS IN PHARMACEUTICAL MANUFACTURING PLANTS.	to	....	....	....
	Page 4	of	4	

7) DOCUMENT ISSUE

Based on the above information the design brief is to be prepared, then circulated to production, maintenance, and Q.A. for comment. A review meeting shall be held at which the design brief shall be revised and approved. The design brief is then to be issued to all tendering suppliers of the HVAC installation.

Prepared By:	Reviewed By:	Approved By:	Authorized By:
Date:	Date:	Date:	Date:
Positon:	Positon:	Positon:	Positon:

STANDARD OPERATING PROCEDURE

TITLE	SOP # ..25-0002/ 1.....
	Effective Date from .... . to ....
PREPARATION OF MAINTENANCE PROCEDURES FOR AIR HANDLING SYSTEMS IN PHARMACEUTICAL APPLICATIONS	Page 1 of 5

1) PURPOSE

To outline the steps to be followed when a SOP is established for the operation and maintenance of air handling plant., in compliance with GMP guidelines and company policy.

2) SCOPE

This procedure applies to all SOP's relating to air handling equipment in Pharmaceutical Facilities. This document contains guidelines for the operation and maintenance only. It is not intended to be implemented before full validation and handover to the owner of the air handling equipment. The operating parameters of the equipment must be based upon the validation documentation.

3) RESPONSIBILITY

The QA manager is responsible that the instructions in this SOP are followed when SOP's are prepared.

4) GENERAL GUIDELINES

- Refer to SOP #_____"SOP Guidelines" for detailed instructions for the preparation of SOP documents.
- Establish a central indexed filing system for all manufacturers literature, certified drawings, installation drawings, wiring diagrams, control schematics, commissioning data and test certificates.
- Maintain a planned maintenance program, for all items of mechanical plant throughout the factory.
- Keep an inventory of all spares held in stock.

Prepared By:	Reviewed By:	Approved By:	Authorized By:
Date:	Date:	Date:	Date:
Positon:	Positon:	Positon:	Positon:

STANDARD OPERATING PROCEDURE

TITLE	SOP # ..25-0002/ 1.....
PREPARATION OF MAINTENANCE PROCEDURES FOR AIR HANDLING SYSTEMS IN PHARMACEUTICAL APPLICATIONS	Effective Date from .... D . M . Y to ....
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- Maintain an up-to-date list of original equipment suppliers with contact names and telephone numbers.
- Set up a reporting system to record and act upon any equipment malfunctions.
- Monitor system performance regularly, to note and rectify any change in plant performance.
- Update record drawings commissioning records to show any modifications to the installed systems.

5) FLOW CHART

	ACTIVITIES	RESPONSIBLE
1.	IDENTIFY all systems for which SOP to be prepared	Engineering Manager
	⇓	
2.	RECORD SOP titles	Q.A. Manager
	⇓	
3.	DESIGN standard layout	Q.A.Section
	⇓	
4.	WRITE SOP	Engineering Section
	⇓	
5.	REVIEW and APPROVE SOP	Engineering Manager
	⇓	
6.	AUTHORIZE SOP	Q.A. Manager
	⇓	
7.	ESTABLISH review survey of SOP's	Q.A.
	⇓	
8.	LIST Exhibits	Engineering Manager
	⇓	

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9.	SET UP glossary of terms	Engineering Manager
	⇓	
10.	DISTRIBUTE SOP	Q.A. Manager
	⇓	
11.	REVIEW SOP	Engineering Section
	⇓	
12.	DON'T REVISE/REVISE/DELETE SOP	Q.A. Manager
	⇓	
13.	FILE SOP	Q.A. Manager
	⇓	
14.	ISSUE New SOP	Q.A. Manager

6. DETAILED INSTRUCTIONS

6.1 ESTABLISH a filing index

- List all air handling systems and activities for which SOP's have to be written (e.g. Sterile unit-injectables-HEPA filter change)
- Allocate to each system or activity a unique number.

6.2 RECORD SOP - titles

- State on which topics SOP must be written
- Select the most appropriate title which reflects the topic (e.g. HEPA filter changing for sterile systems)
- Index all titles of SOP's by allocating each a unique 6 digit number;
  first two digits: refer to the system;
  last four digits: sequential number.

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6.3 USE standard layout

- Obtain standard SOP layout from Q.A.
- Include the following items: the company name
  purpose, scope and title of SOP
  unique SOP number
  authorizing persons, the preparer and their signatures
  date of review
  revision number
  reason for revision
- Number the pages (of total number of pages)

6.4 WRITE SOP

- Decribe — briefly the system to which the SOP applies.
- Quote — manufacturersdrawing numbers and operating manual references.
- Describe — all individual components in the system, their function and location.
- Indicate — associated systems upon which the operation of this system is reliant e.g. chilled water system for air handling unit, cross referencing this SOP to the associated system SOP's.
- State — responsible functionaries for implementing the SOP
- List — the operations to be carried out for each component of the system
- Summarise — the activities in a chronological order, tabulating them on a bar(Gant) chart. Highlight earliest and latest dates for each function. or activity.

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- Describe the instructions in detail in the imperative.
- Writing and language used must be consistent and clear.
- Design exhibits and refer to them to clarify the meaning of the text.
- Fill in and sign the Document Review Form.
- Sign the SOP

6.5 REVIEW and APPROVE SOP

Review approve and authorize theSOP in accordance with the SOP Guidelines SOP#_____

During the effective period

Ensure that operations are carried out according to written procedures

Revise the SOPwhen any modifications to the air handling system are carried out. A revised SOP reflecting the plant changes must be in place before the plant revisions can be accepted by maintenance or production departments

Update manufacturers and contractors record drawings and manuals to show all changes to the systems.

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STANDARD OPERATING PROCEDURE

TITLE	SOP # 25-0004/ 1.....			
	Effective	D	M	Y
PROCEDURE FOR THE LEAK TESTING OF HEPA FILTERS IN CLEAN ROOM INSTALLATIONS	Date from	....	....	....
	to	....	....	....
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1) PURPOSE

To establish a standard for the testing of HEPA filters in Clean Room installations.

2) SCOPE

This procedure applies to all HEPA filter installations in clean rooms. The procedure is to be read in conjunction with the appropriate standard to which the installation is required to comply.

3) RESPONSIBILITY

The engineering manager is responsible for ensuring that this procedure is followed when filters in clean rooms are tested.

4) GENERAL GUIDELINES

A copy of the 'Genera! Arrangement' drawing of the facility, showing all ventilation supply and exhaust grilles and diffusers shall be obtained. Each HEPA filter shall be assigned a unique identification number for the purpose of recording test data.

5) PREPARATORY MEASUREMENTS

5.1 Room Pressures

Before beginning any leakage detection tests, the difference in air pressure between the controlled space under test and any adjacent areas of lower classification including void spaces, shall be undertaken. The results of the pressure tests shall be recorded and comparison made with the specification for the room. If any deviation of greater than or equal to +/- 5Pa is detected the room shall be rebalanced and the test for air pressure repeated.

5.2 Air Velocity Measurement

Air flow velocity through the HEPA filters or workstations being tested should be measured using a calibrated hot wire or vane type anemometer accurate to within +/-3% of full scale.

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The air flow velocity through each filter should be no greater than +5% above the manufacturers recommended maximumair flow velocity, and no greater than -5% below the manufacturers recommended lower air flow velocity limit.

All air flow velocities should be recorded and a review of the overall results undertaken to confirm uniformity of velocity for the filters in each room.

6) INTRODUCTION OF AEROSOLS

6.1 Where possible aerosols should be introduced upstream of individual filters in such a manner as not to affect other filters on the air distribution system.

6.2 Where it is not possible to introduce an aerosol in accordance with item 6.1, it shall be introduced in the air handling unit fan section preferably immediately in front of the fan to ensure adequate mixing of the aerosol with the air stream.

6.3 The test aerosol shall consist of particles with the following size distribution:

More than 20% by mass of particles less than 0.5×10^{-6}m
More than 50% by mass of particles less than 0.7×10^{-6}m
More than 75% by mass of particles less than 1.0×10^{-6}m

7) PROCEDURE

7.1 Disperse the test aerosol upstream of the filter to produce a uniform challenge concentration across the filter and sealing frame.

7.2 Maintain this concentration throughout the test, and measure it at a point as close as possible to and ideally not more than 150mm from the filter face.

7.3 Adjust the aerosol generator so that the challenge concentration at the upstream filter face is at a level such that the photometer can be set and maintained at a stable reading of 100%.

7.4 Set the photometer at 100%. For all measurements the photometer shall be set to use the logarithmicscale in order to minimise background or,

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7.5 Using the same photometer, scan all of the downstream face and perimeter of the filter including the sealing device with the sampling probe. Hold the probe approximately 25mm away from the area being tested and pass it over the entire area in slightly overlapping strokees, at a traverse rate of not more than 0.05m/s. Make separate passes around the entire periphery of the filter, along the bond between the filter pack and the frame and around the seal betweeen the filter and retaining device.

7.6 Record the location of any steady repeatable reading of the photometer which exceeds the value set by the standard for the relevant class of environmental cleanliness.

7.7 Where an unacceptableconcentration is detected, the filter including all recesses shall be cleared of all aerosol using a vacuum cleaner. A narrow nozzle shall be used so that aerosols which may have collected in stagnant or inaccesible points around the filter assembly can b adequately cleared.

7.8 The scanning procedure will be repeated in accordance with 7.5 after a period of 30 seconds has elapsed following the cleaning in accordance with 7.7.

a) if no concentrations above the permissible level are detected the filter will be deemed to be acceptable.

b) if an aerosol concentration above the permissible level detected the actions in 7.7 are to be repeated.

7.9 If after repeating the above procedures 3 times an unacceptable aerosol concentration is still detected its position (or positions) is to be noted so that remedial action as described below can be carried out.

7.10 Prior to further investigation, the remaining filters and filter assemblies are to be tested before detailed actions taken to pinpoint a leak.

8) LEAK LOCATION

8.1 If the primary scans of a suspect filter indicate a failure of the media the filter shall be rescanned. If a point failure is found, the upstream aerosol concentration shall be checked for compliance

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wih the specification, and if the challenge is within limits then the filter has failed and must be replaced with a new filter.

8.2 If a failure is located at the edge of the filter a small diameter nonozzle shall be used to detect the axact position of the leak. Static or slow scanning< .01m/sare acceptable.

Once the position of the leak is detected the upstream aerosol concentration shall be checked for conformance, and a report issued.

9) TEST REPORT

The test report shall include at lest the folowing:

a) Number and date of the standard to which the clean room is to comply.

b) Title of the test method.

c) Class of environmental cleanliness and occupancy state.

d) Result, i.e. whether or not the installation was deemed to leak.

e) The location of any leak.

f) The nature of the challenge aerosol.

g) Name and address of the testing authority.

h) Any special conditions relating to the test, or departures from the test method.

I) Date on which the test was carried out.

j) An identification for the controlled space tested.

k) Details of apparatus used, together with those of the apparatus calibration certificate, showing the date of calibration.

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ANNEX 5

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

The air handling and air conditioning systems are one of the most important parts of the facilities equipment providing the essential supplies for the operations of the pharmaceutical industry. The air handling as part of the environmental monitoring has been listed among the top 10 current technical issues in the pharmaceutical formulation and packaging industry.

Many issues exist in the filed of environmental monitoring, including:

- appropriate techniques to obtain accurate data on quantitative air microbial contamination levels;

- appropriate protocols to record and scheduling to obtain useful and relevant monitoring data;

- appropriate processing and organization of monitoring data for easy review and valid decision making; and

- appropriate criteria and methodology on how data will be used to determine acceptability of lots manufactured.

USP has recently proposed new guidelines for levels of microbial contamination in different classified areas of pharmaceutical manufacturing. For example, in critical aseptic processing areas, where sterile products are processed and yet unsealed, the proposed limit of microbial contamination is < or = 1 CFU/m^3. To obtain a reliable estimate of this level of air contamination at least 5 m^3 of air should be sampled. This raises a serious technical problem because no single air sampler in the market is capable of sampling 5 m^3 of air without causing turbulence and therefore disturbing the laminarity of the airflow.

Clean room classifications

Class		USP CFU/m^3	EU Criteria CFU/m^3
100	A	1	1
None	B	-	5
10,000	C	18	100
100,000	D	88	500

The above example well illustrates the complexity of the validation of the utilities for the pharmaceutical industry. The scrutiny of environmental monitoring data has increased substantially in the recent past forcing the industry to seek more organized and systematic methods to monitor, evaluate and control these data. Without this scrutiny the pharmaceutical enterprises cannot

cope with the national regulation and have no chance to enter and be present in the international market.

The containment is another aspect that must carefully be examined in the pharmaceutical manufacturing facilities because of the potential cross-contamination of products. During an audit, the type of organisms and products that have been produced in the facility should be determined. It should also be identified how these products are separated and contained during manufacture and storage. Ideally, complete physical separation of each production line and each unit operation of the process should be in place, along with appropriate HVAC of adequate classification. Assurance should be sought that adequate isolation and methods are available to prevent contamination of product from concurrent or previous production runs.

Containment technology is increasingly being used in the manufacture of pharmaceutical products with the aim of protecting the product from contamination and protecting the operator and the environment from exposure to potentially hazardous substances.

The expert's report not only a correct description of his work but it could also be used for training purposes in air handling and air conditioning systems in the pharmaceutical industry. The factory visit reports are good examples for problem identification and decision making. The material of the seminar and the sample Standard Operating Procedures provides enough material for thoughts for the managers of the pharmaceutical industry.