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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 DEVELOPMENT OF PHARMACEUTICAL INDUSTRY IN THE SYRIAN ARAB REPUBLIC

DU/SYR/92/008

SYRIAN ARAB REPUBLIC

Technical report: Consolidation of SOPs, protocols, quality assurance and TQM site inspections and audits, product registration*

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

Based on the work of Mr. John Brown,
STC on standard operating procedures

Project Manager: Zoltan Csizer
Chemical Industries Branch

* This document has not been edited.

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TABLE OF CONTENTS

Page

ACKNOWLEDGMENTS.

I wish to express my sincere thanks to the Minister of Health for the Syrian Arab Republic, H.E. Dr. I. M. Shatti, and to the Assistant Minister responsible for Pharmaceutical Affairs, Dra. Kaukab Al Daya for their commitment to the implementation of the final UNIDO component of Project DP/SYR/92/008.

Much of the work for this mission was performed at the factories of the general sector company, Thameco, in Damascus, and also in the Serum Factory at Aleppo; I would like to express my sincere thanks to the General Director, Ms. Rajwa Jbeily, and her technical staff for the assistance they provided.

The Resident Representative of UNDP in Syria, Mr. Per Janved, has been greatly supportive of this project; extremely valuable support and encouragement has been provided by Ms. N. Kozak, Project Officer.

The mission was implemented concurrently by three UNIDO STCs and I wish to acknowledge the assistance and support provided by my colleagues in the field Dr. Gabor Szepeci, and Mr. John Clark.

Finally, the encouragement and support of my colleagues in UNIDO, Vienna.

SUMMARY

1) The mission covered by the following Report is the final phase of the UNIDO component of project No. DU/SYR/92/008. The Agency fielded concurrently, three STCs with more than 90 years of practical, hands-on, pharmaceutical industry experience between them. The observations made by the individual STCs on the state of pharmaceutical industry in Syria were generally consistent to a very high degree. The present Report relates only to the work of the STC on Operating Procedures; the findings of the other UNIDO STCs are provided in their individual Reports

2) The UNIDO component of the project has provided the Syrian authorities with a wide spectrum of pharmaceutical development by way of :-
   * a study tour of a parallel industry (i.e. mixed public sector/private sector, and multinational companies) in Thailand,
   * a Global Workshop on GMP in the Pharmaceutical Sector in Montreal Canada, and
   * a panel on Woman's Health and its relation to Industry in Beijing China.

3) Although the private manufacturing sector continues to grow, rationalisation is being seen, as some of the smaller manufacturers cease to exist. There is an excess of manufacturing capacity in the Nation and it is likely that other less well resourced Companies will be forced to withdraw in the near future. There may be the risk that counterfeit medicines will appear.

4) The General Sector company Thameco has implemented many of the recommendations provided by UNIDO in previous missions and is seen to have achieved significant improvements in its operations and in the enthusiasm, commitment, and confidence of its technical staff. The company has been successful in re-entering the export market. Thameco continues to have excellent resources many of which are under-utilised.

5) UNIDO has provided a range of suggestions for utilisation of the unused production areas at the Thameco Aleppo site.

6) In accordance with the terms of the Job Description for this project, UNIDO has provided:-
   * the system of manufacturing documents and SOPs upon which Thameco's Aleppo Serum Factory is able to successfully operate
   * a range of model Job Descriptions and Responsibility Charts for senior technical staff
   * a range a specifically relevant Industry Standards taken from the more than 5000 Australian Industry Standards and the British Standards Institute
   * a range of model Protocols, SOPs, Manufacturing Master Documents, Logbooks, Record Books,
   * an objective system of AQLs (acceptable quality levels) based upon the British Government and the United States' Military systems

* a recommended system for the provision of Site Information related to new and existing factories to provide the platform for development of a database for the pharmaceutical sector
* a recommended system for the internal inspection and regulatory audit of manufacturing facilities based upon the requirements of ISO 9000
* a recommendation for an improved method of Product Registration, based upon the systems used in Britain and Australia, adapted for the Syrian situation
* a range of standard conditions and equipment for the more common dosage forms and packing lines
* a model, and an understanding, of the DERIVATION of Quality Assurance(QA) and Total Quality Management(TQM) from the integrated implementation of Industry Policy and Drug Policy
* an understanding and acceptance of the merits of factory planning, to incorporate, from the design stage, the features necessary for attainment of Quality Assurance
* an understanding and acceptance of the philosophies of Critical Path Analysis in the development of facilities and systems, coupled with the concept of the KISS (Keep It Simple) approach to problem solving
* seminars have been introduced to, and understood, the complementary roles of the manufacturing pharmacist and the professional engineer in the elaboration of manufacturing plants; seminars have been introduced to the future direction of pharmaceutical manufacturing through the system known as CIMTAB (computer integrated manufacturing of tablets)

7) UNIDO has been able to illustrate the value to Syria of introducing computerisation to its manufacturing operations and to its regulatory authorities; this will form an element of the SIS project planned for implementation in 1996. This project will also explore the feasibility of Agency support in the provision of a Pharmaceutical Technology Service Centre and subsequent development of a Syrian Food, Drugs and Cosmetic Regulatory Authority.

8) In support of the points mentioned above, the following Report provides, in the text, or as Appendices, examples of all material.

RECOMMENDATIONS

1) Secure UNIDO support for the proposed SIS project for the introduction of Pharmaceutical Quality Management techniques, and consequent support for a Pharmaceutical Technology Service Centre and a Syrian Food, Drug, and Cosmetic Administration.

2) Implement proposals for improvement of operating and registration standards; namely:-
   * Site Information File
   * Internal Inspection and Audit systems
   * Industry Database
   * Product Registration

3) Develop and implement plans for the safe and efficient handling of beta-Lactams and steroids according to technical assistance provided by UNIDO.

4) Develop and expand the Serum Factory at Aleppo; utilise the available production spaces at Aleppo according to suggestions communicated under separate cover.

5) Continue industrial development by utilisation of SOPs, Industry Standards, Critical Path Analysis, and the KISS principle by use of the models provided.

6) Build Quality Assurance and Total Quality Management principles into the sector by the integration of Industry Policy and Drug Policy.

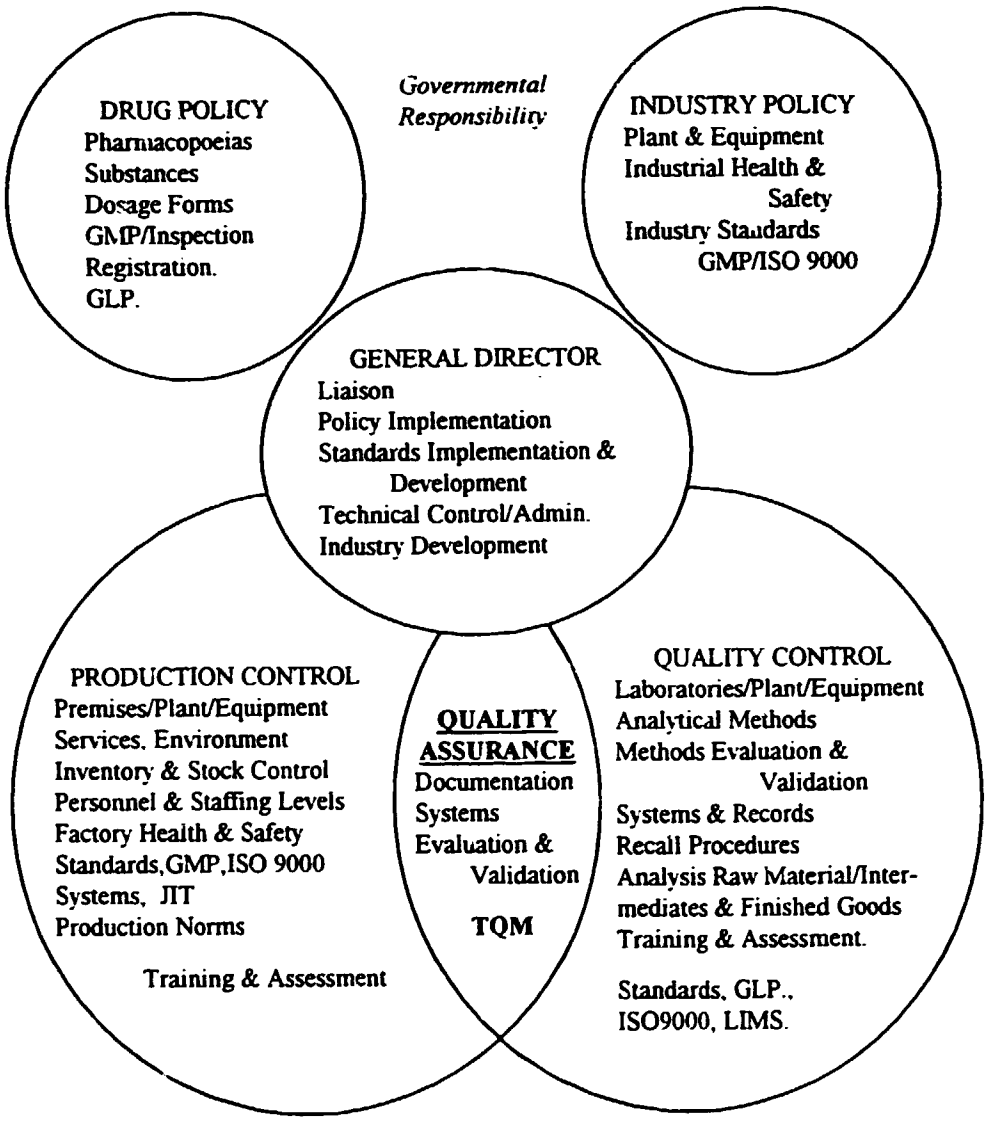
7) Integrate the complementary skills of the manufacturing pharmacist and the professional engineer in the design, planning, implementation and operation of the manufacturing sector so as to attain a GMP/Quality Assurance compliant industry.

8) Secure membership of an international standards organisation, obtain and utilise their newsletters and listings of available standards. (*addresses provided below*)

British Standards Institution
2 Park Street
London W1A 2BS
England

Standards Australia
80 Arthur Street
North Sydney 2060
Australia

SCHEMATIC FRAMEWORK FOR THE EVOLUTION OF AN EFFECTIVE NATIONAL PHARMACEUTICAL INDUSTRY.



NB: In the interest of simplification, the schematic framework shown above does not incorporate any of the Commercial or Financial responsibilities of business operation.

DEFINITIONS

ISO 9000	Published by the International Organisation for Standards defines key quality terms and principles: it is GENERIC and applicable to any industry.
JIT	Just in Time; a current philosophy of QA related procurement and manufacturing.
LIMS	Laboratory Information Management System based on QA requirements.
TQM	Total Quality Management: the attainment of the requirements of ISO 9000.

STANDARDS - THE NEW INTERNATIONAL PASSPORT.

The internationalisation of standards is accelerating rapidly.

World-wide, countries realise that to stay competitive, they have to

align their standards internationally.

The universal acceptance of the international ISO 9000 quality management standards demonstrates this.

In Australia, around 35% of standards are based on international standards,

and in the most recent year,

nearly half of the new standards published

were adopted from existing international standards.

Courtesy of STANDARDS AUSTRALIA,
CANBERRA
AUSTRALIAN CAPITAL TERRITORY.

AUSTRALIAN STANDARDS

during the Mission, Australian Standards were used to demonstrate the

format, contents and application of Industry Standards.

The following Titles were used:

Cleanrooms, Workstations and Safety Cabinets
Methods of Test
AS 1807.0

As above - Method 19 - Sizing and Counting of Particulate
contaminents in and on Cleanroom Garments
AS 1807.19

As above - Method 24- Determination
of Recovery Times of Cleanrooms
AS 1807.24

Cleanroom Garments - Product requirements
AS 2013.1

As above - Processing and Use
As 2013.2

Cleanrooms and Clean Workstations
Non-laminar Flow # < 350
AS 1386.3

Note: for copyright reasons it is not possible to provide photocopies of these Standards for general use.

PROCESSES AND CONDITIONS

FOR HANDLING A RANGE

OF STANDARD DOSAGE FORMS

Includes :

Dry Syrups and Capsules (Antibiotic)

Sterile products (Ampoules) & Sterile Topical Products (Eye Drops)

Uncoated Tablets

Effervescent Products

Steroids

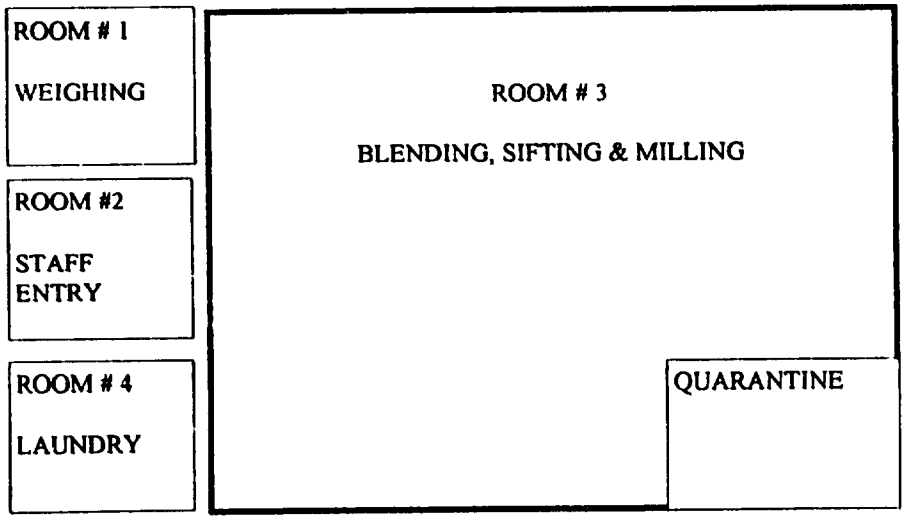
Packaging Lines

PROCESS AND CONDITIONS FOR HANDLING DRY SYRUPS AND CAPSULES (ANTIBIOTIC)

*NOTE THAT GMP REQUIRES THAT PROCESSING OF ANTIBIOTICS IS PERFORMED IN **DEDICATED** PRODUCTION AREAS.*

With minor modifications to the formulae, the production stages weighing, blending, milling, sifting are identical for both Dry Syrups and Capsules

PROCESS FLOW FOR WEIGHING - SIFTING **GENERAL LAYOUT ONLY : NOT TO SCALE**



PROCESS AND CONDITIONS FOR HANDLING DRY SYRUPS
AND CAPSULES (ANTIBIOTIC)

ROOM # 1 WEIGHING

EQUIPMENT
Balances of appropriate capacity
Benches and work surfaces Stainless Steel
Misc. powder handling equipment
Containers (stainless steel or plastic)

CONDITIONS
Temp. 24 C / 40 % RH
Unclassified

ROOM # 2 STAFF ENTRY

EQUIPMENT
Airlock/Change Room
Clothes hanging facilities
Washing facilities
Swing over bench Wash-hand basin/Drying

CONDITIONS
Temp 24C / 40% RH
Classification : Class C
Pressure 15 Pa Positive
Air changes 20 per hour minimum

ROOM # 3BLENDING, SIFTING, MILLING

EQUIPMENT
NOTECONTACT PARTS TO BE TYPE 316 LSTAINLESS STEEL
Pin or Hammer Mill
Sieving machine Russell Finex or equivalent
Blender; double cone/ vee or equivalent
Dust Control
Storage containers

CONDITIONS
Temp 24C / 40% RH
Classification: Class C
Pressure 15 Pa Positive
Air changes 20 per hour minimum
NOTE THIS ROOM CONTAINS A QUARANTINE AREA; THIS MAY BE A PARTITIONED OFF ROOM OR A CHAIN-LINK FENCED SECTOR.

PROCESS AND CONDITIONS FOR HANDLING DRY SYRUPS
AND CAPSULES (ANTIBIOTICS)

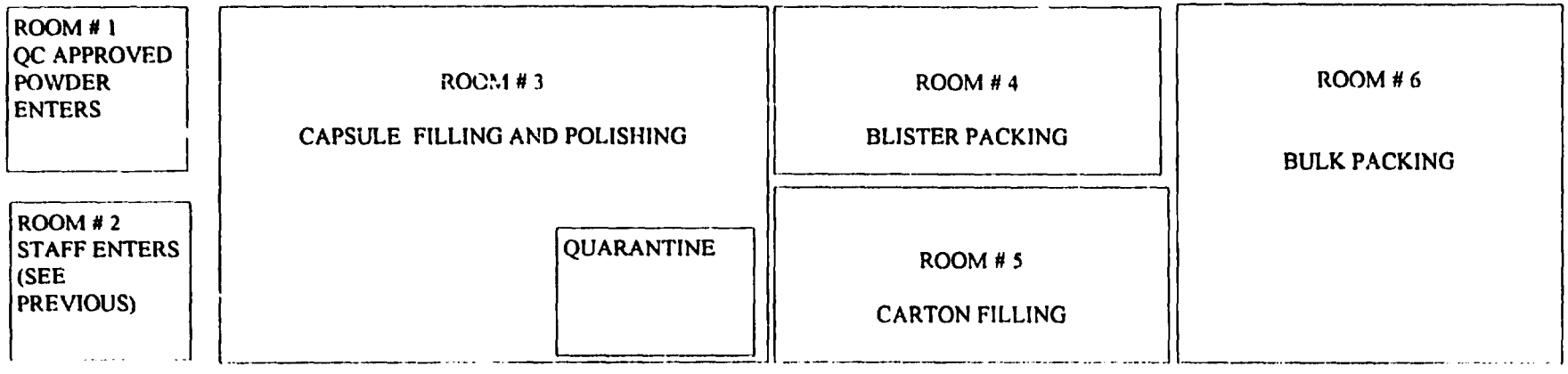
ROOM # 4 LAUNDRY

EQUIPMENT	CONDITIONS
Washing Machine	Temp.24 C No requirement for Humidity Control
DryingMachine	Air Changes 20 per Hour minimum.
Sewing Machine	Direct extract from Dryer to Atmosphere
Drying Facilities	Wash Water neutralisation Tank
Benches and working surfaces	

The processes described above are common to Dry Syrups and Capsules.
Specific requirements for the Filling operations are provided in the followng pages

PROCESS AND CONDITIONS FOR FILLING AND PACKING CAPSULES

GENERAL ARRANGEMENT ONLY - NOT TO SCALE



ROOMS # 1 & # 2 POWDER AND STAFF ENTRIES

Room # 1
EQUIPMENT
Stainless Steel wheel truck and containers

Room # 2 Extension of Room # 2 previous

CONDITIONS As Room # 3 previous

ROOM # 3 CAPSULE FILLING AND POLISHING

EQUIPMENT FOR CAPSULE FILLING
Automatic capsule filling machine with appropriate containers for filled capsules, and supplies of capsule bodies .
NOTE THAT IT IS NOT PERMITTED TO BRING CAPSULE BODIES INTO THE ROOM IN CARD OR FIBREBOARD DRUMS. STAINLESS STEEL OR PLASTIC CONTAINERS MUST BE EMPLOYED

CONDITIONS
Temp 24 C RH 40%
Classification C
Room Pressure 30 Pa
Air Changes 20 per hour Minimum.
Dust extract from Capsule Filling Machine

EQUIPMENT FOR CAPSULE POLISHING DEDICATED polishing belts and materials Stainless steel or plastic containers *NOTE THAT THE COMPANY MAY WISH TO PERFORM IPQC BEFORE PROCEDING TO PACKING; IF SO A SMALL QUARANTINE AREA AS DESCRIBED IN ROOM # 3 ABOVE*	CONDITIONS Temp 24 C RH 40% Classification C Room Pressure 30 Pa Air Changes 20 per hour Minimum. Dust extract from Capsule polisher

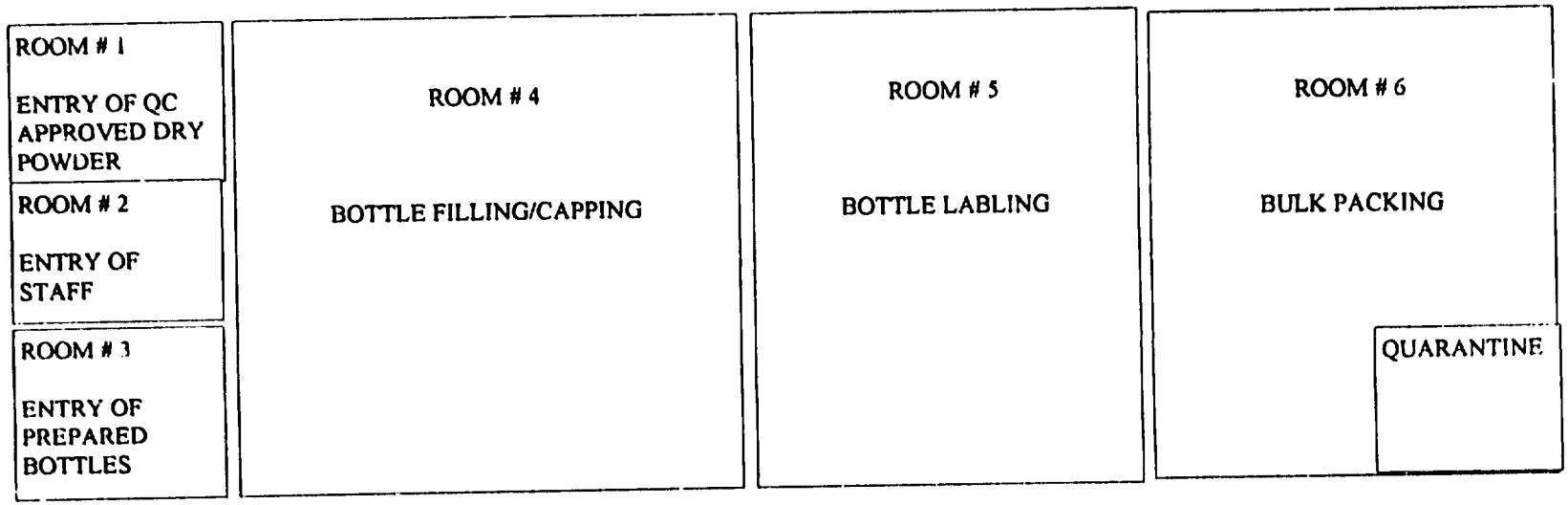
ROOM # 4 BLISTER PACKING	
EQUIPMENT Appropriate Blister Pack Machine (Hassia, Uhlmann, or similar) Storage accommodation for packing materials Containers (stainless steel or plastic) Slugs for overprinting Batch No. & Exp. Date Plastic containers for removal of waste blister material.	CONDITIONS Temp 24 C RH No Standard Classification : unclassified Room Pressure 15 Pa Air Changes 20 per hour Minimum.

ROOM # 5 CARTON FILLING	
EQUIPMENT Carton Erecting and Filling machine with appropriate printing slugs and materials for application of Batch No. & Exp. Date *NOTE THAT IF MANUAL CARTON ASSEMBLY/FILLING IS TO BE UNDERTAKEN THE OPERATION SHOULD BE BUILT AROUND A CONVEYOR BELT AND EACH PACKING OPERATOR SHOULD BE PROVIDED WITH A COUNTING FRAME* Bulk handling equipment	CONDITIONS Temp 24 C RH No Standard Classification : unclassified Room Pressure 15 Pa Air Changes 20 per hour Minimum.

ROOM # 6 BULK PACKING (This also applies for dry Powder Area)	
EQUIPMENT Box making/stapling equipment/Bulk handling equipment	CONDITIONS Min. 20C

PROCESS AND CONDITIONS FOR FILLING AND PACKING
DRY SYRUPS (ANTIBIOTICS)

GENERAL LAYOUT ONLY; NOT TO SCALE



ROOMS # 1& # 2 ENTRY OF QC APPROVED POWDER /STAFF

EQUIPMENT
For POWDER refer Identical rooms in Capsule filling
For STAFF refer identical rooms in Capsule filling

CONDITIONS
Airlocks/Pass throughs 24C/40% RH Staff entry as previous

PROCESS AND CONDITIONS FOR FILLING
DRY SYRUPS (ANTIBIOTICS)

ROOM # 3 ENTRY OF PREWASHED BOTTLES

EQUIPMENT
Pallet truck & pallets,Covers to prevent contamnation of the washed bottles.
NOTE THAT NO FIBROUS MATERIALS MAY BE USED OR INTRODUCED INTO THE FILLING AREAS

CONDITIONS
Pass-through 24C/40%RH

ROOM # 4 BOTTLE FILLING AND CAPPING

EQUIPMENT
Appropriate bottle filling and capping machine with conveyor belt
NOTE THAT ALL CONTACT PARTS SHOULD BE CONSTRUCTED FROM TYPE 316 STAINLESS STEEL.
Roll-on Capper
Pallet truck and pallets (*TIMBER PALLETS NOT ALLOWED)*

CONDITIONS
Temp 24 C RH 40%
Classification C
Room Pressure 30 Pa
Air Changes 20 per hour Minimum.
Dust extract from Bottle Filling Machine

ROOM # 5 LABELLING

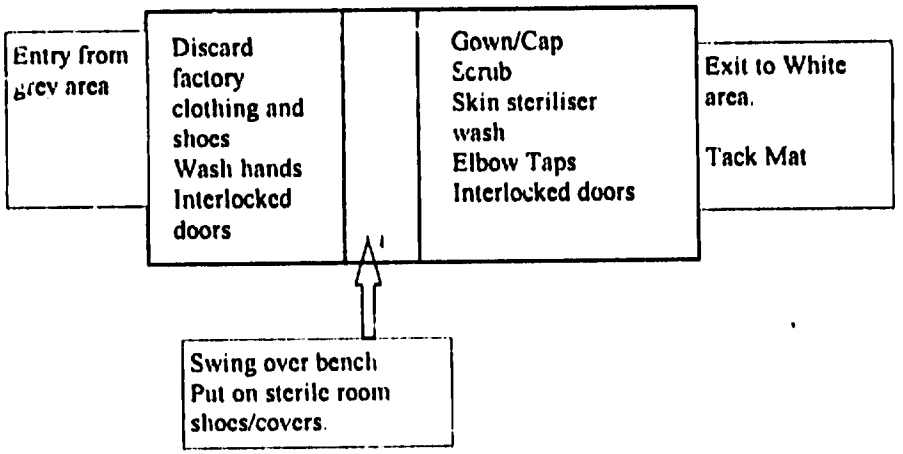
EQUIPMENT
Appropriate belt fed labelling machine with ability to overprint Batch Nos. & Exp. Dates *NOTE THAT ALL UNUSED OVERPRINTED PACKING MATERIALMUST BE DESTROYED.* Appropriate printing slugs and inks

CONDITIONS
Min. 24C
RH No Standard.

GENERAL AND SERVICES REQUIREMENTS FOR PROCESSING OF STERILE PRODUCTS AMPOULES AND STERILE TOPICAL PRODUCTS (EYE DROPS)

SERVICES:
Steam @ 80-100psi
Vacuum as necessary
Nitrogen as necessary
Lighting (General to industrial norms, task lighting to be provide as required for close operations

PERSONNEL ACCESS:



PROCESSING

Dispensing:
Bench with impermeable surface, balances of appropriate capacity with check masses, miscellaneous glassware and stainless steel scoops ,stirring rods etc.

Mixing:
Appropriate mixing vessel and electric agitator, inert gas as required.

Filtration:
Filter bank with medium (bubble-test facility as required), pH meter, sampling pipette.

NOTE THAT ALL NECESSARY DOCUMENTATION, PHOTOCOPIED FROM CURRENT MASTERS SHALL BE IN USE AND ALL EQUIPMENT SHALL BE CORRECTLY LABELLED WITH DETAILS OF THE BATCH BEING PROCESSED

PROCESSING CONTINUED

FILLING
Appropriate filing and sealing equipment for the volumes being handled. Appropriate gas purging equipment .
NOTE THAT ALL CONTACT PARTS IN FILLING EQUIPMENT SHALL BE STAINLESS STEEL TYPE 316 L

AMPOULE PRINTING
Appropriate ampoule printing equipment with ceramic or solvent inks and printing slugs.

LEAK TESTING
Die bath with appropriate colour and vacuum line, rinsing bath.

STERILISING

Clothing
Dressings autoclave with appropriate cycle,suitable wrapping paper with exposure sensitive marking.

Filled product
Steam steriliser with appropriate capacity, dummy load facility, loading trolleys, appropriate control gear and recorders in working order.

OR

Hot air oven with appropriate capacity, control and recording gear in working order.

OR

Special steriliser (eg ETOX) purpose designed for the specific product.

LAUNDRY AND DRYING ROOM

Record books for cycling of garments, sewing machine for small repairs,wrapping bench and paper, drying area.

NOTE THAT ALL LAUNDRY OPERATIONS SHALL BE PERFORMED IN AIR AND WATER CONDITIONS OF EQUAL STANDARD TO THAT IN THE STERILE AREA

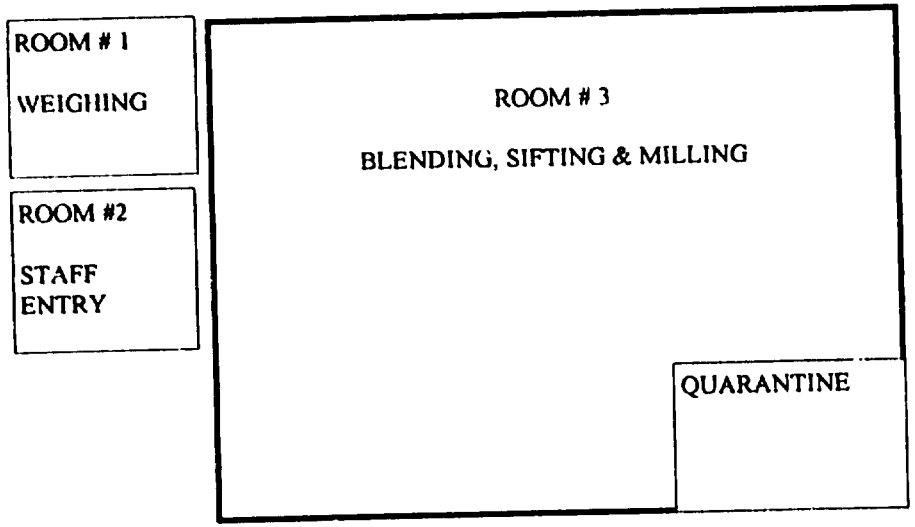
PROCESS AND CONDITIONS FOR MANUFACTURE OF UNCOATED TABLETS

For the purpose of this Standard anUncoated tablet is defined as follows:-

- Round/Normal Concave(NC), Flat Bevelled edge(FBE),Deep Concave(DC)
- Plain with no Breakline or Decoration
- No surface treatment: no sustained action,delayed release or effervescence

PROCESS FLOW FOR WEIGHING - SIFTING

GENERAL LAYOUT ONLY -NOT TO SCALE



PROCESS AND CONDITIONS FOR MANUFACTURE OF UNCOATED TABLETS

ROOM # 1 WEIGHING

EQUIPMENT
Balances of appropriate capacity
Benches and work surfaces Stainless Steel
Misc. powder handling equipment
Containers (stainless steel or plastic)

CONDITIONS
Temp. 24 C / 40 % RH
Unclassified

ROOM # 2 STAFF ENTRY

EQUIPMENT
General changing , washing, and hygiene facilities as for the main factory.
NOTE THAT FACTORY GARMENTS MUST BE CORRECTLY WORN, CLEAN AND IN GOOD REPAIR

CONDITIONS
Temp 21 - 24C Generally No RH requirement
Classification : Black area to Grey
Pressure Generally No Requirement
Air changes 20 per hour minimum

ROOM # 3 BLENDING, SIFTING, MILLING

EQUIPMENT
NOTE ALL CONTACT PARTS TO BE TYPE 316 L STAINLESSSTEEL
Pin or Hammer Mill
Sieving machine Russell Finex or equivalent
Blender; double cone/ vee/Diosna/ Sigma or equivalent
Dust Control
Storage containers

CONDITIONS
Temp 21 - 24C Generally No RH requirement
Classification : Grey area
Pressure Generally No Requirement
Air changes 20 per hour minimum
Dust Control

PROCESS AND CONDITIONS FOR MANUFACTURE OF UNCOATED TABLETS

NOTE THAT AFTER THE BLENDING OPERATION HAS BEEN COMPLETED A QUARANTINE STAGE SHOULD FOLLOW TO ENSURE THAT THE CORRECT FORMULATION HAS BEEN ATTAINED

EQUIPMENT FOR GRANULATION AND COMPRESSION

A) for SLUGGING:
- a heavy duty press fitted with large diameter tools
- a suitable mill with ss trays
- suitable ss or plastic containers

B) for WET GRANULATION
- a suitable paddle blender, Diosna or equivalent
- appropriate drying facilites - Tray Drier or Fluid Bed

C) for COMPRESSION
- appropriate tablet press, segregated, with Dust Control facilities at the hopper and compression area
- De-Duster Manesty-Boots or equivalent
- appropriate ss containers
- misc. bulk handling equipment

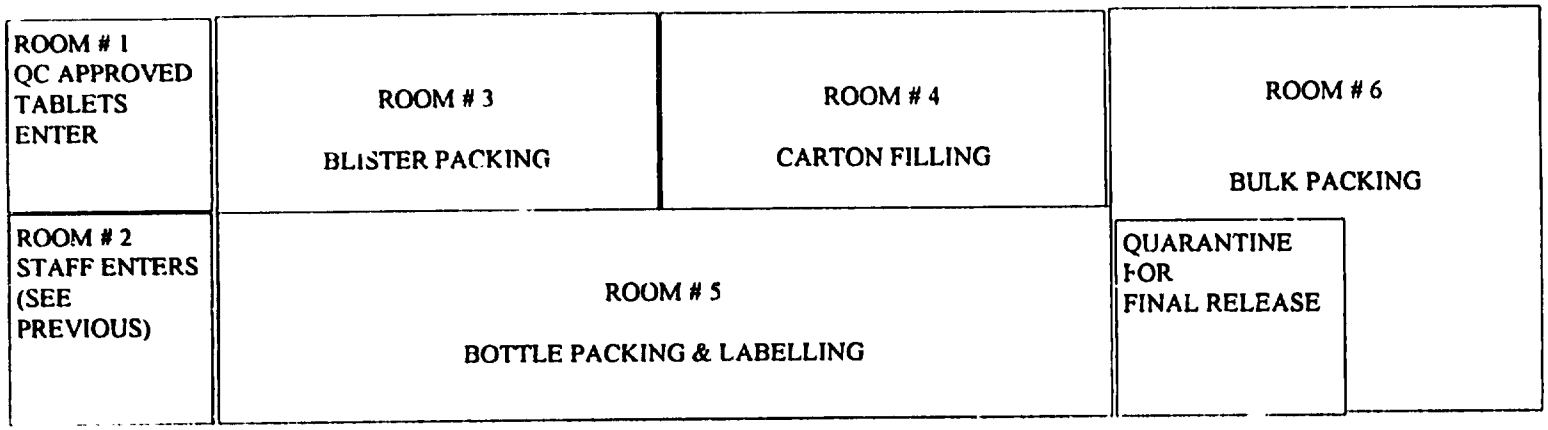
CONDITIONS
Temp 21 - 24C Generally No RH requirement
Classification : Grey area
Pressure Generally No Requirement
Air changes 20 per hour minimum
Dust Control

Note that it is imperative in the manufacture of compressed tablets that press tools are maintained in perfect condition and are cleaned, polished and any surface damage or edge chipping corrected after each use. The use of a Punch Polishing Kit is a pre-requisite for conditioning Press Tools

When not in use, press tools must be lightly lubricated and carefully stored inprotective boxes.

*NOTE THAT **ALL** MACHINERY AND CONTAINERS MUST BE CLEARLY IDENTIFIED WITH DETAILS OF THE PRODUCT BEING HANDLED*

PROCESS AND CONDITIONS FOR PACKING UNCOATED TABLETS



ROOMS # 1 & # 2 TABLETS AND STAFF ENTRIES

ROOMS #1 #2
EQUIPMENT
Stainless Steel wheel truck and containers

Room # 2 Extension of Room # 2 previous

CONDITIONS
Temp 21 - 24C Generally No RH requirement
Classification : Grey area
Pressure Generally No Requirement/Dust Control
Air changes 20 per hour minimum

PROCESS AND CONDITIONS FOR PACKING AND LABELLING UNCOATED TABLETS

ROOM # 3 BLISTER PACKING

EQUIPMENT
Appropriate Blister Pack Machine (Hassia, Uhlmann, or similar)
Storage accommodation for packing materials
Containers (stainless steel or plastic)
Slugs for overprinting Batch No. & Exp. Date
Plastic containers for removal of waste blister material.

CONDITIONS
Temp 21 - 24C Generally No RH requirement
Classification : Grey area
Pressure Generally No Requirement/Dust Control
Air changes 20 per hour minimum

ROOM # 4 CARTON FILLING

EQUIPMENT
Carton Erecting and Filling machine with appropriate printing slugs and materials for application of Batch No. & Exp. Date
NOTE THAT IF MANUAL CARTON ASSEMBLY/FILLING IS TO BE UNDERTAKENTHE OPERATION SHOULD BE BUILT AROUND A CONVEYOR BELT AND EACH PACKING OPERATOR SHOULD BE PROVIDED WITH A COUNTING FRAME
Bulk handling equipment

CONDITIONS
Temp 21 - 24C Generally No RH requirement
Classification : Grey area
Pressure Generally No Requirement/Dust Control
Air changes 20 per hour minimum

ROOM # 5 BOTTLE FILLING AND LABELLING

EQUIPMENT
Pallet truck & pallets,Covers to prevent contamnation of the washed bottles.
NOTE THAT NO FIBROUS MATERIALS MAY BE USED OR INTRODUCED INTO THE FILLING AREAS
Tablet counting machine E.C.King or equivalent
Pilfer-proof capping machine
Containers for removal of waste

CONDITIONS
Temp 21 - 24C Generally No RH requirement
Classification : Grey area
Pressure Generally No Requirement/Dust Control
Air changes 20 per hour minimum

PROCESS AND CONDITIONS FOR MANUFACTURING UNCOATED TABLETS

ROOM # 5 LABELLING (continued)

EQUIPMENT
Appropriate belt fed labelling machine with ability to overprint Batch Nos. & Exp. Dates.
Appropriate printing slugs and inks

NOTE THAT ALL UNUSED OVERPRINTED PACKING MATERIALMUST BE DESTROYED

CONDITIONS
Temp 21 - 24C Generally No RH requirement
Classification : Grey area
Pressure Generally No Requirement/Dust Control
Air changes 20 per hour minimum

ROOM # 6 BULK PACKING

EQUIPMENT
Carton box erecting equipment and staplers
Bulk handling pallets and trucks

NOTE THAT FINAL QC RELEASE MUST BE OBTAINED BEFORE BULK PACKED PRODUCTS CAN BE REMOVED TO THE FINISHED GOODS STORE

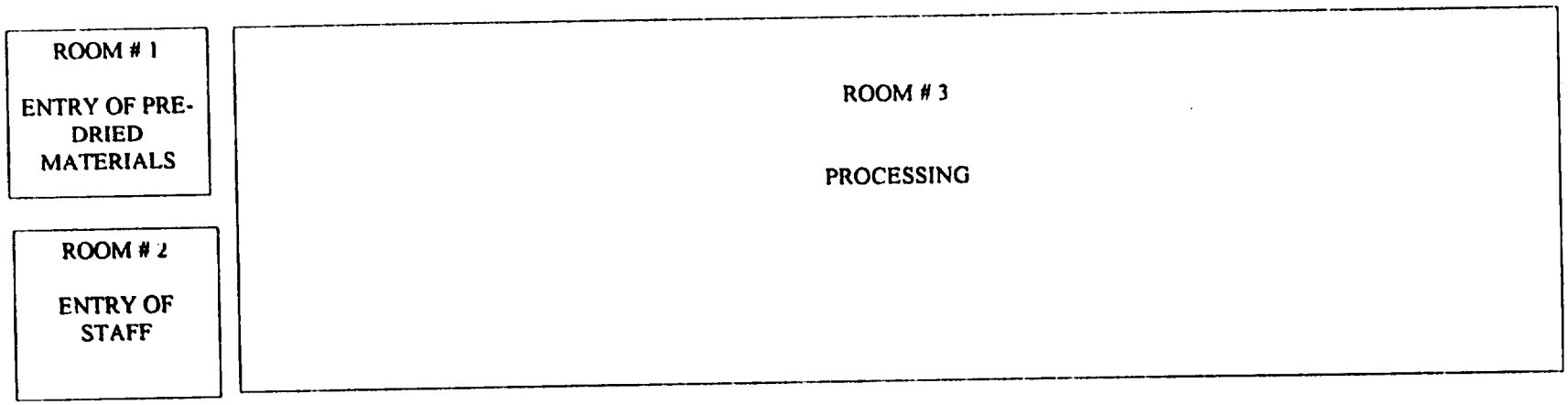
CONDITIONS
Temp 21 - 24C . No RH requirement
Classification :BLACK AREA
Pressure Generally No Requirement/Dust Control
Air changes 20 per hour minimum

PROCESS AND CONDITIONS REQUIRED FOR MANUFACTURING EFFERVESCENT PRODUCTS

Note: Effervescent Products are formulated as POWDERS or as COMPRESSED TABLETS. The equipment and conditions detailed belowrelate to POWDERS since tablets are a more technically demanding product and their specific processing and conditions are identified in the PRODUCT DEVELOPMENT stage. The general principles are identical for both Effervescent Powders and Effervescent Tablets.

Note all materials employed in the manufacture of EFFERVESCENT PRODUCTS must be PREDRIED to a moisture content determined by the manufacturer which provides product stability and adequate flow characteristics.

GENERAL ARRANGEMENT - NOT TO SCALE



Note that owing to the cost of maintaining the humidity / temperature conditions required for handling effervescent products it is acceptable practice to minimise production areas and segregate processing areas within a single room.

PROCESS AND CONDITIONS REQUIRED FOR MANUFACTURING
EFFERVESCENT PRODUCTS

ROOMS # 1 & # 2 -ENTRIES

EQUIPMENT	CONDITIONS
Airlocks	Temp. 21 - 24C
Bulk handling equipment	Relative Humidity 30% max.
Dust Extract venting into the room	Dust Extract venting into the room

ROOM # 3 PROCESSING

PROCESS AND EQUIPMENT

A) Introduce the materials into the Processing Area with the Air Handling equipment running; allow 30 minutes for the ambient conditions to stabilise. Confirm that correct Temp./Humidity have been attained using SLING PSYCHROMETER or equivalent instrument.

B) Weigh, blend, and sift the powders in conventional manner. Blending should be performed in a sealed DRUM ROLLER.

C) On completion of blending, a sample of the powder is subjected to QC analysis for Carbon Dioxide yield, Residual Alkalinity, and moisture content in accordance with the parameters established by the manufacturer.

D) Concurrent with the QC analysis, the bulk powder may be sieved in a Russell Finex sieve or equivalent.

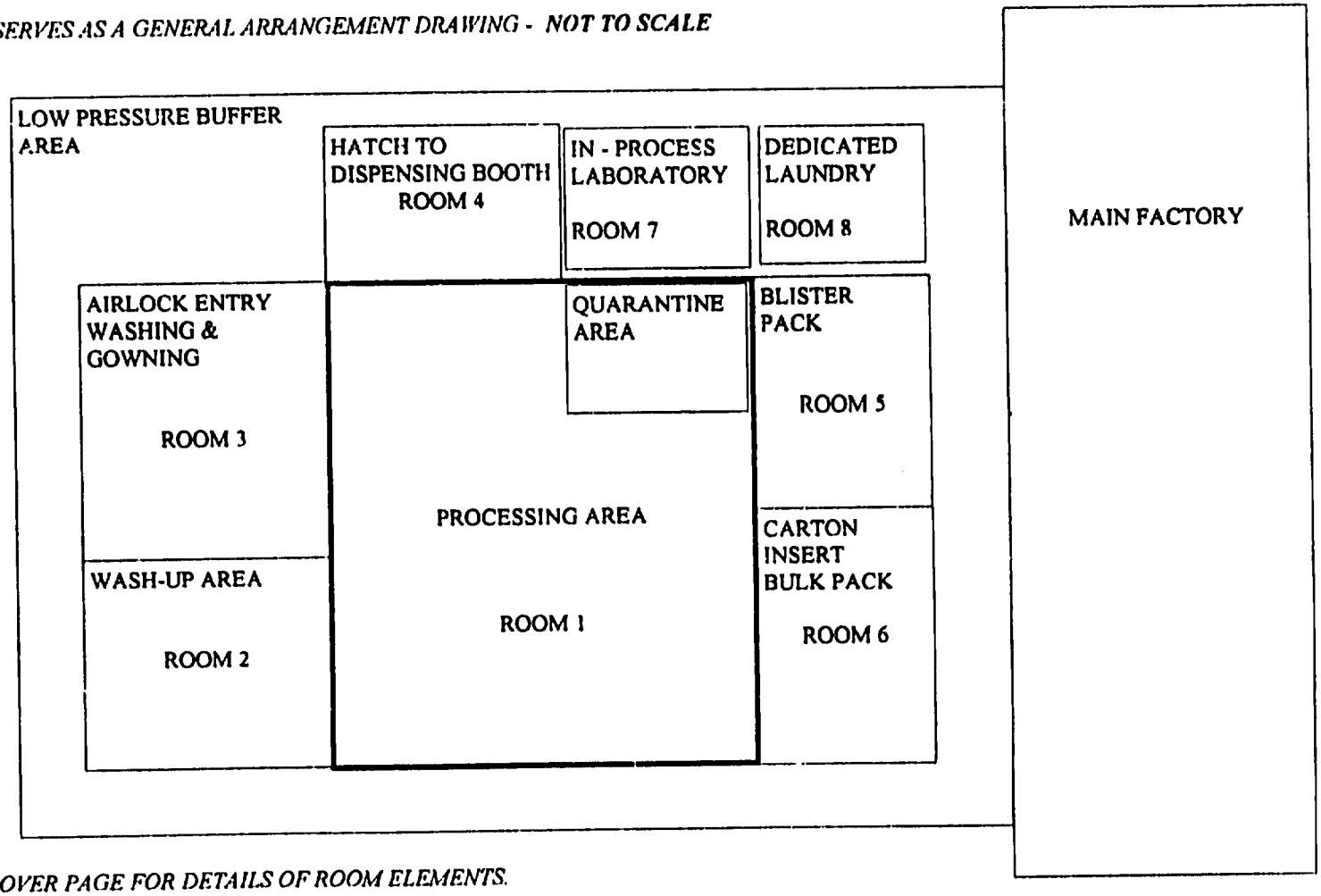
E) With minimum delay the QC approved powder should be filled into SACHETS or BOTTLES according to the manufacturer's requirement. WOLKOGON or equivalent filling equipment may be employed. If sachets are filled on a Wolkogon machine, type slugs for Batch No. & Exp. Date must be available. In order to minimise sealing problems with the foil or laminate it is accepted practice to allow this material to stand for a while in the low humidity area before use.

F) Filled bottles should be sealed in the low humidity area and removed to a standard atmosphere for labelling: it is accepted practice to performm a DYE BATH leak test on sealed bottles.

CONDITIONS
Temp. 21 - 24C
Relative Humidity 30% max.
Dust Extract venting into the room

SUGGESTED LAYOUT FOR THE SAFE HANDLING OF STEROIDS

*THIS SERVES AS A GENERAL ARRANGEMENT DRAWING - **NOT TO SCALE***



SEE OVER PAGE FOR DETAILS OF ROOM ELEMENTS.

STEROIDS HANDLING - SUGGESTED MINIMUM EQUIPMENT/CONDITIONS

ROOM #1 PROCESSING & QUARANTINE

EQUIPMENT

Balances x2	Tablet press x 1	Film coating machine
SS truck x1	Press tools	small Glatt or Accelacota
Misc. Glassware	Misc. Spatulas etc	

CONDITIONS
Temp 24 C RH 35%
Room Class. WHO #C
Room Press. 30 Pa POSITIVE

ROOM #2 WASH - UP

EQUIPMENT

Steam Lance	Running water/ Holding area
Drainage to Neutraliser tank	
Low sinks for washing tanks etc	

CONDITIONS

temp 24 C	RH Not Specified
Classification Unclass	Pressure -15Pa NEGATIVE
Direct exhaust ex washbay	

ROOM # 3 AIRLOCK / ENTRY

EQUIPMENT

Washing/gowning	Swing - over bench
Full length gowns	Activated Charcole Masks
Gloves	Hoods
Shoes	Hand washing / drying facilities

CONDITIONS
As Room #1
Room Pressure 15 Pa POSITIVE

ROOM # 4 HATCH TO DISPENSING BOOTH

EQUIPMENT

Interlock doors	SS Truck x 1

CONDITIONS As room #1

CONTINUED PAGE #3

STEROIDS HANDLING SUGGESTED MINIMUM EQUIPMENT / CONDITIONS continued

ROOM # 5 BLISTER PACKING

EQUIPMENT
Blister pack Machine
Drums for waste
Drums for filled blisters

CONDITIONS
As Room # 1
Room Pressure 15 Pa POSITIVE

ROOM # 6 CARTONING & BULK PACKING

EQUIPMENT
Carton Box Erection and loading machine with capacity for insertion of leaflets
Storage racks for materials
Bulk packing facilities/stapling machines etc.
Stencils and inks

CONDITIONS
No Requirements

ROOM # 7 IN-PROCESS LABORATORY

EQUIPMENT
Physical Test Equipment for tablets

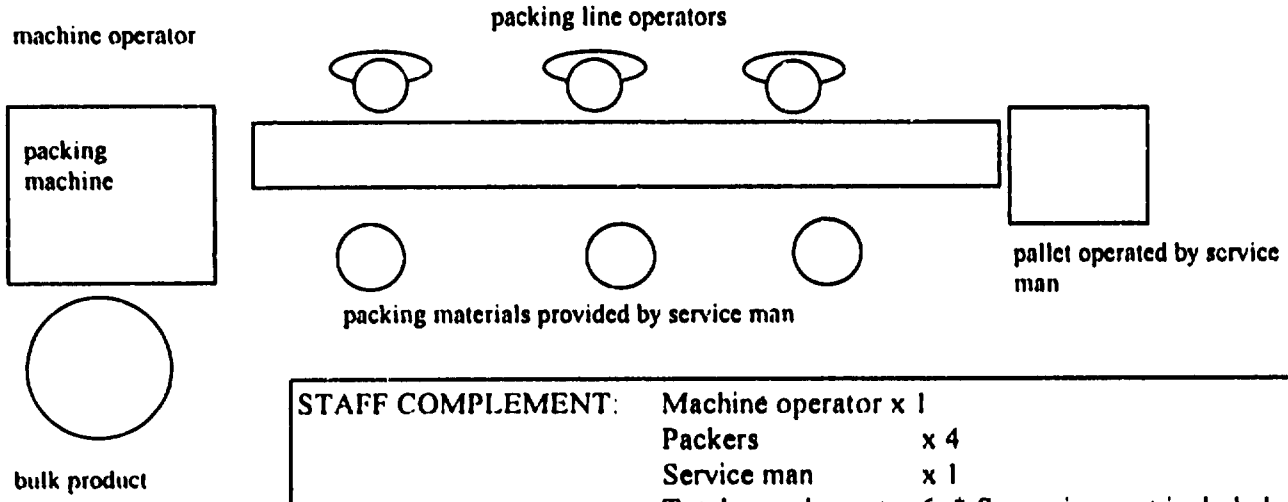
CONDITIONS
As Room # 1

ROOM # 8 DEDICATED LAUNDRY

EQUIPMENT
Washing / Drying machines
Sewing Machine
Benches (Stainless Steel) and Racking

CONDITIOONS
Supply and extract Ventilation Minimum 20 air changes per hour
Temp 15C minimum Classification # C
Washing machine drain into a neutralising tank

LAYOUT AND CONDITIONS FOR OPERATION
OF A PACKAGING LINE



STAFF COMPLEMENT:	Machine operator x 1	
	Packers	x 4
	Service man	x 1
	Total complement	6 * Supervisor not included.

EQUIPMENT
Appropriate Filling machine
NOTE: ALL CONTACT PARTS TO BE STAINLESS STEEL.
Containers for QC approved bulk products
Conveyor belt
Chairs for Packing Operators
Containers for packing materials
Pallets and pallet truck.
NOTE: PACKING LINES MUST BE CLEARLY IDENTIFIED WITHBATCH DETAILS

CONDITIONS
NOTE: WHEN TEMP/HUMIDITY SENSITIVE PACKING MATERIALS ARE EMPLOYED, THESE SHOULD BEEXPOSED TO THE CONDITONS OF THE PACKING ROOM FOR ENOUGH TIME TO REACH STABILITY: refer Product Development department.
Temp. 21 - 24 C Humidity: generally No Standard.
Air changes 15 per hour.
Conditions mainly for operator comfort.

STANDARD OPERATING PROCEDURES

(SOPs)

Includes:

What they are and why we need them

Identification System

Critical Path method for identifying the need for SOPs

Some model SOPs previously issued:-

Laboratory Accidents
Decontamination
Damaged Consignments of Raw Materials
Receival of Raw Materials in Production Departments
Complaints and Recall Procedure
Receival of New Tablet-Press Tools
Use of Protective Clothing.

SOPs WHAT THEY ARE AND WHY WE NEED THEM.

Standard Operating Procedures (SOPs) are a principal tool of Quality Management.

They derive from the interlocking functions of QC/QA/GMP.

SOPs are merely a formalised system for recording the routine activities of a factory. They are not confined to the pharmaceutical industry but are recognised as Quality Management tools in every industry where quality is of major importance.

The International Standard ISO 9000 places great importance on SOPs. The requirement for SOPs will increase over time, and so Syrian pharmaceutical industry should adopt the philosophy now rather than struggle to catch-up lost time in years to come.

Three of the principal reasons for SOPs are:-

i) because GMP demands it
ii) because they represent a valuable training and supervisory tool
iii) because they give credibility to industry by ensuring consistently high quality standards and reducing waste.

Since every factory has individual premises, it must also have individual SOPs. written according to the special conditions applicable in that factory.

Examples of SOPs provided in this Report represent MODELS for the guidance of factory operators when writing specific SOPs for their own factories.

SOPs come in many styles, for example:-

1) manufacturing instructions
2) machine operating instructions
3) company policy statements

If the three categories listed above were all that is necessary for a particular factory; then the factory would need to assemble three SOP Manuals covering :-

1) manufacturing systems
2) operating systems & procedures
3) company policies & systems.

The actual number of SOPs required to operate a company is largely dependent upon the sophistication of the company and of its products. A small company with a single range of products (for instance uncoated tablets produced by Direct Compression) might require only 20 SOPs; a pharmaceutical multinational company, however, will have between 300 - 500 SOPs.

SOPs should be drafted by technical middle management staff who:-

1) perform their duties according to GMP and company policy
2) record information in the appropriate documents
3) write SOPs explaining the operation
4) give regular training to their staff supported by SOPs
5) receive regular training to gain new technology and to broaden their own experience.

From this stage, the draft SOP passes to technical management who :-

1) plan and assign work according to GMP and company policy
2) establish a comprehensive recording and reporting system
3) provide appropriate changes or improvements to the draft SOPs according to current GMP.

Finally, it is the responsibility of senior management to accept the philosophy of GMP & SOPs and to incorporate it into company policy by providing qualified staff to undertake the work and to accept the responsibility for its implementation. Senior management has the additional responsibility of following up on the implementation of the policies, reviewing them and suggesting development. (note: the foregoing is based upon the outline developed by the Pharmaceutical Technology Service Centre PTSC of Chulalongkorn University Bangkok Thailand).

It is imperative that SOPs are arranged in logical sequences or families to avoid confusion/duplication; A model for a numerical arrangement is provided in the following chapter. The measure of a good system is that a specific SOP can be retrieved immediately.

STANDARD OPERATING PROCEDURES.

To be of maximum value it is imperative that each SOP is given a unique and individual identity.

As computerisation becomes more widely employed in Syrian pharmaceutical industry the numerical system of idetification will become standard. Thus, in establishing a system of SOPs it is appropriate at this time to use an identification system which can easily be converted for use in the computer.

It is proposed that areas which require SOPS to be available should be classified into SERIES.

Thus, for example,

Factories & buildings will be classified Series 01
Machines ---------- 02
Materials ---------- 03
Personnel ---------- 04
Production ---------- 05
Stores ---------- 06
In-process testing ---------- 07
QC/QA ---------- 08
Engineering ---------- 09
Cost accounting ---------- 10
and so on up to Series 99.

Consequently when searching for a particular SOP it is necessary only to know the general classification of the subject.

For greater accuracy, it is necessary to subdivide the SERIES into SUBSERIES.

Thus, for example,

The first SUBSERIES of SOPs on Machines would become 02.1
The first SUBSERIES of SOPs on Stores would become 06.1
and so on.

In order to ensure that SOPs have not gone out of date it is necessary that the year in which the SOP is valid should also appear in the Identification Number.

Thus, for example, the fourth SOP relating to Cost Accounting prepared in 1994 would be identified as follows:-

10.4 - 1994

and the fifth SOP relating to machines prepared in 1995 would be identified as follows:-

02.5 - 1995

In order to provide a starting point for work in Syria on the preparation of some models for SOPs the following SERIES are suggested.

SERIES 01 FACTORIES & BUILDINGS :-
- 01.1 Security
- 01.2 Access
- 01.3 Suitability for purpose
- 01.4 Environment & waste disposal
- 01.5 Surface finishes
- etc.

SERIES 02 MACHINES :-
- 02.1 Selection
- 02.2 Materials & suitability for purpose.
- 02.3 I/Q
- 02.4 O/Q
- 02.5 P/Q
- 02.6 Supply of services
- 02.7 Cleaning & decontamination
- 02.8 Machine logs.
- etc.

SERIES 03 MATERIALS :-
- 03.1 Inventory control
- 03.2 Water
- 03.3 Pharmacopoeial quality/Grade
- 03.4 Ordering
- 03.5 Receival
- 03.6 Classification - Inventory/non-inventory
- 03.7 Allocation of a LOT NUMBER
- 03.8 Quarantine
- 03.9 Acceptable quality limits (AQL)
- 03.10 Documents
- etc.

SERIES 04 PERSONNEL :-
- 04.1 General (terms & conditions)
- 04.2 General (health)
- 04.3 Hygene
- 04.4 Factory clothes
- 04.5 Operating mistakes
- 04.6 Health
- 04.7 Job descriptions
- etc.

SERIES 05 PRODUCTION :-
- 05.1 Production rates
- 05.2 Production lines
- 05.3 Areas & conditions
- 05.4 Services
- 05.5 Planning
- 05.6 Reworks
- 05.7 Documents/Masters
- 05.8 Housekeeping
- 05.9 Cleanrooms
- etc.

SERIES 06 STORES :-

06.1 Housekeeping
06.2 Receipt of materials
06.3 Allocating a Lot Number
06.4 Quarantine
06.5 FIFO
06.6 Palletisation
etc.

SERIES 07 IN PROCESS TESTING :-

07.1 Frequency
07.2 Disposal of sampled material
07.3 Parameters
etc

SERIES 08 QA/QC :-

08.1 Pharmacopoeial standards
08.2 In-house standards
08.3 Equipment and calibration
08.4 Retention of records
08.5 Standards for reagents
08.6 Preparation, validation & review of SOPs
etc.

SERIES 09 ENGINEERING :-

09.1 Protective clothing
09.2 Access to work stations
09.3 Care of press tools
09.4 Factory safety
etc

SERIES 10 COST ACCOUNTING :-

10.1 preparation of Standard Costs
10.2 Comparison of Actual/Standard cost
10.3 Cost estimating for new products
etc

Clearly there is no end to the number of SOPs which could be written, but for the purpose of illustrating the requirements of a logical system of identification the foregoing is sufficient.

THE CRITICAL PATH METHOD FOR IDENTIFYING THE REQUIREMENT FOR SOPs

DEFINITIONS

CRITICAL PATH: The CRITICAL PATH is the route which must be followed in order to attain a specific goal. It can be compared to the road between two towns with the smaller villages along the way representing events in the journey.
For example, to convert powders into tablets represents the journey; the villages along the way represent the events in the manufacturing process. Each event in the process must be given a name and described.

NAME: Each event in the process must be given a Name e.g. WEIGHING, COMPRESSING etc

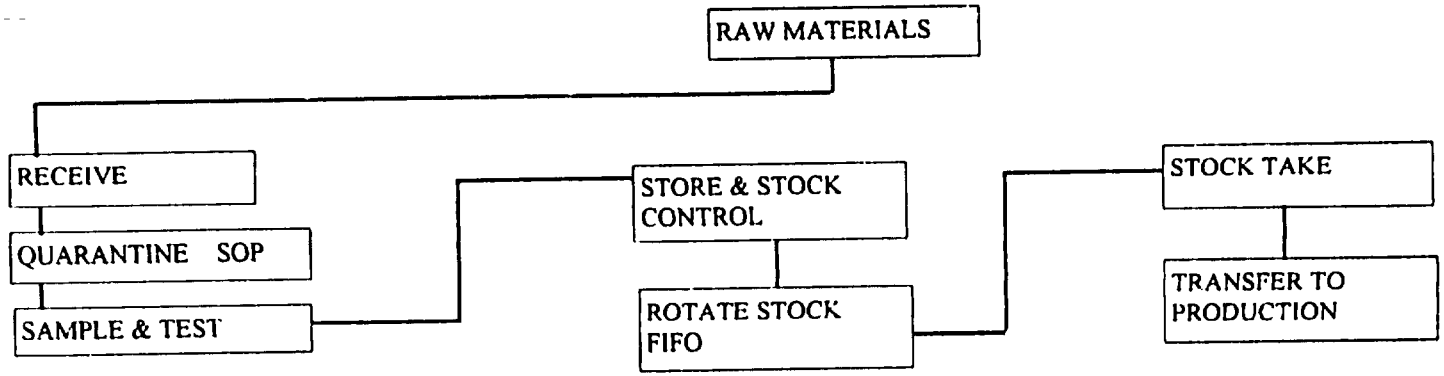
DESCRIPTION: The description of the event describes how the event is performed: the DESCRIPTION becomes the SOP

CHOOSING THE CRITICAL PATH FOR A TABLET MANUFACTURING OPERATION (*Note that this example is provided as a model only)*

SET OUT THE CRITICAL PATH:-

RAW MATERIALS	WEIGH	BLEND	MIX	DRY	GRANULATE	COMPRESS	FINISHED TABLET

INSERT THE OPERATIONS - THIS IDENTIFIES THE SOPs WHICH ARE REQUIRED IN ORDER TO CONVERT THE RAW MATERIALS INTO TABLETS



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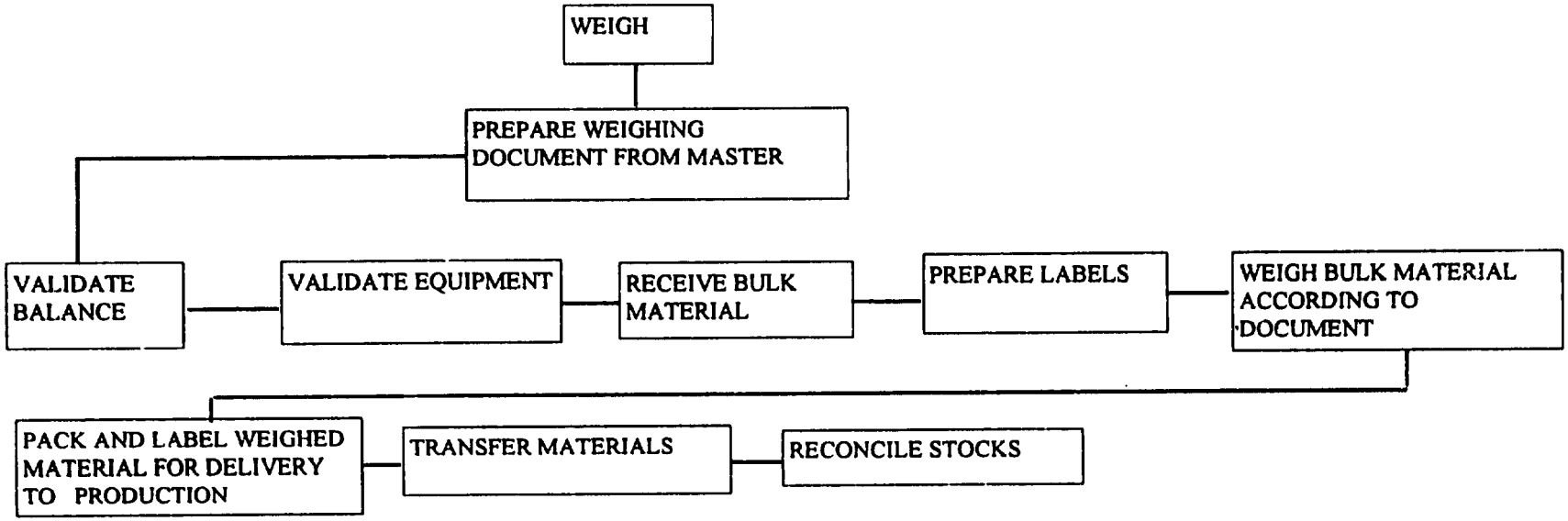
THE CRITICAL PATH METHOD FOR IDENTIFYING THE NEED FOR SOPs

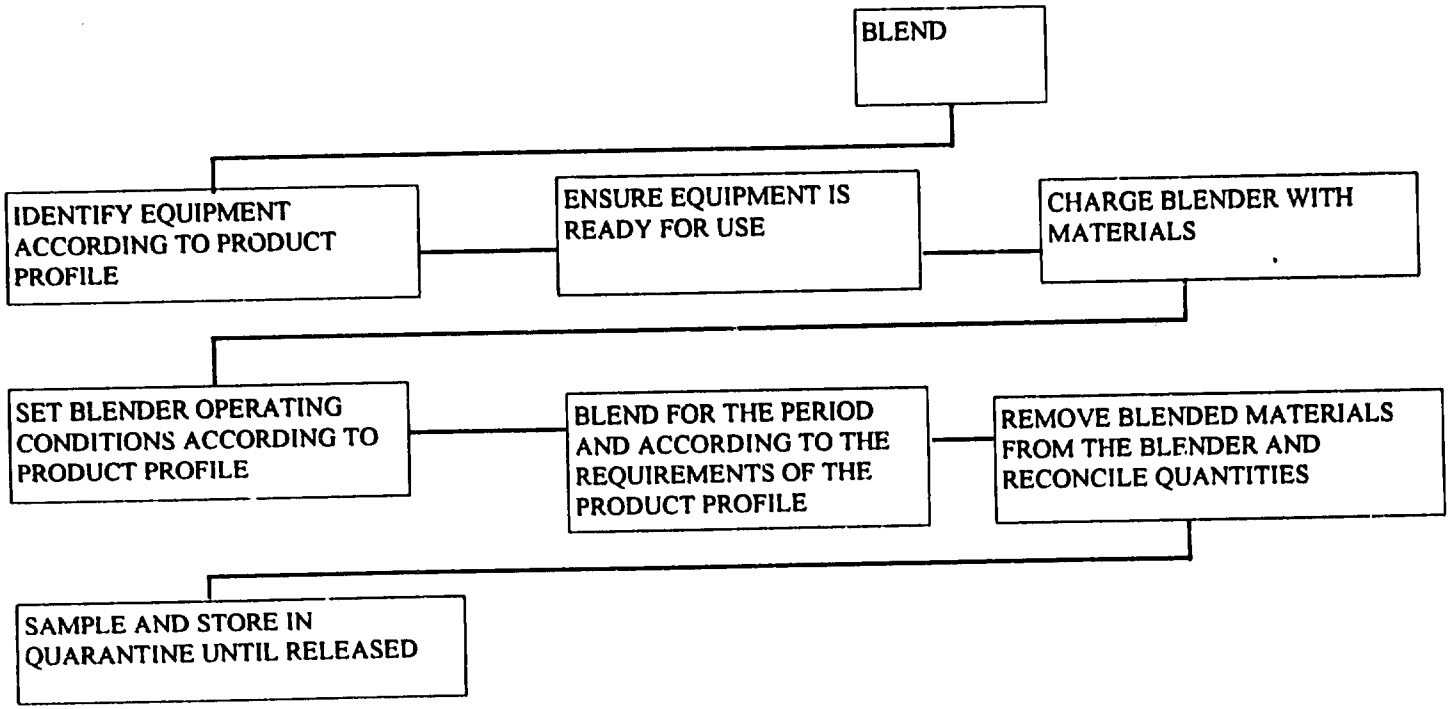


The schematic diagram sets out the EVENTS on the CRITICAL PATH between RECEIPT of Raw Materials and the PRODUCTION of a finished tablet..

It is the responsibility of the Production Staff to identify each EVENT, draw out the PATH as above, and prepare SOPs for thecorrect performance of each event .

continued page 3

THE CRITICAL PATH METHOD FOR IDENTIFYING THE NEED FOR SOPs



THE EXAMPLES PROVIDED FOR IDENTIFICATION OF THE NEED FOR SOPs IS INTENDED TO BE A GUIDE ONLY. ALL OPERATIONS IN THE MANUFACTURING OF A PRODUCT SHOULD BE IDENTIFIED AND THE APPROPRIATE SOPsWRITTEN

SOP ON LABORATORY ACCIDENTS

Scope: this SOP defines FIRST AID action to be taken in the event of an accident in the laboratory.

Responsibility: the responsibility for providing the equipment to deal with the accident is with the laboratory manager; the responsibility for providing FIRST AID is with the laboratory staff close to the scene of the accident.

IF THE ACCIDENT INVOLVES CHEMICAL OR ACID SPLASH.

1) Remove superficial clothing carefully.
2) Place the victim under a COOL (not cold) running water shower for at least five minutes.
3) If possible remove more clothing to allow the shower water to wash the skin.
4) Remove the victim from the shower and provide relaxed seating.
5) Carefully dry the area of skin around the injury taking care not to touch the accident area.
6) Keep the victim warm, do NOT give tea, coffee, or other stimulants.
7) Call supervisor for assistance.
8) If necessary refer the victim for medical or hospital treatment.

IF THE ACCIDENT IS TO THE EYES.

1) Remove the victim to the eye-bath and irrigate the affected area for at least five minutes with fresh, clean, running water.
2) Provide relaxed seating, keep the victim warm.
3) Do NOT give tea, coffee, or other stimulants.
4) Call supervisor for assistance.
5) If necessary refer the victim for medical or hospital treatment.

IF THE ACCIDENT INVOLVES FIRE.

1) DO NOT APPLY WATER TO THE FLAMES. If the flame is caused by Sodium or Phosphorus application of water will intensify the burning.
2) Remove the victim from the accident location, place on the ground and cover with a fire blanket.
3) Use the fire blanket to smother the flames.
4) Do not move the victim; do not give tea, coffee, or other stimulants.
5) Immediately call the supervisor for assistance.
6) If necessary, refer the victim for medical or hospital treatment.

SOP: DECONTAMINATION.

Background: Decontamination is a word which should not be heard in pharmaceutical industry routine manufacturing operations. Decontamination represents the exact opposite of the preferred system in which DEDICATED areas and equipment are provided for critical activities. A situation in which Decontamination is a regular occurrence implies a deficiency in the manufacturing facilities.
Decontamination has to be undertaken when mutually antagonistic materials have to be processed in the same area or on the same equipment.
Decontamination presents the following difficulties:-

1) it is in conflict with the basic philosophy of GAMP.
2) it is wasteful in context of the worker hours taken to decontaminate an area and a machine.
3) it is wasteful in context of the volume of production lost during non-productive cleaning.
4) it is almost impossible to guarantee that total decontamination has been achieved.
5) if total decontamination has not been achieved, there is every possibility that resistant micro-organisms will develop in the community.
6) there is a risk that sensitivity and/or allergy will develop in patients taking a medication which is contaminated with trace quantities of an antagonistic material..
7) it jeopardises the integrity of whatever products are handled in the area.

SCOPE: This SOP sets out the minimum requirements for the process of decontamination of a work area and a machine.

RESPONSIBILITY: THE RESPONSIBILITY FOR A DECONTAMINATION EXERCISE RESTS MAINLY WITH THE PRODUCTION CONTROLLER WITH EVALUATION PROVIDED BY THE QUALITY CONTROLLER.

SEQUENCE OF EVENTS.

1) whenever possible the machine should be removed from the production area to a specific cleaning location.
2) the empty work room should be mechanically cleaned with a vacuum cleaner fitted with high quality outlet filters to prevent spreading contamination throughout other parts of the factory in the form of an aerosol. Vacuum cleaning should be repeated at least three times over a period of two days or more so as to allow any airborne particles raised in the first cleaning to settle.
3) the room should now be free from most particulate material. Contaminants lodged in porous surfaces; cracks; and imperfections in walls, ceilings, and floors should now be removed by the application of live steam from a steam lance. (naturally this will have a disastrous effect on any loose or flaky paint or plaster finish). Excess water should be removed from walls and floors with a rubber scraper. The room should then be left for several days to dry completely.

4) all surfaces in the room should be given a thorough wash with a suitable organic solvent (taking appropriate fire precautions and due regard for the workers' health).

5) finally the room surfaces should be washed with an aqueous solution of detergent, taking care not to dislodge any light fittings or ventilator ducts which may still contain unwanted dust.

6) machines should be located in a cleaning area where they can be completely stripped, de-dusted, steam cleaned, solvent or detergent washed, serviced, re-lubricated and re-assembled. Subsequently the decontaminated machine may be relocated in the work-room, again taking care not to dislodge any dust which may remain in fittings or ducts.

7) workers' clothing is extremely difficult to decontaminate due to dust entering the woven fabric of the material and being almost impossible to remove. Workers in a freshly decontaminated area should be provided with new protective clothing which is dedicated to the product.

8) the Quality Control department must monitor the progress of a decontamination exercise and confirm that ABSOLUTE decontamination has been achieved.

SOP ON DEALING WITH DAMAGED CONSIGNMENTS OF RAW MATERIALS

Scope: this SOP refers to action to be taken when imported Raw Materials are received in damaged condition.

Responsibility: the initial responsibility for the implementation of this SOP rests with the Stores Supervisor.

1) Take delivery of the goods and record on the truck-driver's invoice that the material was received damaged. If possible record the number of items from the consignment which were received in damaged condition.

2) Separate out all containers which show ANY evidence of damage; mark the Goods Received Note showing the number of damaged containers.

3) Call the QC laboratory to immediately examine the material and advise on future action to be taken.

SOP ON RECEIVING OF RAW MATERIALS IN PRODUCTION DEPARTMENT

Scope: this SOP details the procedures for receiving of materials from Stores into Production Department according to GMP Documentation.

1) Visually inspect the consignment of materials to ensure that all containers are securely closed and labelled, and that there is no evidence of interference between the Stores and the Production Department.

2) Take the Weighing Document which accompanies the material, and compare the listed quantities with those stated on the Production Document.

3) If the quantities are identical, commence to remove the delivered materials from their container or pallet, one by one; confirm that the description on the Delivery Label conforms with what is stated on the Weighing Document and score off each item from the Weighing Document until the container or pallet is completely empty.

4) Confirm that the number and quantities of materials received is exactly as stated on the Weighing Document and sign the Weighing Document to acknowledge receipt of the material and accept responsibility for it.

5) Retain the duplicate copy of the Weighing Document to become part of the Batch Documentation; return the top part of the Weighing Document to the Store to become part of their Inventory Records.

6) Transfer the material to the preparation room.

SOP ON COMPLAINTS AND RECALL PROCEDURE.

Scope: this SOP deals with the immediate actions to be taken whenever a complaint is received or recall procedure may be necessary.

Responsibility: The initial responsibility for establishing a complaints and recall procedure rests with the company management. The implementation of the procedure is the direct responsibility of the Production Controller, the Quality Ccntroller, or their nominated deputies, acting either alone or together.

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

2) A complaint may lead to the need for a product recall. Any action taken as the result of a complaint, must be immediate, and must be in accordance with this SOP.

3) This SOP must be read and understood by all staff involved in its implementation.

4) Records of complaints should be reviewed regularly by the Production Controller, the Quality Controller and the General Director together. Specific problems should be addressed immediately.

5) A written recall procedure must be capable of implementation at any time, day, night and vacation included.

6) Persons responsible for initiating a recall include:-

the General Director
the Production Controller
the Quality Controller
or their appointed and trained nominees.

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

7) Having established a recall procedure it should be tested for effectiveness and practicality. It should be reviewed from annually. In the event of changes of senior staff, newcomers must be thoroughly trained in the operation of a product recall.

8) In the event of a drug recall, the directorate of the Drug Control Unit at the Ministry of health must be advised immediately. Also, the drug distributors and agents must be instructed to quarantine their remaining stocks and to recall the stock which is in the market. Any defective material which is in transit at the time of the recall must be immediately quarantined when it reaches its destination.

9) All recalled material must be immediately placed in quarantine to await investigation and disposal instructions.

10) A notification of recall must include:-

a) product name, strength & Batch Number
b) the date upon which the recall was initiated
c) the nature of the defect
d) action to be taken and URGENCY
e) warning to the recipient to retain this notification in order that goods in transit may be checked.

SOP ON RECEIVAL OF NEW TABLET PRESS TOOLS.

Introduction: Press tools are a major investment for any manufacturer of tablets. Without due care and attention a set of tools can be damaged irepairably within a very short time.

Scope: This SOP defines the actions which are to be taken to maximise the life of a set of press tools and to assure the quality and consistency of the tablets which they produce.

1) Immediately upon receipt of the tools from the manufacturer, visually examine the shipping container for damage.

2) If the container is damaged, pay special attention to tools which are in the container close to the damage, they also may be damaged.

3) Place a piece of corrugated cardboard or plastic roofing material on the bench, this will serve as a safe locater for the tools as they are removed from their shipping container.

4) If the container is undamaged, open it and remove each component, separate these into three groups, namely Top Punches, Dies, and Lower Punches. Layout the top and bottom punches in the valleys of the corrugated material on the bench.

5) Taking great care to avoid the tools coming into contact with each-other remove the moulded plastic protection from each component and replace the unwrapped tools into the valleys of the corrugated material.

6) There are now three sets of components each piece being exactly in accordance with its manufacturer's specification. Use a micrometer to measure the critical dimensions of one component Top Punch, Bottom Punch, and Die. Record these dimensions and retain them with the tools.

7) Make a simple "Go" / "No Go" gauge from sheet metal or other suitable material; this will be of value in the future since it identifies the acceptable limits of the overall length of the punches. Make a similar "Go" /"No Go" gauge for the tip dimensions of the punches. These gauges should be retained with the tools for the entire life of the tools.

8) Using a vibratory engraving tool mark each die with a unique, sequential number from #1 - #28 (or whatever is the final number of the set). Also engrave a mark on each die to indicate upper and lower surfaces. Thus, for instance the upper surface will be engraved #A, and the lower surface will be engraved #B. The reason for doing this is that the bore of a die wears unevenly with most of the wear taking place in the top 30%; thus by interchanging the upper and lower faces of the dies this differential wear can be balanced so giving twice the lifespan to the dies.

9) Using the "Go" / "No Go" gauges provide each die with a top punch; Using the engraving tool mark the punch on some part which is not exposed to friction e.g. its neck, with the same number as appears on the die. Repeat this procedure for the bottom punch. There will now be a set of tools identified as follows -- one die marked #1/A & #1B
one top punch marked #1
one bottom punch marked #1

10) This set must always be set up together in the tablet press. It is not permitted to mix sets after the initial identification has been performed.

11) Remove any finger prints from the tool by wiping with a soft cloth; the reason for this is that skin acids will rapidly corrode press tools. Apply a light coating of machine oil to all surfaces of the tools.

12) Place the tools in their sets in a specially constructed box or drawer for safe storage.

NOTE: ON NO ACCOUNT SHOULD A MECHANIC'S CENTRE PUNCH BE USED TO ENGRAVE PRESS TOOLS. IT IS IMPERATIVE THAT A VIBRATORY ENGRAVING TOOL IS EMPLOYED.

USE OF PROTECTIVE CLOTHING

Protective clothing serves two purposes in a pharmaceutical factory:-

i) to protect the product from the operator and
ii) to protect the operator from the product.

Scope: this SOP is confined to the handling of general products: its contents should not be confused with the more demanding protective clothing necessary for the processing of sterile materials.

Responsibility: the responsibility for compliance with this SOP lies initially with the Factory Management to provide adequate supplies of appropriate garments and laundering facilities, and secondly with Departmental Managers to ensure that operators in their sections are aware of the need for, and use of appropriate protective clothing.

1) Appropriate factory clothing must be worn at all times in the production areas.

2) The minimum acceptable standard comprises:- factory shoes, factory gown, and head cover.

3) In production areas in which the operator is in direct contact with the products, e.g. in a blending department, the minimum acceptable cover must be worn, together with a face mask covering mouth and nose and cotton or disposable gloves.

4) In areas where toxic, hormonal, or antibiotic dust is generated, the face mask may be replaced by a respirator with a disposable activated charcoal filter.

5) In all cases, protective clothing must be in a good state of repair with no tears or holes; buttons, zips or other closures must be in good condition and fully closed during work.

6) The protective clothing provided must be of the correct size for the wearer.

7) Head covers must be worn so as to contain the entire hair of the operator; wearing the head cover pushed to the back of the head is not acceptable.

8) Protective clothing should be clean each day.

9) When a change of product occurs e.g. a batch of Aspirin tablets is completed and a batch of Paracetamol is to commence, the protective clothing must be completely changed. It is not permitted to wear contaminated protective clothing for handling different materials.

10) Failure to conform to this SOP may result in a worker being suspended from production activity.

MODEL MASTER DOCUMENTS.

Includes

Product Specification

Raw Material Specification

Tablet Compression

Sterilisation

In-Process Control

Blending

Packaging & Reconciliation

Liquid Mixing

Granulating

Weighing

PHARMCO	PRODUCT SPECIFICATION MASTER DOCUMENT	
DOCUMENT REFERENCE NUMBER:		
Document Prepared by:	Document Checked by:	Date:
Document Revised by:	Revision Checked by:	Date:
Product Name and strength:	Company Reference:	
Pharmacopoeial Standard:	In House Standard:	
PRODUCT DESCRIPTION:		
Sampling Instructions:	Resampling Period:	

PHARMCO

RAW MATERIAL SPECIFICATION MASTER DOCUMENT.

Document Reference number:

Document prepared by: Document checked by:
Date: Date:

Document revised by: Revision checked by:
Date: Date:

Material Name: Company Reference Code:

Pharmacopoeial Standard: Other Standard:

Approved Suppliers: 1)
2)
3)

Storage Instructions:

Sampling Instructions:

Retest Date:

Tests to be performed for IDENTITY/PURITY/LIMITS

DETAILS OF TESTS	RESULTS OF TEST		PASS/FAIL	ANALYST	DATE
	Theoretical	Actual			
1)					
2)					
3)					
4)					

This material COMPLIES/FAILS TO COMPLY with the accepted standard: it is therefore ACCEPTED/REJECTED.

Instructions for STORAGE/DISPOSAL:

Quality Controller: (signature) Date:

Circulation: Original to Production Dept. Copy #1 to Stores
Copy #3 to Administration Copy #4 retained by QC.

PHARMCO

TABLET COMPRESSION MASTER DOCUMENT

DOCUMENT REFERENCE NUMBER:

Document Prepared by: Document Checked by: Date:

Document Revised by: Revision Checked by: Date:

Product Name/Strength: Batch Number: Date Started:

Expirey Date: Batch Size: Kg. Date Completed:

Theoretical Yield: Kg. Theoretical Yield: Number of tablets:

Actual Yield: Kg. Actual Yield: Number of tablets:

TABLET DESCRIPTION

Diameter: Shape: FBE/DC/NC/Other (describe)

Thickness: Hardness: Strong -Cobb units Weight per Tablet: mg.

Disintegration Time: Dissolution Time: Friability:

Colour: Tablet Markings:

Continued on page 2

PHARMCO	TABLET COMPRESSION MASTER DOCUMENT	Page 2 of 2

TABLET PRESS.

Identity of press: Machine #

Press Tools installed: (size/shape/markings etc) Grease Cups fitted: (Yes/No)

Any special precautions:

REMOVE THE "MACHINE CLEANED" STICKER AND ATTACH TO THIS DOCUMENT FOR QA PURPOSES.

Machine tooled up by: Date: Time:

COMPRESSION.

Compression started Date: Time:

Compression completed Date: Time: Compression performed by: (signature)

Number of Containers filled:

Container #1 (Weight)	Container #2 (Weight)	Container #3 (Weight)
Container #4 (Weight)	Container #5 (Weight)	Container #6 (Weight)

TOTAL WEIGHT OF TABLETS OBTAINED Kg.

NO FURTHER PROCESSING TO BE PERFORMED UNTIL MATERIAL APPROVED BY QC

Quality Control to advise APPROVED/REJECTED in this space. Attach documents and calculations to this form.
Quality Controller: (signature) Date:

PHARMCO	STERILISATION MASTER DOCUMENT	
DOCUMENT REFERENCE NUMBER:		
Document Prepared by:	Document Checked by:	Date:
Document Revised by:	Revision Checked by:	Date:

Product Name/Strength:	Company Reference:	
Batch Number:	Batch size:	
Time Commenced:	Time Completed:	Date:

Steriliser used: (name) Machine number:

INSTRUCTIONS

Signature of operator:

1) Ensure that Dummy Load is correctly installed.
2) Ensure that a new Recorder Chart is fitted and the recorder is functioning correctly.
3) }
4) } Insert specific sterilising instructions.
5) }
6) Remove completed Recorder chart and attach to this document.
7) Report a y abnormal operations in the sterilising cycle.
8) Provide a sample of the sterilised product for Quality Control Assessment.

DO NO FURTHER PROCESSING ON THIS BATCH UNTIL ADVISED BY QC.

Quality Control to advise APPROVED/REJECTED in this space. QC documents and calculations to be attached to this form.

Signature (Quality Controller) Date:

PHARMCO	IN-PROCESS CONTROL MASTER DOCUMENT	
DOCUMENT REFERENCE NUMBER:		
Document Prepared by:	Document Checked by:	Date:
Document Revised by:	Revision Checked by:	Date:
Product Name/Strength:	Company Reference:	Batch Number:
Date of Testing:	Tested by:	Batch Size:

TESTS PERFORMED

Details of tests:	STANDARD	ACTUAL RESULTS.
1)	Pharmacopoeial	
2)	In - House	
3)		
4)	etc	

RESULTS: A) The Batch complies with ALL standards and is released for further processing.
B) The Batch FAILS to comply with standards and requires adjustment, or disposal, as follows.

ADJUSTMENTS: *Quality Control to identify in this space the adjustments to be made in order for production to continue. Quality Control documents and calculations to be attached to this form for QA purposes.*

Quality Controller: (signature) Date:

PHARMCO

BLENDING MASTER DOC'JMENT

Document Reference Number:

Document Prepared by: Document Checked by: Date:

Document Revised by: Revision Checked by: Date:

Product Name/strength: Company Code:

Batch Number: Batch Size: kg/l.

MATERIALS USED.

Name:	Quantity Used	Used by:	Checked by:	Date

BLENDER USED.

Attach MACHINE CLEANED sticker to this document for QA purposes.

Name of Blender and description of the tools used :

Continued on page 2

PHARMCO BLENDING MASTER DOCUMENT Page 2 of 2

Required blending time: minutes.

Time blending commenced: Time blending completed:

Total time for blending:

YIELD FROM BLENDER

Yield in Kg. Number of Containers obtained

DO NO FURTHER PROCESSING OF THIS BATCH UNTIL APPROVED BY QUALITY CONTROL

IN - PROCESS QC.

Number of samples taken:			
Tests performed: a) b) c)	Results Pass/Fail	Signature of Analyst	Date

Quality Control to notify APPROVED/REJECTED in this space, together with instructions for adjustment/disposal if appropriate QC documents and calculations to be attached to this form.

Quality Controller (Signature) Date:

PHARMCO	PACKAGING MASTER DOCUMENT	
		Page 1 of 4
DOCUMENT REFERENCE NUMBER:		
Document Prepared by:	Document Checked by:	Date:
Document Revised by:	Revision Checked by:	Date:

PRODUCT DESCRIPTION.

Product Name and Strength:

Company Code #: Batch Number: Expiry Date:

Batch Size: Kg.

Projected Yield / Finished Packs.

PACK DESCRIPTION.

Unit Pack:

Sales Pack:

Distribution Pack:

PACKING MATERIALS.

Specify in this area the details of ALL packing materials which will be employed in the Packaging Operation:
(laminate, foil, bottles, cotton wool wadding, caps, cartons, labels, overwrap, etc)

PACKING LINE.

Equipment:

Specify in this area the details of ALL packaging equipment which will be employed. For major equipment, the Machine Number should be provided.

ALL EQUIPMENT SHALL BE CLEARLY IDENTIFIED WITH DETAILS OF THE PRODUCT NAME/STRENGTH AND BATCH NUMBER.

REMOVE "MACHINE CLEANED" STICKER AND ATTACH TO THIS DOCUMENT FOR QA PURPOSES.

Refer Page 4 for details of the packing line layout and rates.

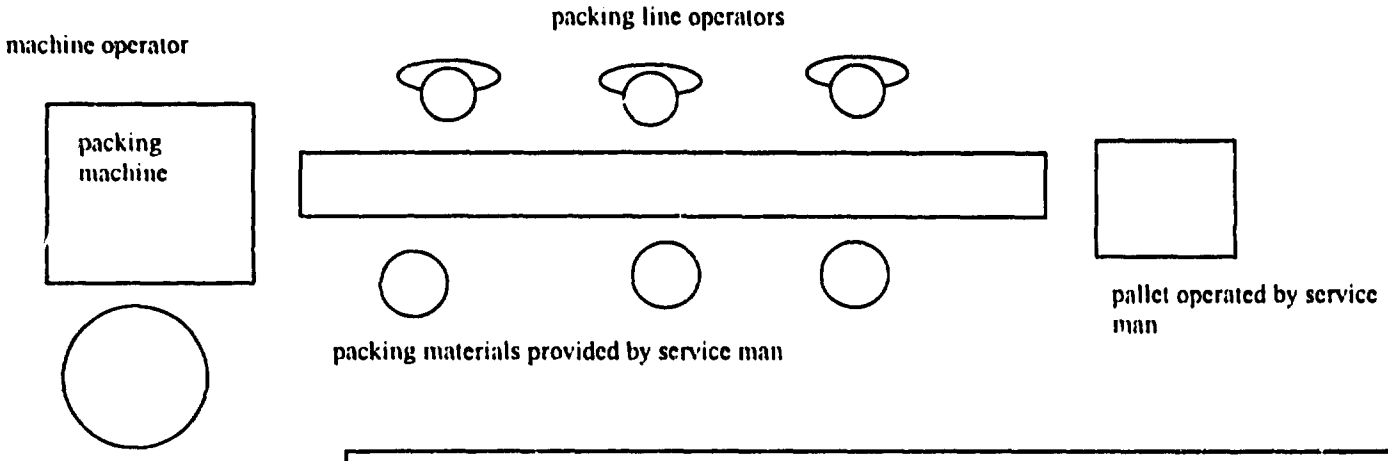
RECONCILIATION OF MATERIALS USED.

Printed or overprinted materials CANNOT be returned to Stores for subsequent use on other Batch. ALL disparities between amounts taken, and amounts used MUST be explained. Explanations MUST be verified and authorised by Quality Control.

Identity of Material.	Amount taken	Amount used	Residual or Shortage	Explanation	Disposal Instructions

Confirmed by Production Supervisor: (signature) Date:

Checked and authorised by Quality Controller: (signature) Date:



STAFF COMPLEMENT:	Machine operator x 1	
	Packers	x 4
	Service man	x 1
	Total complement	6 * Supervisor not included.

HOURLY PRODUCTION RATES

Target packs per hour

HOUR#1	HOUR#2	HOUR#3	HOUR#4	HOUR#5	HOUR#6	HOUR#7	HOUR#8	TOTAL FOR RUN

Hourly Production RateAchievement as % of Target.

Packing Supervisor: (signature) Date:

PHARMCO	LIQUID MIXING MASTER DOCUMENT	
DOCUMENT REFERENCE NUMBER:		
Document Prepared by:	Document Checked by:	Date:
Document Revised by:	Revision Checked by:	Date:
Product Name/Strength:	Company Code:	Date commenced:
Batch Size:	Batch Number:	Date completed:
Expiry Date:		

MIXING INSTRUCTIONS

Remove "MACHINE CLEANED" stickers from ALL equipment to be used and attach to this document for QA purposes.

Equipment Used: (machine name/reference #) Performed by:

1) }
2) }
3) } Insert Specific Mixing instructions.
4) }
5) Provide a sample of the mixed product to Quality Control.

Do no further processing on this batch until QC Approval, Adjustment or Disposal instructions have been received.

Quality Control to Approve/Reject/Adjust in this space. QC documents and calculations to be attached to this form.

Signature (Quality Controller) Date:

PHARMCO GRANULATING MASTER DOCUMENT page 1 of 3

DOCUMENT REFERENCE NUMBER:

Document Prepared by: Document Checked by: Date:

Document Revised by: Revision Checked by: Date:

Product Name/Strength: Batch Number: Date:

Batch Size:

MATERIALS USED

Name of Material.	Quantity Used.	Used by.

Attach TRANSFER TICKETS to this document for QA purposes.

WET GRANULATION.

Attach "MACHINE CLEANED" sticker to this document for QA purposes.

Equipment used: (Machine Name) Machine #

Granulating Fluid: Volume required:

Volume Used:

Granulation started Date: Time: Granulation completed Date: Time:

Granulation completed by: (Signature)

Continues on Page 2

DRYING

Attach "MACHINE CLEANED" sticker to this document for QA purposes.

TRAY DRYING:

Oven Identification: (Name) Machine #

Number of trays filled: Drying temperature: C

Time Drying Commenced: Time Drying Completed:

FLUID BED DRYING:

Use only clean or dedicated bags.

Dryer Identification: (Name) Machine #

Drying Temperature: Inlet C Outlet C

Time Drying Commenced: Time Drying Completed:

Drying completed by (signature) Date:

Continues on page 3

PHARMCO

GRANULATING MASTER DOCUMENT

MILLING.

Attach "MACHINE CLEANED" sticker to this document for QA purposes.

Identifation of Milling Machine: (Name) Machine #:

Screen Mesh: (Size) Rotation: Blades/Hammers Forward:

Dust control equipment functioning properly? (Yes/No)

Time Milling Commenced: Time Milling Completed:

Yield of granules: (Number of drums): Total Weight of Granules.

DO NO FURTHER WORK ON THIS PRODUCT UNTIL APPROVED BY QUALITY CONTROL

Milling completed by: (Signature of operator): Date:

Quality Control to APPROVE/REJECT in this space. QC documents and calculations to be attached to this form.

Signature of Quality Controller: Date:

PHARMCO

WEIGHING MASTER DOCUMENT

DOCUMENT REFERENCE NUMBER:

Document Prepared by:

Document Checked by:

Date:

Document Revised b

Revision Checked by:

Date:

Product Name and strength:

Company Reference:

Batch Number:

Batch Si

Date:

Active Materials Required:

Standard:

Quantity per Unit:

Quantity per Batch: kg/l

WEIGHING DETAILS

Material	Batch #	QC #	Weight Req.	Weight taken	Weighed by	Checked by	Date

Material Delivered by (Signature Weighing Dept)

Material Received by (Signature Production Dept)

Date

RESPONSIBILITIES

Includes:

Model Job Description Production Controller

Model Job Description Quality Controller

Senior Executive Responsibility Chart

Model Job Description

PRODUCTION CONTROLLER

1) In conjunction with the Quality Controller, establish a written program of GMP, SOPs, and QA. Specific responsibilities must be clearly defined.

2) Recruit and train appropriate staff for production areas, stores, plant & equipment, operations and records.

3) Develop and implement training protocols for production operators; assess effectiveness and update as necessary. Develop Job Descriptions for operators, implement and assess performance.

4) Establish production norms, and develop the system of Production Lines; evaluate attainment and update as necessary.

5) Procure and store correctly, all necessary Raw Materials, Packing Materials, , Intermediates and Finished Goods, reconcile stock levels/usage, investigate disparities.

6) Manufacture, store, and distribute Finished Goods, according to agreed standards of GMP, and Quality Assurance in line with the quantities and times specified by Management.

7) Maintain production areas, stores and surrounding areas in "Inspection Condition" at all times.

8) In conjunction with the Quality Controller, establish, maintain and implement a system of manufacturing and packaging documentation.

9) Continuously monitor, and record the foregoing matters; reconcile the actual achievements with the theoretical performance and investigate non - compliance.

10) Report directly and independently to the General Manager.

Note: This document represents a committment between the employer and the employee; it should be signed and dated by both parties in order to formalise the responsibilities. Both parties should retain a copy.

ACCEPTANCE: I confirm that I have read, understood and accept this Job Description:

Signature of Employee Date

Signature of Employer Date

Model Job Description.

QUALITY CONTROLLER *

1) In conjunction with the Production Controller establish a written program of GMP, SOPs, and Quality Assurance; specific responsibilities must be clearly defined.

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

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

4) Prepare written standards for all laboratory reagents and procedures.

5) Establish a system for allocation of valid Expiry Dates.

6) Establish, formalise, and implement a system of Acceptable Quality Limits (AQL) for all materials used in production and packing.

7) In conjunction with the Production Controller, establish, formalise, and implement a system of manufacturing and packaging documentation.

8) Independent of the Production Controller, approve or reject materials in accordance with the agreed standards.

9) Establish, formalise, and implement "In Process" test procedures.

10) Recruit and train appropriate staff to fulfil the requirements of the laboratory; develop, implement and assess training protocols for all laboratory staff, regularly review and update training procedures. Develop Job Descriptions for laboratory staff and assess performance.

11) Provide appropriate accommodation and safeguards for all aspects of Chemical, microbiological, and animal testing.

12) Operate the laboratories according to the requirements of Good Laboratory Practice and implement a Laboratory Information Management System (LIMS)

13) Continuously monitor the above and continue review and development of the systems.

14) Report directly and independently to General Management.

Note: This document represents a committment between the employer and the employee; it should be signed and dated by both parties in order to formalise the responsibilities. Both parties should retain a copy.

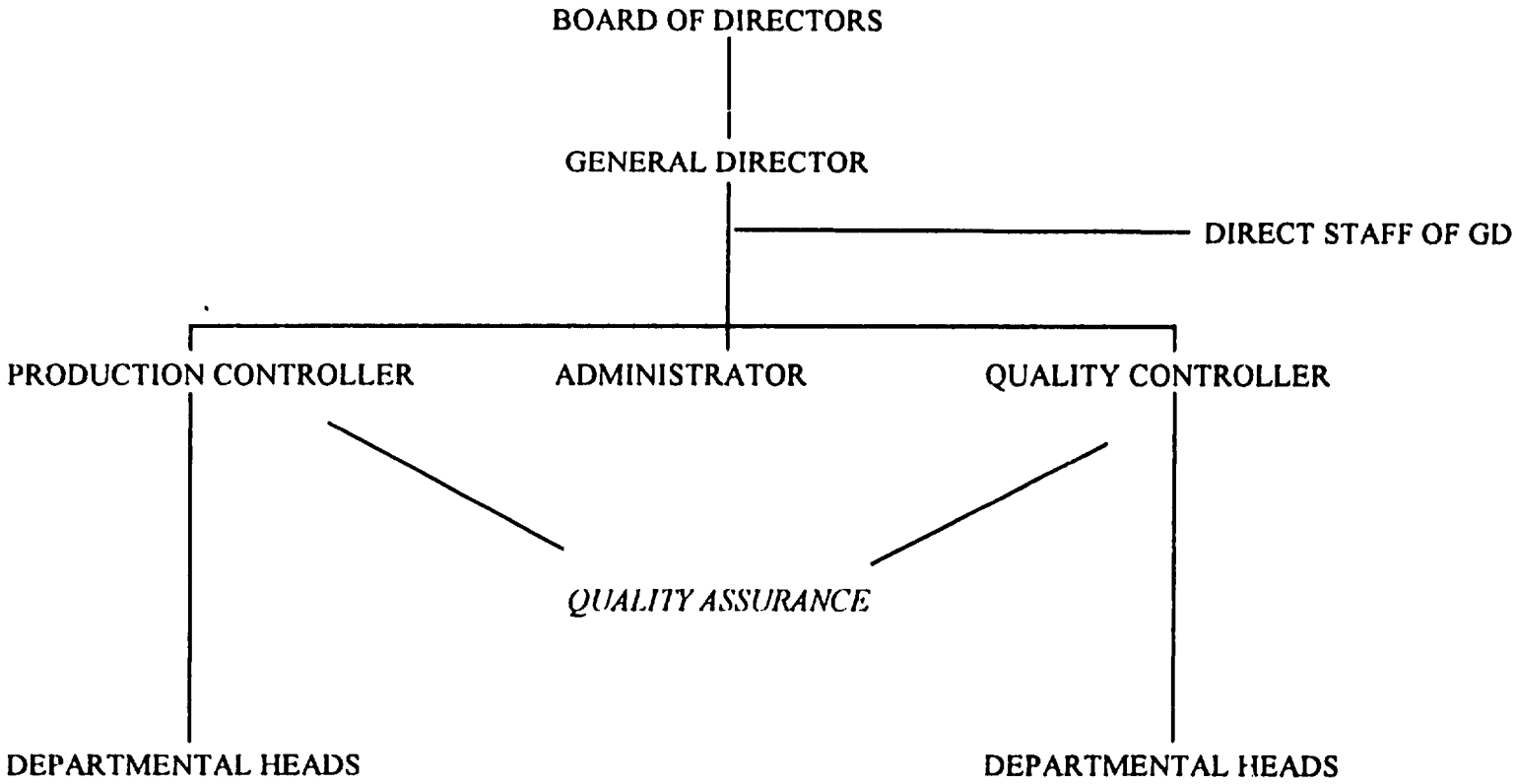
ACCEPTANCE: I confirm that I have read, understood and accept this Job Description.

Signature of Employee Date

SIgnature of Employer Date

* *In keeping with international convention, it is recommended that the title QUALITY CONTROLLER should be adopted in place of Technical Manager.*

SENIOR EXECUTIVE RESPONSIBILITY CHART



Note: It is common practice to appoint a QUALITY ASSURANCE MANAGER in large Companies.In this case, the QA Manager would be located BELOW the General Director and ABOVE the PRODUCTION & QUALITY CONTROLLERS.

EXAMPLES OF BOOKS, LABELS, ETC

Includes:

Goods Received Notes

Production Book

Transfer Ticket

Machine/Room/Equipment Condition

In-Process labels

Machine Logs and Diary

MODELS FOR MACHINE/ROOM/EQUIPMENT CONDITION STICKERS

MACHINE/ROOM/EQUIPMENT
IN QUARANTINE

THIS MACHINE/ROOM/EQUIPMENT HAS NOT BEEN CLEANED

DO NOT USE

Machine Name and Number: Previous Batch Identity:

Machine Quarantined by: (signature of supervisor)

Date Quarantined

Label BLACK TEXT on a
RED background

MACHINE/ROOM/EQUIPMENT
CLEANED

THIS MACHINE/ROOM/EQUIPMENT HAS BEEN CLEANED
it is

AVAILABLE FOR USE

Machine Name and Number

Cleaned according to Cleaning SOP #

Cleaned by (signature of Cleaner) Date Cleaned

Label BLACK TEXT on a
GREEN background

EXAMPLES OF IN -PROCESS LABELS.

PHARMCO

MATERIAL IN QUARANTINE

Date received: GRN number:

Material Name: Supplier:

Container # of containers.

NOT TO BE USED UNTIL APPROVED BY QC

BLACK TEXT ON A RED BACKGROUND

PHARMCO

MATERIAL SAMPLED FOR TESTING

Date sampled: GRN number:

Container # of containers

Sampled by:

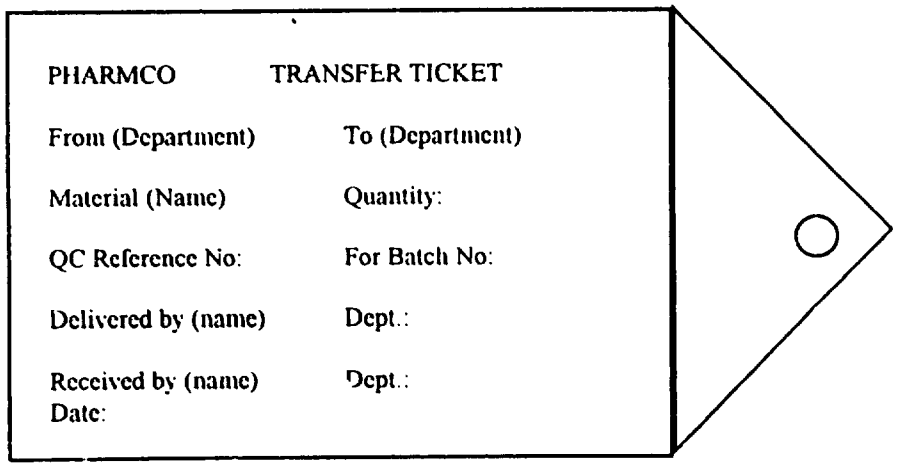
NOT TO BE USED UNTIL APPROVED BY QC

BLACK TEXT ON A YELLOW BACKGROUND

EXAMPLE OF A TRANSFER TICKET

A Transfer Ticket is the preferred method for moving goods between Departments in a factory; for instance between Stores and Blending Departments. A Transfer Ticket clearly identifies the material being moved and also identifies the persons responsible for the transaction. On completion of the transaction, the Transfer Ticket is removed from the consignment of goods and attached to the Production Documents where it becomes an intrinsic part of the Batch Record and complies with the requirements of Quality Assurance.

NB Writing the details of a consignment with indelible ink on the plastic bags or drums containing the materials being transferred is NOT an acceptable alternative to the use of a Transfer Ticket for the reason that the plastic bag is thrown away after the material has been used and NO record of the transaction remains for QA purposes.



Transfer Ticket should be cut from light cartridge paper or thin cardboard.

In use the Ticket should be TIED with string to the bag or drum containing the material being transferred.

After the material has been used, the Transfer Ticket should be removed from the container and attached to the Batch Documents as a permanent record that the transaction occurred.

Use of a Transfer Ticket has the added benefit that it removes the need to mark plastic bags with an indelible ink pen with consequential risk of contamination of the contents.

PHARMCO
PRODUCTION BOOK
(Sample Page)

MANUFACTURING DATE	EXPIRY DATE	BATCH NUMBER	COMPANY REFERENCE #	BATCH SIZE	PRODUCT NAME/STRENGTH & STANDARD	BATCH INITIATED BY

SAMPLE OF A PAGE FOR GOODS RECEIVED NOTE BOOK (GRN)

PHARMCO Received from: Carrier; Material Description: Manufacturer's Batch No:	GRN NUMBER: Date: Pharmacopoeial Standard:
QUANTITY:	Number of containers: Quantity per container: kg/l Total Quantity: kg/l
CONDITION OF GOODS:	Physical Damage Containers. Water Damage Containers. Other Damage Containers. (Provide details of damage) Total Number of damaged containers
APPLY QUARANTINE *STICKERS AND PLACE MATERIAL IN QUARANTINE STORE.*	
CIRCULATION: Original to Production Controller. Third to Administration	Second to Quality Controller. Fourth retained in Store

MODEL PAGE
MACHINE LOG AND DIARY

MACHINE No.: LOCATION (Room No.):

MACHINE DESCRIPTION: MANUFACTURER'S SERIAL NUMBER:

MACHINE MANUFACTURER: (Name/Address/ Telephone/ 'fax)

LOCAL AGENT: (Name/ Address/ Telephone/ 'fax) (MAINTENANCE CONTRACT REF:)

PURCHASE ORDER REFERENCE No.:

DATE MACHINE RECEIVED: DATE MACHINE COMMISSIONED:

FILING REFERENCE FOR DRAWINGS & INSTRUCTION BOOKS:

SPARE / CHANGE PARTS PROVIDED: LOCATION

RELEVANT SOPs: OPERATIONAL:
MAINTENANCE

SERVICES REQUIRED:

Continues Page 2

MODEL PAGE

MACHINE LOG AND DIARY

SCHEDULE	WORK ACCORDING TO
DAILY	SOP Nos
WEEKLY	SOP Nos
MONTHLY	SOP Nos
SIX MONTHLY	SOP Nos
ANNUALLY	SOP Nos

PROGRAM PREPARED BY:	DATE PREPARED:
PROGRAM CHECKED AND AUTHORISED BY:	DATE AUTHORISED:

Continues page 3

MODEL PAGE
MACHINE LOG AND DIARY

RECORD OF WORK DONE				
DATE	WORK DONE	DONE BY	CHECKED BY	COMMENTS

PROTOCOLS

Includes:

Acceptable Quality Levels (AQL)

How to apply for a Production Licence

Personal Hygiene

Sampling

Laboratory Practice

Complaints and Product Recall

Validation of Balances

Pre Start-up Procedure

House Cleaning

PROTOCOL - ACCEPTABLE QUALITY LEVEL (AQL) SAMPLING INSPECTION CHART.

(Simplified and adapted for the use of Pharmaceutical Industry in Syria from UK publication DEF 131 A, HMSO London)

Explanation.

AQL: The Acceptable Quality Level is the method employed to determine the sample size to be taken from any Batch Size ranging from units to 150,000 units. In 8 columns, the chart lists AQLs from 0.1% up to 2.5%.

n: This symbol identifies the number of samples to be taken from a batch of the size shown.

P: This symbol identifies the number of non - complying items from the sample which still allows the entire batch to be classed as ACCEPTED.

F: This symbol identifies the number of non - complying items from the sample which will result in the entire batch being REJECTED.

Examples.

Assume that a consignment of 10,000 Aluminium ointment tube has been received from a supplier and that the user has set an AQL of 0.4%, then, entering the table in the Batch Size row 3201 - 10,000, and column for 0.40%, it is clear that the required sample size is 200 tubes. Reference to the Company's in - house standard for Aluminium tubes may indicate a specific dimensional requirement for the concentricity of the threaded neck; consequently the sampled tubes would be examined in this dimension. If there are found to be not more than 2 tubes which fail to comply then the entire batch will be ACCEPTED. If, however, there is found to be more than 3 tubes which fail to comply, then the entire batch will be REJECTED.

As a second example, assume that 500 bags of an excipient have been received and an AQL of 1.5% has been set; then, entering the Table in the Batch Size row 251 - 500 and the column for 1.5% then it is clear that a sample of 50 bags should be examined ; if not more than two bags are found to be substandard then the entire batch will be ACCEPTED, however, if three or more bags are found to be substandard, then the entire batch of 500 bags will be REJECTED.

Responsibility for establishment of AQLs

In the first example given above, the purpose of the AQL is to ensure that the tubes are of sufficient accuracy to be run on an automatic tube filling/capping machine in the production department of the factory; thus the AQL would be agreed between the Production Controller and the Quality Controller and monitored by QC.

In the second example, however, the standard may be Official or Pharmacopoeial, in which case the Quality Controller alone will be responsible for implementing the requirements of the AQL

SIMPLIFIED AQL SAMPLING CHART

(Ref. DEF 131A HMSO London England)

	AQL. 0.10%			AQL 0.15%			AQL 0.25%			AQL 0.40%			AQL 0.65%			AQL 1.00%			AQL 1.5%			AQL 2.5%		
BATCH SIZE UNITS	N	P	F	N	P	F	N	P	F	N	P	F	N	P	F	N	P	F	N	P	F	N	P	F
2 - 50	ALL			ALL			ALL			32	0	1	20	0	1	13	0	1	8	0	1	5	0	1
50 - 90	ALL			80	0	1	50	0	1	32	0	0	20	0	1	13	0	1	8	0	1	5	0	1
91 - 150	125	0	1	80	0	1	50	0	1	32	0	1	20	0	1	13	0	1	32	1	2	20	1	2
151 - 250	125	0	1	80	0	1	50	0	1	32	0	1	20	0	1	50	1	2	32	1	2	20	1	2
251 - 500	125	0	1	80	0	1	50	0	1	32	0	1	80	1	2	50	1	2	50	2	3	20	1	2
501 - 1200	125	0	1	80	0	1	50	0	1	125	1	2	80	1	2	80	2	3	80	3	4	32	2	3
1201-3200	125	0	1	80	0	1	200	0	2	125	1	2	125	2	3	125	3	4	125	5	6	50	3	4
3201 - 10,000	125	0	1	18	0	1	20	0	2	200	2	3	200	3	4	200	5	6	200	7	8	80	5	6
10,001 - 35,000	500	1	2	315	1	2	315	1	3	315	3	4	315	5	6	315	7	8	315	10	11	125	7	8
35,001 - 150,000	500	1	2	500	2	3	500	2	4	500	5	6	500	7	8	500	10	11	500	14	15	200	10	11

PROTOCOL

HOW TO APPLY FOR A PRODUCTION LICENCE

Background:

* It is not lawful for any person to manufacture, wholesale, sell, supply, or deal in medicinal products unless they are in possession of a valid licence relating to the products.
* A Production Licence is a legally binding document which authorises manufacture, or processing of the product identified on the licence, by the authorised person, at the nominated location. Transfer of licences is not permitted.
* A Production Licence is issued for a specific product/strength/packaging format, variation of any of the conditions of the licence are not permitted.
* Any variations from the conditions of the original licence must be advised in writing to the Licensing Authority **before** the variation is incorporated into the product; the Licensing Authority has the right to re-evaluate the modified product and may require a new product submission.
* Product Licences are issued by the Licensing Authority for a period of up to five years; a licence will not automatically be renewed at the expiration of its lifetime. The Licensing Authority may grant, refuse, revoke, suspend or vary the terms of a licence. If a licensee contravenes the terms of a licence, a notice of suspension or withdrawal of the licence may be issued by the Authority. Contravention of the terms of a licence include but are not restricted to :-
    1) giving false or misleading information
    2) contravention of the terms of the licence
    3) failure to meet specific standards
    4) failure to provide required information
    5) contravention of labelling standards
    6) incorrect marking of a carton
    7) substitution or variation of active materials or excipients
* When a licence, or a licence application, is refused or withdrawn, the Authority will provide written notification of the reason(s) for the action. The Licensing Authority may require a licensee, or an applicant for a licence to make representation in writing or to appear before the Authority to provide reason why the licence should be issued.

Definitions:

Product, a formulated, processed or assembled item intended for human or animal treatment, including medicaments, cosmetics, foods, and devices.

Licence, a legally binding document issued by the Licensing Authority to a nominated manufacturer, at a specific location, for the processing, assembly or dealing in a specified product.

Application Fee, the prescribed fee which must accompany any application for a new licence or re-issue of an existing licence; the Application Fee is determined by the Licensing Authority and may be varied from time to time by the Authority who will advise manufacturers in writing of the current system of fees.

Scope:

This SOP serves to inform prospective licensees of the steps which must be followed when applying for a Production Licence relating to any medication, cosmetic,device, or formulated food intended for human or animal treatment.

Procedure:

1) Complete the Licence Application Form in all details.
   * Name and address of the applicant
   * The period for which the licence is required where it is for less than five years
   * A statement of the activities to be covered by the licence
   * The intended market for the product (eg domestic/export)
   * A statement of the intended use of the product (eg for administration to human beings, for administration to animals, for use as an ingredient in the preparation of a substance or an article which is to be administered to humans or to animals for a medicinal purpose etc.)
   * A statement of the manufacturing or assembling operations including equipment and environmental conditions.

2) The name or proposed name under which the product will be sold or supplied.

3) A description of the product and its packing specification; i.e. a PRODUCT PROFILE.

4) A statement of the qualitative and quantitative composition of the product covering all active constituents, all colouring matter, flavours and perfumes.

5) A statement of all other materials which were employed in the manufacture of the product, including transient materials such as granulating fluids which may not appear in the final product.

6) In respect of each constituent, whether active or not, the approved name or monograph name. (where there is no approved or monograph name, the non-proprietary designation or other descriptive name by which it can be readily identified). Where appropriate the Official Monograph may be given in stead of a specification.

7) A statement of any precautions which must be observed during the manufacturing or packing operations to control the quality of the finished product.

8) The identity of the person within the manufacturing company who will be responsible for deciding whether the product is fit for sale.

9) In the case of ALL materials used in the manufacture of the product, a statement of the testing procedures employed to ensure that those materials comply with the nominated quality standards.

10) In the case of therapeutically active materials, a statement of the methods employed to ensure that the materials comply with the nominated standards of efficacy and availability in the finished product.

11) A statement of the method employed to ensure uniformity of active substance throughout the product.

12) Data supporting the Expiry Date, and storage conditions recommended for the product.

13) A description of the containers to be used for the product and any special directions for transportation, shipment, or storage.

14) Data on any known or anticipated incompatibilities of any component of the product.

15) Particulars of the method of administration of the product.

16) Particulars of the recommended dosage.

17) Any directions related to contra-indications, or warnings to be included in package labelling or leaflets.

18) Copies of any pre-clinical work, trials, experimental or biological studies, references to any relevant publications, clinical trials which may have a bearing on the safety or efficacy of the product.

19) A specimen or mock-up of the labelled container or package in which the product will be sold, together with any inserts, or leaflets which will be included in the final packing.

NOTE

The foregoing SOP is based upon the Licensing Requirements current in Australia and in UK, augmented to meet the special requirements of the pharmaceutical manufacturing/Licensing process in Syria.

PROTOCOL

PERSONAL HYGIENE.

1) PURPOSE.

1.1 In the handling of pharmaceuticals, personal hygiene is of the greatest importance. The human body is probably the most serious source of contamination in the factory, and it is one of the most difficult to control.

1.2 Contamination from air, water, and machinery can be controlled by good design and engineering; human contamination can be controlled only by paying strict attention to the hygiene standards established by management.

1.3 Human contamination has two principal sources:-
a) skin flakes &
b) hair.

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

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

Particles 0.3 microns or larger.

Source: Design and Operation of Cleanrooms : Austin Dr. P.

1.5 The most important methods of reducing human particulate contamination include:-
a) limit the number of staff working in critical areas to the minimum required to do the job properly.
b) provide and use appropriate protective clothing.
c) install and implement the highest standards of personal hygiene.
d) design and install efficient work practices which reduce operator movement to the minimum.

1.6 Achievement of the above demands a serious commitment from the company and from each individual employee, rigorous supervision from management is imperative.

2) SCOPE.

2.1 This Protocol applies to ALL employees and visitors to production, packing and laboratory operations.

3) RESPONSIBILITY.

3.1 Responsibility for preparing this Protocol, for design and implementation of SOPs, and implementing the policy is the responsibility of the Production Controller.

3.2 Responsibility for controlling the activities of employees is with each Departmental Head.

3.3 Responsibility for monitoring the efficacy of the policy, performing plate counts etc. is with the Quality Controller.

4) GENERAL QA GUIDELINES.

4.1 The factory operator shall provide appropriate protective clothing and footwear for each employee working in areas which may have an effect on the quality of the product. The factory operator shall provide training on the correct utilisation of the clothing.

4.2 The company and the employees shall agree on the most suitable system for laundering the factory clothing; it is however the responsibility of the factory operator to ensure that the clothing is properly laundered; wherever possible laundering shall be an in-house activity.

5) SPECIFIC REQUIREMENTS.

5.1 Only factory clothing and footwear shall be worn in the factory; this requirement applies to ALL persons in the factory, including visitors.

5.2 Food and drink shall not be brought into production areas, stores, or laboratories..

5.3 Smoking is forbidden in the factory.

5.4 Showers must be taken at least once per day BEFORE entering clean areas.

5.5 Cleanroom staff leaving their workstation shall go through the complete de-gowning procedure; before re-entering the cleanroon staff shall complete the entire scrub-up and gowning procedure.

5.6 Any employee having a skin infection or abrasion, a hair or finger nail infection, common cold, intestinal, respiratory or diarrhoeal disease shall report the condition to the supervisor. Such employees shall be sent home or given alternative, non-critical work until the condition is completely cured.

5.7 Management shall provide regular medical checks for all employees who regularly come into contact with product. These medical checks shall be at least on an annual basis but for employees in especially sensitive areas such as sterile rooms or steroid/antibiotics processing the medical checks shall be more frequent.

PROTOCOL

SAMPLING PROCEDURE

1) PURPOSE.

1.1 Correct sampling procedures are of vital importance in the development of the Quality Assurance profile of a product.

1.2 Correct sampling procedures imply that the samples taken are statistically representative of the batches of materials from which they are taken.

2) SCOPE.

2.1 This Protocol applies to ALL consignments of Raw and Packing Materials received.

3) RESPONSIBILITY.

3.1 The responsibility for preparing this Protocol, for design, updating & implementing SOPs and monitoring conformity rests with the Quality Controller.

4) GENERAL QA GUIDELINES.

4.1 Sampling instructions shall be in writing and provide the following information:-

a) the method of sampling
b) the equipment to be used
c) the quantity of sample to be taken
d) instructions for the subdivision of the sample
e) the type of container to be used for keeping the sample and the details to be provided on the container label.

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

4.3 Special precautions are required to be observed whenever samples are taken from sterile, highly potent, or toxic substances. (For example antibiotics, steroids, anti-neoplastics)

4.4 A common cause of spoilage in materials results from improper closing of containers which have been opened for sampling. The responsibility for the proper sealing of sampled containers rests with the sampler.

5) SPECIFIC REQUIREMENTS.

5.1 Each sampled container shall be clearly identified with an adhesive label giving the following information:-

a) the name of the material
b) the manufacturer's Batch Number
c) the date the sample was taken
d) the signature of the sampler
e) an instruction that no further production activity can take place until the material has been released by QC.

5.2 Every container which has been opened for sampling shall be effectively resealed in such a manner as to prevent the access of contamination or spoilage due to atmospheric conditions.

PROTOCOL

LABORATORY PRACTICE

1) PURPOSE.

1.1 The facilities of comprehensive laboratory facilities and practices are imperative to the safe and efficient production of pharmaceuticals.

1.2 There is a wide range of interpretations of what constitutes appropriate facilities and practices; this Protocol provides guidance on the minimum standards acceptable for pharmaceutical industry laboratories.

2) SCOPE.

2.1 This Protocol covers the facilities and practices appropriate for the laboratory control of:-

a) Raw materials
b) Intermediates
c) Finished products
d) Packing materials

2.4 Testing methods include:-

a) physical
b) chemical
c) biochemical
d) microbiological
e) biological

3) RESPONSIBILITY.

3.1 The responsibility for preparing this Protocol, for design, updating, and implementing SOPs rests with the Quality Controller.

4) GENERAL GLP GUIDELINES.

4.1 Control laboratories shall be designed and equipped to fully support the operations performed in them.

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

4.3 Chemical, microbiological, and biological laboratories shall be separated from each other and from production areas.

4.4 Animal houses shall be completely segregated from other laboratories and from production areas.

4.5 Sensitive laboratory equipment shall be properly protected and located so as to function correctly.

4.6 Physical equipment shall be regularly validated and serviced by trained technicians. Equipment logs shall be kept up to date, showing work done and dates for follow - up service visits.

4.7 Any equipment which is malfunctioning or overdue for service shall be withdrawn from operation.

4.8 Operating instructions, and manufacturer's handbooks for all equipment shall remain in the laboratory, and be filed for easy access.

4.9 Where possible, analytical methods shall include a stage to verify that equipment is functioning correctly.

4.10 Laboratories and equipment shall be maintained in clean and hygienic condition at all times.

4.11 Laboratory personnel shall wear clean and effective protective garments appropriate to their function; whenever hazardous materials are being used, specific protective garments shall be employed.

4.12 All analyst's records and calculations shall be kept in a bound book together with the basic data from which calculations and test results were derived; such records shall be maintained for at least three years after the date of the final entry. Any corrections which are made shall be entered in such a manner that the original information remains visible.(i.e. blanking or whiting - out is not allowed.) Explanation shall be provided for the necessity of the correction.

4.13 Whenever contract analysis is performed, the nature and extent of the work shall be agreed, and formalised between the parties; signed Protocols of all test methods shall be available for inspection in the laboratories of both parties; the methods and volume of sampling shall be agreed and formalised as shall the retention of keeping samples and test records.

4.14 Whenever contract analysis is performed, the responsibility for the quality of the final product rests entirely with the principal.

PROTOCOL

COMPLAINTS AND PRODUCT RECALLS.

1) PURPOSE.

1.1 A product Complaint or a Recall represents a serious situation for a manufacturer of pharmaceuticals, and, as such, a complaint or a recall shall be handled in a prompt and efficient manner in order to minimise the potential risks to users of the product.

1.2 The following protocol establishes the principles which shall be incorporated into a factory "Complaints and Recall procedure".

2) SCOPE.

2.1 This Protocol applies to ALL products supplied by pharmaceuticals manufacturers, irrespective of the therapeutic classification, dosage form or administration route.

2.2 This Protocol also applies to DEVICES which are supplied for use in human or animal conditions, eg. prostheses, dressings, syringes, giving sets, sample containers etc.

3) RESPONSIBILITY.

3.1 The responsibility for preparing this Protocol, for design, updating and implementation of SOPs, and monitoring conformity, rests with the Quality Controller.

4) GENERAL QA GUIDELINES.

4.1 All complaints relating to the quality of a pack or a product, from whatever source, shall be immediately channelled, in writing to the Quality Controller, in order that a full picture of the status of complaints may be assembled and any trends revealed.

4.2 A complaint may lead to the need for a product recall; all actions taken as a result of a complaint shall be prompt and in accordance with written procedures; such procedures shall be clearly understood by ALL persons concerned with the product recall.

4.3 Records of complaints shall be regularly reviewed by the Quality Controller, together with the Production Controller and the General Director. Specific problems shall be addressed immediately.

4.4 A written Recall Procedure shall be capable of implementation at any time, day, night and holidays included. Persons responsible for initiating a recall include:-

the Quality Controller
the Production Controller
the General Director
or their appointed and trained nominees.

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

4.6 Having designed a Recall Procedure, the Quality Controller shall test it for practicality and efficiency; the procedure shall be reviewed from time to time, at least annually. In the event of variations to the procedure, or personnel changes, thorough training shall be provided in the implementation of the Recall Procedure.

4.7 In the event of a Recall becoming necessary, it is the responsibility of the authorised persons in the Company to advise the Ministry of Health, Directorate of Drug Control. Additionally ALL drug distributors, and agents shall be instructed to quarantine their stocks, and recall goods which are in the market. Any defective material which is in transit at the time of the recall shall be immediately quarantined when it reaches its destination.

5) SPECIFIC REQUIREMENTS.

5.1 ALL recalled materials shall be immediately placed in quarantine pending investigation and disposal instructions.

5.2 A notification of Recall shall include:-

a) product name, strength and Batch Number,
b) nature of the defect,
c) action to be taken,
d) urgency of the action to be taken,
e) warning to the recipient to retain the Recall Notification in order that goods in transit may be checked.

PROTOCOL

VALIDATION OF BALANCES.

1) PURPOSE.

1.1 The use of one or more balances is mandatory in the manufacture of pharmaceuticals; the accuracy of each instrument shall be regularly validated and recorded.

1.2 This Protocol establishes the principles which shall be observed in the validation process.

2) SCOPE.

2.1 This Protocol applies to ALL balances employed in Stores, Production Areas, and laboratories.

3) RESPONSIBILITY.

3.1 The responsibility for preparing this Protocol, for design, updating and implementing SOPs and monitoring conformity rests with the Quality Controller.

3.2 Department Heads shall undertake the day-to-day validation of balances in their departments according to the instructions provided in the relevant SOPs.

4) GENERAL QA GUIDELINES.

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

4.2 Each balance shall have its own Record Card or Logbook which carries the identical number to that marked on the instrument itself, and which remains, at all times, with the instrument. The card shall at all times be available for inspection.

5) SPECIFIC REQUIREMENTS.

5.1 Validation of balances shall be divided into three segments:-

a) for daily attention by Departmental Heads.

b) for weekly attention by QC staff,

c) for six monthly service by manufacturer's agent.

5.2 Daily activities shall include:-

a) assurance that the instrument and its surroundings are clean, fit for use and not influenced by external conditions.

5.3 Weekly activities shall include:-

a) as above and reading correctly with a standard weight .

5.4 Six monthly activities shall include:-

a) as above, plus checking accuracy with a range of weights which represent the working range of the balance.

b) general cleaning and service as necessary.

5.5 On completion of the several activities detailed in 5.2, 5.3, and 5.4, above, the operator shall make an appropriate entry, signed and dated in the balance Record Card or Logbook.

5.6 If the balance conforms to the required standards of accuracy it may be used for any weighings within its capacity; failure to conform shall result in the balance being taken out of service until the fault is corrected and the instrument once again conforms to standard.

PROTOCOL

PRE START-UP PROCEDURE.

1) PURPOSE.

1.1 Before any manufacturing or packing operation can commence the following Protocol shall be observed to ensure that QA is being maintained.

2) SCOPE.

2.1 This Protocol applies to ALL manufacturing and packing operations.

3) RESPONSIBILITY.

3.1 The Production Controller is responsible for the preparation of this Protocol; for developing, updating, and implementing the SOPs which are relevant to each specific Department.
3.2 The Department Head is responsible for implementing the requirements of the relevant SOPs on a routine daily basis.
3.3 The Quality Controller is responsible for ensuring that the requirements of this Protocol have been fulfilled before authorising any production or packing activities.

4) GENERAL QA GUIDELINES.

4.1 All work areas and surroundings shall be free from any material not specifically concerned with the current batch. Particular attention shall be given to Raw or Packing Materials relating to a previous day's activities.
4.2 All controllers, instruments, and warning devices shall be calibrated and functioning correctly.
4.3 All machine guards, and covers shall be undamaged and in place.
4.4 Each piece of machinery or equipment to be used in the manufacturing or packing operation shall carry a sticker to confirm that it has been cleaned, sanitised, and serviced as appropriate.

4.5 Each piece of equipment to be used in the manufacture or packing operation shall be clearly identified with relevant details of the batch in process.

4.6 All personnel working with the product, and supporting staff, shall be appropriately dressed in protective clothing; garments shall be clean, in good repair and correctly fastened.

4.7 All personnel in contact with the product shall confirm verbally that they have understood the Protocol on Personal Hygiene and are free from any condition which may be prejudicial to the product.

5) SPECIFIC REQUIREMENTS.

5.1 Conformity to the requirements of this Protocol and the SOPs which derive from it shall be recorded in a "PRE START-UP" diary, which is signed, and dated, as being correct, jointly by the Quality Controller and the Production Controller or their nominees.

PROTOCOL

HOUSE CLEANING

1) PURPOSE.

1.1 Manufacture of pharmaceuticals is a very demanding activity. Conditions of air, water, and engineering have been designed to minimise all risks from operator to product and from product to operator.

1.2 The ambience in which pharmaceuticals are processed changes according to the work being performed in it. This may result in number of risks to the quality of the product, (for example contamination with micro-organisms, with non-related chemicals, or with human skin scales, hair etc.). Such risks must be prevented; prevention is accomplished mainly by good housekeeping.

1.3 The purpose of this Protocol is to establish and formalise the fundamentals of good housekeeping.

2) SCOPE.

2.1 This Protocol relates to all housekeeping activities in production areas, stores, and laboratories.

3) RESPONSIBILITY.

3.1 The Production Controller is responsible for the preparation of this Protocol. for developing, updating, and implementing the SOPs which are relevant to each specific Department.

3.2 The Quality Controller is responsible for ensuring that the standard of housekeeping attained is of an acceptable level.

4) GENERAL QA GUIDELINES.

4.1 The performance of the requirements of this Protocol shall be delegated to a nominated and suitably trained SUPERVISOR.

4.2 The training shall be reviewed and updated every six months.

4.3 The supervisor shall be provided with a detailed, written Job Description which shall be explained verbally to the supervisor by the Production Controller.

4.4 The supervisor shall be provided with sufficient appropriate staff and equipment to fulfil the requirements of the Job Description.

4.5 The supervisor shall maintain a DAILY CLEANING LOG which is monitored and signed by the Production Controller each week. All deficiencies such as damaged woodwork, broken windows, non-functional doors etc. shall be recorded in the Cleaning Log.

4.6 The Cleaning Log shall clearly identify the cleaning and sanitising methods employed.

5) SPECIFIC REQUIREMENTS.

5.1 All toilets, showers and wash-hand basins shall be cleaned and sanitised daily.

5.2 All lockers and changing rooms shall be cleaned out daily, employee's personal lockers shall be regularly cleaned, personal effects shall not be allowed to accumulate. Food, drinks, cigarettes etc. shall not be placed in changing rooms or personal lockers.

5.3 All waste paper, plastic covering, and residual materials from previous production batches shall be removed BEFORE further production activity shall commence.

5.4 All horizontal surfaces, window ledges, tops of doors etc. shall be cleared of extraneous materials DAILY.

5.5 All walls shall be washed and sanitised WEEKLY.

5.6 All black and grey area floors shall be vacuum cleaned DAILY.

5.7 All white areas, clean rooms etc shall be washed DAILY with detergent solution and sanitised.

5.8 Sanitising agents shall be varied WEEKLY to minimise the development of resistant micro-organisms.

5.9 In Stores, Air-conditioning plant rooms, and other warm, dark, moist or humid places great care shall be taken to prevent contamination by insects &/or vermin. Goods shall be stored on pallets and all rubbish shall be removed on a regular basis; the area shall be decontaminated regularly with an appropriate aerosol insecticide taking care to avoid the insecticide coming into contact with raw or packing materials. Vermin bait shall be laid and its locations mapped; baits shall be regularly inspected and replaced as necessary. When bait has been disturbed by vermin, the dead vermin shall be located and disposed of safely.