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

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INTEGRATED DEVELOMENT OF PHARMACEUTICAL INDUSTRY IN THE SYRIAN ARAB REPUBLIC

DU/SYR/92/008

SYRIAN ARAB REPUBLIC

Technical report: Findings and recommendations*

Prepared for the Government of the Syrian Arab Republic
by the United Nations Industrial Development Organization

Based on the work of Mr. John Clark
STC on pharmaceutical industrial standards

Project Manager: Dr. Zoltan Csizer,
Chemical Industries Branch

* This document has not been edited.

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I. ACKNOWLEDGEMENTS

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II. ABSTRACT

A technical mission to Syria was undertaken by the UNIDO Technical Expert to support the project "Integrated Development of the Pharmaceutical Industry in The Syrian Arab Republic" (UNDP/UNIDO DU/SYR/92/008). The principal aim of the mission was to provide technical assistance and training on the implementation of Pharmaceutical Industrial Standards to support Good Manufacturing Practice. The mission was to include assistance with the preparation of suitable standards, and advice on sources of existing suitable internationally accepted criteria. The subjects of the training activities were professionals and senior personnel involved in the manufacturing of pharmaceutical products in Syria. To assess the requirements of local industry, the two public sector manufacturers were visited, and also a number of private sector companies.

III. ABBREVIATIONS

BP	British Pharmacopoeia
BS	British Standard
BSI	British Standards Institute
cGMP	current Good Manufacturing Practice
GMP	Good Manufacturing Practice
HEPA	High Efficiency Particulate (air filter)
HVAC	Heating, Ventilation Air Conditioning
ISO	International Standards Organisation
QA	Quality Assurance
SOP	Standard Operating Procedure
STC	Short Term Consultant
UNDP	United Nations Development Program
USP	United States of America Pharmacopoeia
UV	Ultra Violet
WHO	World Health Organisation

IV. BACKGROUND

Project DU/SYR/92/008 was originated at a time when the private sector pharmaceutical manufacturing industry in Syria was created under the national investment law. Up to that time, all pharmaceutical manufacturing took place in two public sector factories, Thameco and Dimas. Most of Dimas production was not available to the public, Thameco was thus at that time the major supplier of pharmaceuticals to the people of Syria.

When the pharmaceutical manufacturing sector was de-regulated in 1989, many factories were set up by private entrepreneurs, throughout the country. National standards did not exist in Syria for the design and construction of pharmaceutical manufacturing facilities, each factory was created according to the owners interpretation of GMP. To assist with the establishment of quality standards within the industry, UNIDO offered the government of Syria a project intended to introduce standards for pharmaceutical production, based on internationally accepted practice. This project became DU/SYR/92/008, a joint WHO/UNIDO project to strengthen the industry in Syria through the regulatory body, and education of the industry principals in the necessary techniques.

V. THE TECHNICAL MISSION

On 22 August 1995, a Technical Mission was undertaken to Syria to support the project UNDP/UNIDO DU/SYR/92/008.

The mission's objective was to give technical support to the project by providing training and technical advice to local industrialists and engineers, and also to review documentation relating to pharmaceutical industrial standards available in Syria.
The terms of reference for the technical mission are shown in the original job description attached as appendix 1.

A standard is that which has been selected as a model to which objects or actions may be compared. Standards for industry may be devices or instruments used to regulate physical product attributes, or may be written mathematical or symbological descriptions, drawings, or formulae setting out the important features of objects to be produced or actions to be performed. Standards to be applied in an industrial setting include engineering standards, such as properties of materials, dimensions, terminology, and product standards intended to describe attributes and ingredients of manufactured items, and embodied in drawings, materials lists, descriptions or drawings. In order that the manufactured item complies with the product standard, it is frequently necessary to invoke standard procedures and operating methods, for the guidance of manufacturing personnel.

In the pharmaceutical industry, the product standard is in most cases well established as the drug specification defined in the applicable pharmacopoeia (USP, BP, etc.). Quality Control tests can determine the properties and components of a product Unless rigorous and consistent (standard) manufacturing conditions and procedures are implemented, the QC tests only confirm the quality of the individual item tested, they are not of themselves a substantiation of the quality of any item not tested. To create sufficient confidence in the quality of a product, every item must be manufactured in exactly the same way, using the same raw materials, solvents, environment, equipment, containers, cleaning procedures, etc. That is, the product must be manufactured according to a Standard Operating Procedure.

To determine the manufacturing conditions for every product and factory individually would be extremely time consuming, therefore Industrial Standards for common components of processes have been internationally established, to which engineers and factory operators can refer for guidance.

In Syria, at present, documentation relating to building construction to pharmaceutical Industrial Standards has not yet been developed, and comprises a translation of the WHO GMP guidelines into Arabic.

The STC discussed at length with the local manufacturing pharmacists and engineers, both private and public sector, how improvements in facilities could best be achieved. The local engineers did appreciate the basic requirements for air filtration, temperature and humidity controls, cleanable crevice-free construction etc., but no standards for methods of construction etc. are yet available in

Syria. In order that suitable standards can be implemented, as a first step the STC is to send to the Drugs Control Inspectorate engineers within the Ministry of Health a list of the appropriate established British Standards, together with overseas membership costs for the British Standards Institute.

The STC visited several Syrian private manufacturers, and the public sector factories, meeting with pharmacists and engineers, and also discussed industrial requirements with the drugs inspectors. An area of great interest to all parties was the procedure for validation of clean and sterile facilities, both in terms of air systems and GMP for personnel. It was stressed that the air treatment in such environments must be supported by a planned maintenance program and personnel training. To this end, the STC gave a brief talk on Validation of Clean Rooms at a seminar organised by the WHO very soon after arriving in Syria.

The factory visits were extremely useful, in that they gave the STC an opportunity to see where the implementation of standards is most needed. The original construction of the establishments visited is in most cases adequate, but the major failing is in maintaining the engineering systems, building fabric and operating methods to an adequate standard. When visiting factories, it was unusual to be asked to wear protective clothing or overshoes. For this reason the author prepared for the engineers, in particular at Thameco, sample SOP's relating to maintenance of equipment and testing of air handling and air conditioning systems.

During visits to Thameco, the STC arranged to present a workshop to their engineers, with the Industrial Pharmacist STC, dealing with design and validation of pharmaceutical facilities, in particular testing of clean rooms and sterile suites. At the request of the Minister of Health this workshop was widened in scope, and invitations extended to the private sector manufacturers and the Ministry Engineering Department.

During the course of the mission, with the Industrial Pharmacist STC, several documents were prepared summarising the requirements for various production environments, including equipment, personnel, facilities, utilities etc. Copies of these are included in the Industrial Pharmacists Final Report.

VI. RECOMMENDATIONS FOR THE FUTURE

A) Training of staff

The great majority of engineers, factory operators and pharmacists the STC spoke to while in Syria were very interested in ways to improve their facilities. Several of the more recently constructed factories are very good in terms of materials of construction, product and personnel flow, environmental control, etc. but this has largely been achieved by the use of foreign consultants. The Syrian engineers whom the STC met were quite able to design and construct a facility, but they do not have access to recognised international standards, or design guides, such that the use of pressure gradients, airlocks, material pass-throughs, low level exhaust outlets, dust extract systems etc. are not fully understood.

Also apparent was the lack of understanding of the philosophy behind GMP, on the part of some production staff. The STC understands that several courses in GMP have taken place as part of this WHO/UNDP project, attended by the factory managers, but it seems that the people literally on the factory floor have not had the benefit of similar courses. As well as the senior staff, shift supervisors should also be given training in implementation of GMP. This training should do more than just re-iterate the basic requirements of GMP, but also try to communicate the philosophy behind the rules, so that all staff try to improve the production environment.

Several questions were asked repeatedly by both pharmacists and engineers, usually taking the form 'How do I test a clean room?'
'Why integrity test HEPA filters and take room particle counts?'
'Do I need to test the air filters if I have a UV lamp in the room to ensure it is sterile?'
'How soon before occupation do I need to start my clean room air handling plant?'
'How big should the sterile area be?'

These type of questions were easily answered, but also indicate that the factory managers (usually in Syria a pharmacist) are not familiar with the engineering reasons for a particular installation, and that the engineers do not always understand the pharmaceutical reasons for a production or process operating requirement.

As part of the professional development of managers and engineers in pharmaceutical factories, a short course should be established at the Ministry of Health to introduce the pharmacists to the basic technology necessary to build a factory, and similarly to help the engineers communicate with the pharmacists.

B) The establishment of an Engineering Department within Thameco

Thameco is the largest pharmaceutical manufacturing facility in Syria, and yet has no

coordinated policy for procurement of equipment, planning of utilities, preventative maintenance of installations or planning future requirements.

At present the engineering functions within Thameco are not the responsibility of any one department, and thus devolve upon the General Director.

A single engineering department can coordinate maintenance activities with production shutdowns, install new systems with the minimum of effect on production operations, plan and design new installations to best utilise existing services and facilities, and establish and maintain a consistent standard and method of construction in the factory. The department will be able to initiate 'fast track' projects to take advantage of market conditions, shortcutting the normal lengthy purchasing procedures, to advantage. The department will standardise and coordinate activities between sites, to avoid unnecessary duplication of installations, and where similar equipment is required on two or more sites, can improve efficiency and reduce spares stocks and training costs by sourcing from one supplier.

The department will comprise initially:

Engineering Manager	reporting to the General Director
Projects Manager	reporting to the Engineering Manager
Maintenance Manager	reporting to the Engineering Manager
Validation Engineer	using engineering facilities, and responsible to the Quality Assurance Manager

After the first appointments and establishment of the department, additional staff will be required, such as:

Purchasing Officer	reporting to the Engineering Manager

Projects engineers, Maintenance engineers, Clerical staff.

The job descriptions of the principal positions will be as follows:

JOB DESCRIPTION 1

Post Title: Engineering Manager

Department: Engineering

Responsible to: General Director

Responsibilities:

To ensure all facilities on Thameco sites are designed, installed, and maintained to the highest possible standards, in accordance with cGMP and ISO 9000, including all utilities, effluent treatment, air and water systems, construction methods and finishes, fire protection, security systems, etc.

Select and train suitable staff for Maintenance Manager, Projects Manager, and Validation Engineer.

With general management, identify future production requirements, plan and implement construction and installation of new facilities and equipment to realise production objectives.

With General Director set budgets for expenditure on improvements to existing facilities, maintenance and new projects.

Identify and establish cost centres for maintenance, projects etc., institute budget control system.

JOB DESCRIPTION 2

Post Title: Maintenance Manager

Department: Engineering

Responsible to : Engineering Manager

Responsibilities:

To ensure all equipment on Thameco sites is maintained in accordance with cGMP, ISO 9000 and the manufacturers instructions.

Establish a planned maintenance scheme for all production equipment in accordance with the manufacturers instructions.

Catalogue all engineering equipment including such things as vessels, pallet trucks, air handling plants, refrigeration machines, tabletting machines, etc. issuing a unique identification number, establish a machine log for each item, either manual or computer based.

Establish a filing system to hold all validation records from project engineering department.

Administer communications system (such as pagers) so that maintenance staff can be contacted easily to attend breakdowns, etc.

Select and train maintenance staff.

Set up staff reporting system such that any incidental damage to building fabric is identified, and repaired without delay

Establish a purchasing system for engineering consumables.

Establish a routine inspection and testing regime for all pressurised components

Establish a comprehensive maintenance facility, with parts store for all consumables and engineering goods, e.g. air and water filters, nuts, bolts, belts, pulleys, etc. maintain an up to date catalogue of items in stock, instruments etc.

JOB DESCRIPTION 3

Post Title: Projects Manager

Department: Engineering

Responsible to : Engineering Manager

Responsibilities:

Plan and execute new engineering systems within the factory.

With Engineering Manager, plan and program construction of new production facilities.

Specification and procurement of engineering systems, including staff training and commissioning.

Visit suppliers factories for inspections. Supervise machine tests before final specifications determined. Negotiate with suppliers.

Supervise on-site contractors.

Establish standards library for construction, finishes, air & water systems, etc.

Select project engineering staff.

On completion of projects, hand over completed installation to maintenance engineering section, with all operating procedures, record drawings, validation documentation and maintenance requirements, as approved by validation engineer.

JOB DESCRIPTION 4

Post Title: Validation Engineer

Department: Engineering

Responsible to : Quality Assurance Manager

Responsibilities:

Supervise commissioning, testing and validation of all factory systems.

Validation of control software for production machinery plc., etc.

Procure and maintain, calibrate test equipment.

Calibration of production measurements.

Establish SOP for testing of factory systems.

Establish planned program of engineering testing for all clean & sterile facilities.

Retrospective validation of existing installations.

Selection and training of test engineers.

Approve validation documentation to be provided by projects manager.

APPENDICES

1. STC Job Description
2. List of British Standards
3. Sample SOP's used in Presentations
4. Diary of Activities
5. Guidelines for inspection of Air Handling Systems in Factories

Appendix 1

Z. Csizer/el
22 February 1995

JOB DESCRIPTION

DU/SYR/92/008/11-09

Post Title	STC on Pharmaceutical Industrial Standards
Duration	1.1 m/m
Date required	June 1995
Duty Station	Damascus, Syria
Duties	In close cooperation with the STC on Standard Operating Procedures the STC on Pharmaceutical Industrial Standards is supposed to carry out the following duties:

1. Based on the previous mission reports of the Industrial Pharmacist in Syria and particularly in The Arabian Medical Company (Thameco) he should provide assistance and guidance to prepare the basic documentation on Pharmaceutical Industrial Standards that supports Good Manufacturing Practice (GMP).

2. More specifically the basic documentation should consist of the following components:

   Assist in identifying existing documentation on industrial standards that can be applied to the pharmaceutical industry;

   Assist to prepare if it does not exist pharmaceutical industry standards for building facilities (construction materials and final finishes), facility equipment and all main basic pharmaceutical supplies and utilities, e.g. air, water, etc.

3. Assist to prepare a few illustrative samples of each type of the above documents with a full list of document titles which should be prepared by the management of Thameco or other relevant government institutions.

4. Prepare a report on the above.

Qualifications: Engineer, chemical engineer, industrial pharmacist with extensive experience in establishing pharmaceutical industry in compliance with international standards

Language: English

Background information:

The 1995 work plan for SYR/92/008 - Integrated Development of the National Pharmaceutical Industry was discussed during a meeting held on 27 January 1995 at UNDP office in Syria and attended by representatives from the Ministry of Health, THAMECO, WHO, UNIDO and UNDP.

The various activities planned for the second year of the project and those which have been rephased from the first year of project implementation were discussed . Among others it was agreed that STCs on Drug Industrial Standards and SOPs would be required. Two STCs, one m/m each, will be recruited by UNIDO to advise on essential Pharmaceutical Industrial Standards and SOPs. The two STCs will be recruited to take assignment together during April/May or alternatively during September 1995. The STCs have to complete the work which has already been delivered by the Industrial Pharmacist of UNIDO.

APPENDIX 2

British Standards applicable to the Pharmaceutical Industry in Syria

See extract from UK CIBSE (Chartered Institution of Building Services Engineers) design guide, listing British Standards, European Standards and ISO standards relevant to Building Services, as sent to Ministry of Health

For use in the pharmaceutical industry, particular attention is drawn to the following:

BS 229:	Specification. Flameproof enclosures for electrical apparatus.
BS 308:	Engineering Drawing Practice
BS 417:	Specification for galvanised mild steel cisterns and covers, tanks and cylinders
BS 470:	Specification for inspection, access and entry openings for pressure vessels
BS 476:	Fire tests on building materials and structures
BS 848:	Fans for general purposes
BS 1123:	Safety valves, gauges and fusible plugs for compressed air or inert gas installations
BS 1328:	Methods of sampling water used in industry
BS 1710:	Specification for identification of pipes and services
BS 2502:	Specification for manufacture of sectional cold rooms (walk-in type)
BS 2690:	Methods of testing water used in industry
BS 3928:	Method for sodium flame test of air filters
BS 4683:	Specification for electrical apparatus for explosive atmospheres
BS 4773:	Methods for testing and rating air terminal devices for air distribution systems

BS 5295: Environmental cleanliness in enclosed spaces

BS 5500: Specification for unfired fusion welded pressure vessels

BS 5588: Fire precautions in the design, construction and use of buildings

BS 5643: Glossary of refrigeration, heating ventilating and air-conditioning terms.

BS 5682: Specification for terminal units, hose assemblies, and their connectors for use with medical gas pipeline systems

BS 5720: Code of practice for mechanical ventilation and air conditioning in buildings

BS 5750: Quality systems (now numbered as BS EN ISO 9000)

BS 5908: Code of practice for fire precautions in the chemical and allied industries

BS 6068: Water quality

BS 7258: Laboratory fume cupboards

BS 7527: Classification of environmental conditions.

APPENDIX 3

SAMPLES OF STANDARD OPERATING PROCEDURE (SOP's) USED IN PRESENTATIONS

A) Writing of operating and maintenance instructions for air handling plant

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

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
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
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.

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 manufacturers drawing 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.
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 the SOP in accordance with the SOP Guidelines

During the effective period

Ensure	that operations are carried out according to written procedures
Revise	the SOP when 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 how all changes to the systems.

B) <u>The specifying of environmental conditions</u>

1. Purpose

To outline 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 necessary 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 additional desirable but not essential qualities to be considered, such as provision for future expansion, etc.

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 additional to those required by the standards specified in items a) and b).

k) Requirement for periodic or continuous monitoring and associated alarms if required.

l) Special filtration requirements, e.g. laminar flow area above outlet from sterilising oven.

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, constructing 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 heights , materials of construction and where possible

mechanical and electrical services to be provided by others and 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 additional continuous monitoring which could be required is the particle counts to be taken adjacent to filling needles on a sterile indictable 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.

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.

C. A procedure for the testing of HEPA filters in clean rooms

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 'General 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 +/- Pa 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.

The air flow velocity through each filter should be no greater than +5% above the manufacturers recommended maximum air 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 x 10-6m
More than 50% by mass of particles less than 0.7 x 10-6m
More than 75% by mass of particles less than 1.0 x 10-6m

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 logarithmic scale in order to minimise background or

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 strokes, 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 between 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 unacceptable concentration 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 inaccessible points around the filter assembly can be 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 with 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 nozzle shall be used to detect the exact position of the leak. Static or slow scanning< .01m/s are 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 least the following:

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 agency
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.

APPENDIX 4

Diary of Activities:

DATE	ACTIVITY
20/08/95	Arrive Vienna from London. Meet Mr. J. Brown
21/08/95	Attend UNIDO office for briefing meeting. Prepare SIS project document for hand carrying to UNDP Damascus. Night flight to Syria.
22/08/95	Arrive Damascus. Meeting with Ms. N. Kozak at UNDP offices. Meeting with Dr. Dayeh Kawkab, Deputy Minister of Health at Ministry building. She requested we (JC+JB)speak at Aleppo seminar on Validation organised by WHO, on 24 & 25 August.
23/08/95	Meeting with Dr. Haggag, WHO consultant assigned to this project. Dr. Dayeh Kawkab advised us she would be leaving for UN Women's conference in Beijing on 31/08/95. Visited Thameco. Met Dr. Gabor Szepesi at UNDP.
24/08/95	Signed in at UNDP administrative department. Travel to Aleppo for seminar. Delivered brief talk on validation of clean rooms.
25/08/95	Attended seminar, GS talk on Raw Materials, JB on quality assurance. p.m. visited Alpha Co., then lunch & returned to Damascus.
26/08/95	Met Dr. M .Shatti, Minister of Health. Discussion with Dr. Haggag re. engineering of production facilities. He asked if I could offer some inspection guidelines to the ministry inspectors. p.m. Thameco to meet their engineers. Discussed new Beta-lactan plant
27/08/95	Visit to Dimas a.m. p.m. meeting at Ministry of Health with Dimas directors and Minister.
28/08/95	Thameco Detailed look at factory infrastructure, air systems, and maintenance management. Meeting with Dr. Dayeh Kawkab.
29/08/95	With JB at Thameco, long discussion with engineers, from GCEC, roughed out scheme for steroid facility. Detailed engineering. Suggested to Ms. Rajwa Jbeily hold training seminar for engineers at Thameco.
30/08/95	UNDP with Ms. N. Kozak. Planning factory visits. Mme Souad (Director of Drugs Control Inspectorate) to arrange with private sector companies.
31/08/95	UNDP Meeting with Dr. Haggag. Writing standards documents with JB. Revised SIS project document with JB.
01/09/95	All offices closed. Prepared job descriptions for embryonic engineering department at Thameco.
02/09/95	UNDP Report on Thameco visits and findings.

03/09/95	UNDP Meeting with Dr. Haggag. Discussed inspection guidelines . Spoke with JB re. further work with engineers at Thameco, keep maintenance diary, machine logs, etc.
04/09/95	Met Mme Souad at MoH. re visit schedule. Dimas visit, discussed new Beta-lactan facility.
05/09/95	Visited Unipharma, Avensor.
06/09/95	To Homs. Visited Ibn-Hayyan, Medico.
07/09/95	Thameco. Workshop re. Validation procedures and plant maintenance with GCEC engineers. p.m. UNDP
08/09/95	To Malula with staff from Thameco.
09/09/95	a.m. Thameco to discuss CIM and computers with their DP department. p.m. UNDP to write reports re. factory visits.
10/09/95	To Aleppo. Visit Shifa, Oubari.
11/09/95	Visit Thameco, Aleppo. p.m. return Damascus.
12/09/95	UNDP & MoH discuss Aleppo visit
13/09/95	Visit to Quality Control lab. p.m. meeting with Minister. He suggested MoH engineers could attend Thameco seminar widened to include all industry, public & private.
14/09/95	Meeting with MoH engineers. set date for open seminar at MoH
15/09/95	Sightseeing & local shopping - all offices closed
16/09/95	Prepare seminar presentation with JB
17/09/95	Seminar presented by J. Brown and J. Clark to pharmaceutical industry, pharmacists, engineers & inspectors entitled 'Quality assurance and engineering'
18/09/95	With MoH engineers. Discussed new MoH research centre, new hospital cardiac unit, visited construction sites.
19/09/95	UNDP a.m. farewells etc. Thameco met Beta-lactan project technical committee to discuss latest revised scheme. They to fax me final layout for comment. p.m. fly to Vienna.
20/09/95	Vienna
21/09/95	Z. Csizer debriefing a.m. Fly to London p.m.

APPENDIX 5

GUIDELINES FOR THE INSPECTION OF AIR CONDITIONING AND AIR HANDLING IN PHARMACEUTICAL FACILITIES

This document is for the guidance of qualified inspectors and is not intended to be a definitive schedule, or to limit the responsibilities of the Inspector.

DEFINITIONS:

IQ: Installation Qualification - documentation completed at the time of the factory construction, defining materials, workmanship and verifying the quality of the installation.

OQ: Operational Qualification - documentation completed at the time of the factory commissioning confirming that the operation of the plant conforms with the design intent.

PQ; Performance Qualification - documentation recording tests completed after factory commissioning, to confirm the performance of the installation under ALL operating conditions.

The inspector shall be a suitably qualified engineer with at least 5 years experience in the operation and maintenance of engineering services in pharmaceutical or related industry where accurate recording and maintenance of the factory environment is imperative.

DOCUMENTATION:

At the time of the first visit, the factory operator shall make available to the inspector drawings and maintenance records for all air-conditioning plant, air handling systems, refrigeration plant, dust extraction systems, fume cupboards, microbiological safety cabinets, and related devices. Each installation shall be clearly identified and the location of each system described. The components of each system shall be numbered with a unique reference, to be entered in the Maintenance Records.

Drawings shall show the design intent of the original installation, maintenance records shall be continuous from the date of the original IQ/OQ/Validation records. Any modifications to the plant shall be clearly identified on the drawings and revalidation records shall be available

If there is ANY break in the continuity of the records the inspector shall be provided with an explanation, reasons such as holidays or change in management are not acceptable. Records must show that after a break in maintenance and monitoring procedures the area was re-validated. If this is not the case re-validation must be carried out without delay.

AIR HANDLING EQUIPMENT:

For pharmaceutical use, air handling equipment shall comprise one or more of the following components:-

1) Prefilter, bag filter, duct mounted HEPA filter, terminal HEPA filter
2) Cooling coil, either direct expansion, chilled water, or equivalent.
3) Heating coil, steam, hot water, electric.
4) Fan.
5) Humidifier.
6) Dehumidifier.
7) Silencer.
8) Casing and Ductwork.
9) Instruments and controls.

Inspection Procedure:

Filters

a) The inspector shall make note of the manufacturer's recommendations as to the filter pressure drop (minimum/maximum) and verify from the manometers on the air handling equipment that these are within limits at normal operating conditions.

b) With the fan "off" the face of each filter shall be examined for excessive dust load, perforations, deformation or other physical damage.

Should #a or #b not be completely satisfactory the factory operator shall be required to replace the filter element.

HEPA Filters

The inspector shall make note of the manufacturer's recommendations as to the pressure drop (minimum/maximum) and verify from the filter manometers that these are within limits at normal operating conditions.

The inspector shall examine HEPA filter test records to ensure compliance with the Clean Room classification.

At the time of any filter element change, the HEPA filters MUST have been re-tested in accordance with the SOP for HEPA filter testing. (See appendix III c)

IT IS FORBIDDEN TO ATTEMPT TO CLEAN HEPA FILTERS.

Heating & Cooling Coils

The inspector shall examine the face of each coil (which can be plain tube, or finned) to ensure that no obvious corrosion, leaks, or build-up of dust exists.

Fan

The inspector shall verify from OQ documentation that the fan is running within the MAXIMUM current rating.

Humidifier

If Water Bath humidifiers are installed, the inspector shall verify that a biocide agent is used on the water supply side and examine the interior of the unit for biological growth; this shall be removed.

Dehumidifiers

Cold coil dehumidifiers (see Cooling Coils as above). Desiccant wheel dehumidifiers, where installed, have two air supplies, process air and re-activation air. Each air inlet shall be provided with an airfilter; the inspector shall ensure that these elements are included in the maintenance records.

Silencer

Silencers comprise acoustic absorbent material encased in perforated metal duct splitters. The inspector shall examine the acoustic material and note that it has not been eroded and carried into the production space.

Casing and Ductwork

The air-handling unit casing and ductwork shall be provided with sufficient access panels to permit inspection and cleaning of every component.

The inspector shall examine the grills and diffusers and require them to be clean and free from dust.

Instruments

The inspector shall survey the plant to ensure that the following items are present and operational:-

Filter manometers, ductwork test-holes for airflow measurement,(which shall not have been insulated over), water temperature gauges on heating and cooling coil connections.

The record drawings referred to above shall clearly identify the location of every temperature and humidity sensor and indicator.

Controls

The inspector shall examine the main plant control panel(s) and ensure that the maintenance engineers understand the operation of the plant, start-up procedures and control method.

The factory record drawings referred to above shall clearly identify the position of all control sensors, subsidiary starter or control panels, motorised valves and dampers, fire isolation dampers and smoke detectors.

The plant wiring diagrams shall be cross referenced to these drawings. Calibration records for each control sensor shall be available.

DUST EXTRACT EQUIPMENT

Production equipment coated in product dust is not acceptable. Dust extract equipment shall be provided to limit contamination of the factory. This can be either small self contained units adjacent to machines, or a centralised system. Where provided, equipment shall be used, and staff instructed in its use and purpose. The dust collecting bin shall be lined with a plastic liner, which can be tied closed, such that the collected dust can be contained when the bin is removed from the

machine for emptying. The inspector shall verify that the bin is emptied at the end of each shift and the collected dust safely disposed in an approved fashion.

CLEAN ROOMS

Clean rooms shall be identified as such on the record drawings, with the room classification stated. Clean rooms shall have air supply through terminal HEPA filters, with low level exhaust from each room. At the entrance to the clean room shall be provided differential pressure manometers indicating the pressure gradient between spaces. In general the most sensitive areas should be at the highest pressure, cascading down to atmospheric pressure in the external corridors in steps of 15Pa. or greater. The inspector shall make note of the manufacturer's recommendations as to the terminal HEPA filter pressure drop (minimum/maximum) and verify from the maintenance records that these are within limits at normal operating conditions. The inspector shall examine the test records of airflow to verify that the air velocity at the filter face is within the manufacturers limits, and that the increasing filter pressure drop has not reduced the air change rate to below that required for the room classification.

LAMINAR FLOW WORKSTATIONS AND ENCLOSURES

In sensitive areas within the factory special airflow provisions may have been made, in the form of canopies and hoods. Test records showing DOP filter tests, particle counts and airflow velocities shall be examined by the inspector. If the conditions beneath the canopy do not conform to the OQ and validation documentation, they shall be corrected before production is permitted to continue.

FUME CUPBOARDS AND SAFETY CABINETS

Fume cupboards and safety cabinets are provided for the protection of personnel from hazardous chemicals and organisms. The inspector shall verify that these items are operational in accordance with the initial installation. In particular, microbiological safety cabinets shall be fitted ith HEPA filters and test records are available.

APPENDIX 6

Comments of the Substantive Backstopping Officer

The technical report on pharmaceutical industry standards presented here is a concise document carrying very useful technical information and illustrative material user-friendly enough for implementation. Since the source which has been used by the consultant was entirely of UK and EU origin, the substantive backstopping officer would attempt to draw the attention of the project authorities some important technical documentation published by the U.S. Food and Drug Administration (FDA).

Firstly, the "Notes for Guidance" documents published in July 1993 are of worth to be mentioned. These are ten documents covering the pivotal FDA inspection guidelines. Two of them is closely related to pharmaceutical industry standards:

Guide to inspections of validation of cleaning processes; and

Guide to inspections of high purity water systems.

For FDA to require that equipment be clean prior to use is not new, in 1963, the GMP Regulations stated that equipment shall be maintained in a clean and orderly manner. A very similar wording was included on cleaning of equipment in the 1978 cGMP Regulations. The main rationale for requiring clean equipment is to prevent contamination or adulteration of pharmaceutical products. Historically, FDA inspectors have looked for major insanitation problems due to inadequate cleaning and maintenance of equipment and poor dust control systems. Also, FDA was more concerned about the contamination of non-penicillin drug products with penicillins or the cross-contamination of drug products with potent steroids or other hormones. Bulk pharmaceutical chemicals used to produce drug products had become contaminated with low levels of intermediates and degradation products of agricultural pesticides. Cross-contamination in this case was due to the reuse of recovered solvents from pesticide production process.

One of the basic considerations in the design of a high purity water system is the temperature of the system. It has been recognized that hot (65-80^{0}C)systems are self sanitizing. While the cost of other systems may be less expensive, the cost of maintenance, testing and the potential problems may be greater than the cost of energy saved. Whether a system is circulating is also an important design consideration. Obviously, water in constant motion is less liable to have high levels of contaminant.

Secondly, the Parenteral Drug Association published a series of authorative but very pragmatic industry guides for the pharmaceutical and biotechnological sectors. The "how-to" guides have been written by industry experts for use by companies of any size for adoption of cost-effective, scientifically sound validation, design and analytical programmes. For illustration a few titles are given as follows:

Validation of steam sterilization cycles;

Validation of dry heat processes used for sterilization and depyrogenation;

Review of commercially available particulate measurement systems;

Siliconization of parenteral drug packaging components;

Generic test procedures for elastomeric closures;

Aspects for container/closure integrity;

Extractables for elastomeric closures: Analytical procedures for functional group characterization/ identification; and

Glass containers for small volume parenteral products: Factors for selection and test methods for identification.

Thirdly, six modules of training manuals was published by Interpharm Press in 1995 in its GMP Training Series. Here, only three of the most interesting titles are given:

GMP "How to" essentials: How to prepare for an FDA inspection;

GMP "How to" essentials: How to organize a validation file; and

GMP "How to" essentials: How to review and redesign SOP systems.

Finally, the substantive backstopping officer would like to give as reference, in his view, one of the best recently published resource book by Carol DeSain:

Drug, Device and Diagnostic Manufacturing: The Ultimate Resource Handbook, Second Edition, Interpharm Press, Inc. 1993, ISBN: 0-935184-38-4

The references could be very long, but that is not the purpose of these final comments. These comments should only be regarded as an attempt to provide the project authorities with a point of departure for a sustainable development process to strengthen the domestic ethical pharmaceutical industry.