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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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DU/SYR/92/008/11-12 and 11-13

SYRIAN ARAB REPUBLIC

*Technical report: Findings and recommendations**

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

Based on the work of G.Szepesi
UNIDO consultant

Project Manager; Z. Csizer, Chemical Industries Branch

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* This document has not been edited.

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SUMMARY

As a continuation of the project DU/SYR/92/008, a follow-up mission was organized and the writer was fielded aiming to clarify all issues related to purchasing and storage of pharmaceutical raw materials including expiry dates, in-house expiry dates, retesting dates of raw materials, as well as their correlation with the expiry dates of formulated products.

During the previous mission the writer recommended to:

- change the purchasing system to be replaced by direct partnership concept,
- introduce the JIT (Just-in-time) and MSR (Minimum stock requirement) concepts into the purchasing and storage practice of the companies,
- introduce the in-house expiry date and retesting date concept into the routine practice of the storage of raw materials,
- performing accelerated and re-examination stability tests to determine the precise in-house and retesting dates for raw materials, etc.

The present mission served to elaborate these terms and to give practical advices for their introduction.

As a result of this mission, the Ministry of Health accepted and recommended for use the system, and the material containing the most important basic principles have been prepared and it is waiting for the acceptance and final approval of the Technical Committee.

During his mission, the writer presented a lecture entitled: "Expiry dates, In-house expiry dates, Retesting dates and their relation to stability testing" in the Training Course III on QA/GMP concerning Sterile Pharmaceutical Manufacture held in Aleppo on 26-27 September 1996, as well as in a Seminar held in the Ministry of Health in Damascus on 1st October 1996. On both lectures, representatives from private and public sector companies and the Ministry of Health were present.

Brief summary of Good Storage Practice (GSP) has been presented for Thameco's staff, introducing the most important practical aspects. Special emphasis was given to the storage and dispensing of antibiotics. Draft copies of the drawing of the warehousing system as well as the reconstruction of the antibiotic production sections including storage and dispensing rooms, air lock systems and changing rooms have been prepared together with the Production Manager and Technical Director, which may serve as a good base for reconstruction of the presently existing production areas (antibiotic dry syrup and capsule sections).

Real problem exists at Thameco regarding the Central Changing Room, where approximately 600 workers (400 women and 200 men) must change the clothes practically at the same time. The drawing prepared together with the Thameco staff was re-evaluated and reconsidered, preparing such drawing in a new place which can satisfy the GMP requirements. The drawings

of the new Central Changing Room have been submitted for approval to the Industrial Ministry.

Special practical trainings have been performed for:

- National Laboratory for Quality Control and Assurance in context of stability testing,

- Thameco staff regarding water system, batch records used in the production area, SOPs for dry syrup section, etc.

Two main topics closely connected with sterile Drug Manufacture were presented in the forms of lectures during the mission:

(a) Hygienic classes - requirements and recommendations.
(b) Validation of steriliser (autoclave/kinetics of microbial death).

Both lectures were presented in the Training Course III on QA/GMP concerning Sterile Pharmaceutical Manufacture held in Damascus on 17-18 September 1996, as well as in Aleppo on 25-26 October 1996. On both lectures, representatives from private and public sector companies and the Ministry of Health were present.

On 27 September 1996 the writer presented a workshop for about 35 participants at Thameco Serum Factory in Aleppo on the design, construction, installation and commissioning of aseptic/sterile suites in pharmaceutical manufacturing facilities. Among several other topics two major themes have been discussed in details:

- clean room concept including HEPA filtration, on going control and regular preventive maintenance, validation and re-validation of supplying systems and microbiological issues, such as hygienic monitoring system, warning and action limits, personal hygiene, etc.

- clothing rules and special preventive rules regarding aseptic clothes including demonstration.

I. Quality Requirements for Pharmaceutical Raw Materials

A. Expiry date - in-house expiry date - retesting date

The main goal of the first mission of the writer in August-September 1995 was to study the purchasing system of the Syrian pharmaceutical industry with special regard to the correlation between prices, quality and storage conditions of raw materials in the warehouse.

The most important problems connected to this study were as follows:

a. Purchasing system and its contribution to storage conditions, quality and applicability of the raw materials to be used for pharmaceutical production.

b. Standardization of quality of raw materials, including the establishment of purchasing and expiry qualities, expiry date and retesting date problems, and its correlation with the quality of finished product.

Problems found could be classified into three major groups:

1. Quality related problems

   a) Quality of the raw materials are changing from time to time, and from vendor to vendor (lack of consistency).

   b) By using the purchased raw materials the quality of the formulated products fluctuates.

2. Problems related to the formulation technology

   Formulation technology used for the production of finished product is uncertain, and seems to be a function of actual quality of the purchased raw material.

3. Quantity related problems

   a) The storage rooms are filled up with raw materials.

   b) The companies cannot really handle the problems related to the storage time (expiry date) of raw materials.

The most important reasons and consequences can be characterized and summarized as follows:

1. Majority of the problems, reasons and consequences relates to three areas:

   - purchasing of raw materials is tenderized (vendor is selected by the Committee, price of the raw material will dominate at the vendor selection),

- quality and grade of raw materials are not adequately characterized (purchasing quality is not well determined, special requirements relating to formulation technology and possible decomposition of raw materials under the storage are not considered),

- expiry date of raw materials is not adequately handled (in-house expiry date and retesting date system does not work).

2. QC does not effectively work due to the lack of qualified persons and instruments.

3. QA is not established yet.

The most important recommendations can be summarized as follows:

1. Purchase of raw materials

The recommended system includes two principles:

- using the direct partnership concept including vendor selection, vendor certification and partnership based on long term contracts, for purchasing raw materials,

- using the JIT (Just-in-Time) and MSR (minimum stock requirement) concepts as tools, to exclude expiry date problems and to minimize the stock in the storage rooms.

2. Standardization of the quality and grade of purchased raw materials

The analytical test specifications of raw materials should be extended with special tests considering:

- formulation technology used for production;

- decomposition products formed during the production of finished products, and the storage of the raw material, as well;

- safety of the use of the formulated products.

These data, together with the pharmacopoeial requirements are the basis to establish purchasing quality.

Due to lack of the suitable analytical background, the application of a UNIDO consultant specialized in this field as well as in the field of stability testing was highly recommended.

To furnish the QC laboratories with the necessary number of highly sophisticated instruments (as HPLC) was also recommended.

3. Expiry date problems (expiry dates, in-house expiry dates, retesting dates)

Introduction of in-house expiry date-retesting date system at the pharmaceutical companies in Syria was highly recommended. The necessary instructions have been given. Important analytical task is to establish the expiry quality of the raw materials.

4. QA/QC problems

Introduction of QA function to the public sector companies (private sector has it) is absolutely necessary and recommended.

Similarly important task is to strengthen the QC laboratories with analysts trained in the field of separation methods.

When the writer started with the new mission in September 1996, firstly he clarified what had happened during the first year. Which parts of recommendations have been realized.

Summarizing his experiences, the following situation was found:

1. The purchasing system was the same, practically the same situation existed as in 1995, however, there was a confusion by mixing the terms of expiry date of raw material with the expiry date of finished product. (The writer in 1995 has not treated in detail the expiry date of finished product, only those parts which are closely related to the expiry date of raw materials.) Therefore, one of the main objectives of the writer during his mission in 1996 was to re-clarify and re-discuss these issues, to solve the confusions related to the expiry dates of raw materials and finished products.

2. The in-house expiry date and retesting date system has not been introduced neither at the private nor at public sector companies. (Thameco started to introduce the system, but it needs time.)

3. QA at the public sector companies is not presently functioning (at Thameco, as the writer was informed, the organisation has been started).

4. QC laboratories are practically in the same situation as before, with the exception that at Thameco the HPLC equipment was repaired and it works.

The following activities have been made to overcome the difficulties in point 1 above:

- The topic was discussed in detail at National Drug Quality Assurance and Research Laboratory.

- Detailed discussions and demonstration in the Ministry of Health.

- Detailed discussion of the material prepared for the members of Technical Committee in the National Drug Quality Assurance and Research Laboratory.

- Introduction of the topic for the members of Technical Committee in the Ministry of Health in the presence of the Minister and Deputy Minister.

The material, which is obtained by the members of Technical Committee, and now is waiting for the final approval, contains the most important basic principles and recommendations given by the writer. The direct partnership concept, JIT and MSR concepts are accepted, the in-house expiry date and retesting date system will be introduced in the daily practice of the pharmaceutical companies, and in this material the expiry date of finished products is also clarified replacing the old calculation system which included the expiry date of the used raw material with a new system, where the expiry date of finished product is independent from the age of the used raw material.

After the discussions the writer has been requested to present lectures about this topic, to introduce the new system for the colleagues working in the pharmaceutical industry in Syria, and to write the lecture in English for publication.

B. Other activities

1. Outline of Good Storage Practice (GSP)

To improve the GMP status of public sector companies the following outline has been given introducing the GSP principles and based on the material prepared during the previous mission of the writer.

a) To improve the sampling procedure.

Suitable space should be established for sampling of raw materials, which can be adequately cleaned, supported by minimum air extraction terminal, and SOP's are available for sampling.

b) To improve the documentation system.

The following basic documentations should be used in the warehouse:
- Material receiving card
- BIN card
- Sampling chart

c) Introduction of arrival number system for raw materials without batch number

Arrival number system should be introduced for all raw materials which has no batch or lot numbers, to follow the FIFO rules.

d) To introduce inspection check list for raw material handling in the warehouse for inspection and self inspection.

Inspection check list for control of handling of raw materials from the arrival until dispensing has been collected and introduced during a joint inspection with the National Drug Quality Laboratory for inspecting and self-inspecting pharmaceutical companies.

e) To prepare the necessary SOP's for warehousing system.

A list of SOP's required and to be available in the warehouse has been collected, and recommended to prepare them as soon as possible.

2. Sampling rules

Basic sampling rules are as follows:

a) The analytical and retained samples should be taken at the same time in a quantity which is enough to complete minimum five full analytical tests.

b) The expiry date of the retained samples is: expiry date of raw material + 1 year.

c) In respects to sampling, the ordered raw materials can be divided into three groups:

i) Materials, which are not allowed to sampling in the storage room. Mostly the sterile products belong to this group to avoid any contamination.

The analytical and retained samples can be produced:

- in the sterile room, under aseptic conditions, with sterile accessories (glass, spoon, etc.) prior to weighing under similar conditions than at the working,
- in the sterile room, after weighing from the rest of materials,
- by the supplier, jointing the sample to the batch.

ii) Materials, which can be sampled in the storage room under specific conditions.

The following materials belong to this group:

- materials, which are hazardous for the workers and/or the environment (antibiotics, steroid hormones, anticancer drugs, strong acids and base, etc.)
- materials, which are very sensitive to the environmental conditions (atmospheric oxygen, humidity, light exposure, such as vitamins, flavour and colourising agents, etc.), and the quality of raw material (QRM) may be affected by the sampling.

Protection of the workers (first case), or the materials from the environment (second case) is necessary during the sampling.

iii) Materials, which can be sampled without problem.

Written instructions (SOP) dealing with the sampling procedures must be produced for all three cases including:

- objective
- scope (and limitations)
- responsibilities
- construction of sampling chart, filling instructions
- materials, glass ware and other accessories required for sampling including their cleaning, packaging and storage,
- personnel, their qualification and training
- precautions,
- clothing rules,
- sampling conditions (place of sampling, cleaning, air handling, etc.),
- visual inspection of the packaging of raw materials, including the control of the labels,
- number of sample, randomization rules,
- amount of the analytical and retained samples,
- instructions for opening and reclosing of packaging units to be sampled,
- detailed description of the sampling process, separating the materials according to the physical state of the sample (liquid, solid, gaseous, etc.),
- labelling instructions for all packaging units of the batch to be sampled after sampling,
- instructions for closing the sample,
- labelling instructions for the analytical sample,
- labelling instructions for retained samples,
- storage conditions for the analytical and retained samples.

iv) The sampling place in the warehouse has a great importance, advantageously it is made in a sampling booth. If it is not available, a separate clean place can be used for this purpose, which possesses air extraction terminal.

v) Important rules, the sampling procedure:

- should provide samples characteristic to the quality of the individual containers and to the batch, as well,
- should not affect the quality of the raw materials,
- should not contaminate the environment or the other materials,
- should not cause any damage in the packaging materials of the containers,
- homogeneity of the batches should be established.

3. Proper documentation in the storage rooms

Proper documentation system in the warehouse includes the appropriate documentation of the following steps:

- Receipt of the raw material
- Quarantine rules relating to the received materials
- Sampling rules
- Release of the raw materials
- Positioning of the raw materials
- Raw material delivery

The following documentations are required:

- Material receiving card system
- Arrival number system
- Bin cards system

Material receiving card

Material receiving card is one of the most important document related to the arrival of any raw materials. The card contains the following data:

- name of the material
- quality and grade
- batch or lot number
- arrival number
- manufacturing date
- expiry date
- total quantity
- number and net weight of packaging units
- vendor
- date of arrival
- receiver signature
- result of visual control
- label control
- control performed by date and name of resp. person
- date of placing quarantine area
- receiver in the quarantine
- date of sampling
- sampling SOP number
- number of samples
- sampling made by date and signature of responsible person
- labelling made by date and signature of responsible person
- number of analytical file
- qualification made by QC laboratories
- date and signature of QC responsible person
- QA decision
- labelled by date and name of QA responsible person

- position number
- received by date and name of receiver

Arrival number system

For the materials which do not contain batch or lot numbers, respectively, arrival number should be given. The arrival number consists of four digits and the last two numbers of the years are also indicated. The arrival numbering starts with a number 0001/year in each January, and increasing in the order of the arrival of raw materials. For example the first consignment of the year has the following arrival number: 0001/95.

The arrival number should be indicated in each packaging unit of the raw material arriving in the same time.

Arrival number is product specific (not batch specific), if two or more batches of the same raw material are arriving at the same time, the same arrival number must be indicated at each batch. But, if the same batch of raw material is arriving different times different arrival numbers corresponding to the same batch of the same raw material will be indicated in the packaging units.

The FIFO principle will be considered in the following way:

- if the raw material has no batch number, first those packaging units will be delivered, which has lower arrival number,

- if two different batches of the same raw material have the same arrival number, first that batch will be delivered which has the lower batch number,

- if the same batch of the same raw material has two different arrival numbers, first that packaging units of the same batch will be delivered, which have lower arrival number.

Bin Cards

Bin Card serves to demonstrate the actual inventory of the raw material in the storage house. Each time the Bin Card is product specific not batch specific.

The Bin Card contains the following data:

In the Header

Name of the material
Quality and grade
Storage room number
Storage conditions given by the manufacturer
Storage conditions in the storage room
SOP number

In Columns

batch or lot number
arrival number
position number
date of arrival in the storage room
manufacturing date
in-house expiry date
retesting date
quantity at arrival
actual number and net weight of packaging units (not dispensed)
actual number and net weight of packaging units (dispensed)
actual total quantity
date of request for delivery
department to issue the request
issue number
quantity requested
delivery date
delivered quantity
predispensing made by date and signature of responsible person
received by signature of responsible person
remaining number and net weight of packaging units (not dispensed)
remaining quantity and net weight of packaging units (dispensed)
remaining total quantity
signature of responsible person
actual inventory

In Rows

In the next row the remaining quantities (not dispensed, dispensed and total) will be written to the columns containing the actual quantities (not dispensed, dispensed, and total).

If new batch of the same raw material arrives and is placed into the storage room, all data will be written in an empty raw leaving suitable empty space for the previous batch enough until the total quantity of this batch will disappear from the storage room, and the column for actual inventory will contain at each time the remaining subtotal. According to the FIFO principle first the previous batch should be delivered, and later on the next arrival batch.

Other important documentations should be available in the warehouse in each time:

- SOP for quarantine area
- SOP for visual inspection of the packaging units at arrival
- SOP for sampling raw materials
- SOP for cleaning sampling place
- SOP for filling of Material Receiving Card
- SOP for arrival numbering

- SOP for filling BIN Cards
- SOP for cleaning storage rooms - Housekeeping rules
- SOP for storage raw materials
- SOP for introduction in-house expiry date and retesting date
- SOP for avoiding mixing in the storage rooms
- SOP for labelling raw materials - Labelling instructions
- SOP for predispensing raw materials
- SOP for clothing in the warehouse - Clothing rules
- SOP for material transportation in the warehouse
- SOP for using and cleaning palettes
- SOP for handling hazardous materials
- SOP for handling rejected materials

Reconstruction of storage rooms for antibiotics and of antibiotic production sections at Thameco

Special emphasis was given to the storage and dispensing of antibiotics. Draft copies of the drawing of the warehousing system as well as the reconstruction of the antibiotic production sections including storage and dispensing rooms, air lock systems and changing rooms have been prepared together with the Production Manager and Technical Director, which may serve a good base for reconstruction of the presently existing production areas (antibiotic dry syrup and capsule sections).

Central Changing Room

Real problem exists at Thameco regarding the Central Changing Room, where approximately 600 workers (400 women and 200 men) must change the clothes practically at the same time. The drawing prepared together with the Thameco staff was re-evaluated and reconsidered, preparing such drawing in a new place which can satisfy the GMP requirements. The drawings of the new Central Changing Room have been submitted for approval to the Industrial Ministry.

On- the- job training

Special practical trainings have been performed for:

- National Drug Quality Assurance and Research Laboratory in context of stability testing,

- Thameco staff regarding water system, batch records used in the production area, SOPs for dry syrup section, etc.

II. Compliance with International Regulations related to aseptic/sterile areas in Pharmaceutical Manufacturing Facilities

Two main topics closely connected with sterile Drug Manufacture were presented in the forms of lectures during the mission:

(a) Hygienic classes - requirements and recommendations.
(b) Validation of steriliser (autoclave/kinetics of microbial death).

Both lectures were presented in the Training Course III on QA/GMP concerning Sterile Pharmaceutical Manufacture held in Damascus on 17-18 September 1996, as well as in Aleppo on 25-26 October 1996. On both lectures representatives from private and public sector companies and the Ministry of Health were present.

On 27 September 1996 the writer presented a workshop for about 35 participants at Thameco Serum Factory in Aleppo on the design, construction, installation and commissioning of aseptic/sterile suites in pharmaceutical manufacturing facilities. Among several other topics two major themes have been discussed in details:

- clean room concept including HEPA filtration, on going control and regular preventive maintenance, validation and re-validation of supplying systems and microbiological issues, such as hygienic monitoring system, warning and action limits, personal hygiene, etc.

- clothing rules, and special preventive rules regarding aseptic clothes including demonstration.

III. Experiences with the Training Courses organised by the Ministry of Health and WHO

During the writer's missions performed in 1995 and 1996, two different Training Courses have been attended and he presented lectures on the meetings.

The main organiser of the Training Courses was Prof. Ali Haggag (EGYPT) as the expert of WHO.

The experiences and comments of the writer with special regards to the two Training Courses held in Damascus and Aleppo in 1996 can be summarized as follows:

1. The main topic of the Courses was well selected, closely connected to the most important problem of Syrian pharmaceutical industry - sterile manufacturing.

2. Both Training Courses were well organised, with very tight programme, and the lectures and videos presented during the Courses practically covered the most important GMP issues and problems related to them.

3. Approximately 160 participants each were present in the Training Courses and the discussion sessions helped the people clarify the problems, questions and comments raised during the lectures.

4. Lecturers were selected among the Syrian colleagues, with the exception of Prof. Haggag and the writer. In the writer's opinion, this is the best way to establish a well trained staff for lecturing on GMP Courses within Syria in the future.

5. On the whole the writer received a very good impression about the Training Courses organised by the Ministry of Health and Prof. Ali Haggag.

Annex 1

JOB DESCRIPTION

DU/SYR/92/008/11-12

Post title: STC on Quality Requirements for Pharmaceutical Raw Materials

Duration: 0.5 m/m (0.2 m/m in the field, 0.3 m/m home base)

Date required: September 1996

Duty Station: Damascus

Purpose of mission: To create necessary infrastructure for sound drug industrial development and increased efficiency and self-sufficiency in the supply of quality medicines

Duties: The expert should perform the following duties:

1. To complete objectives of earlier assignments on the subject in 1995.
2. To assist in preparing an outline for Good Storage Practice (GSP).
3. To clarify issues related to stable and non-stable raw materials, their storage, their re-test, extending their expiry dates, etc.
4. To put the above in the context of GMP as well as assist to establish a numbering systems for raw materials in GMP documentation.
5. To deliver lectures and provide on-the-job training.

Qualifications: Industrial pharmacist, chemist with managerial working experience in pharmaceutical industry. Experience in developing countries is an asset.

Language : English

Annex 2

JOB DESCRIPTION

DU/SYR/92/008/11-13

Post title:	STC on Compliance with International Regulations related to aseptic/sterile areas in Pharmaceutical Manufacturing Facilities
Duration:	0.5 m/m
Date required:	September 1996
Duty Station:	Damascus
Purpose of mission:	To create necessary infrastructure for sound drug industrial development and increased efficiency and self-sufficiency in the supply of quality medicines

Duties: The expert should perform the following duties:

1. As a case study hold an in-plant workshop on design, construction, installation and commissioning of aseptic/sterile suites in pharmaceutical manufacturing facilities.

2. To deliver the same for validation and re-validation of such facilities.

3. To deliver the same for quality control techniques and maintenance applied in such facilities.

4. To deliver lectures on Validation of Sterilizer (Autoclave/Kinetics of Microbial Death) and provide on-the-job training.

Qualifications:	Industrial pharmacist, chemist with managerial working experience in pharmaceutical industry. Experience in developing countries is an asset.
Language :	English

Annex 3

PHARMACEUTICAL COMPANIES VISITED AND CONTACT PERSONS

A. Pharmaceutical companies

1. Thameco - Damascus
2. Thameco - Aleppo

B. Contact Persons

Prof. Dr. M. IAD El-Chatti	Minister	Ministry of Health
Dr. Kaukab Al Dayeh	Deputy Minister	Ministry of Health
Mrs. N. Kozak	Project Officer	UNDP Field Office
Mrs. Souad Ghoon	Director	Drug Quality Control
Mrs. Sohail Al-Hakim	Director	Pharmaceutical Affairs
Dr. Habib Abboud	Director	National Drug Quality Assurance and Research Laboratories
Ms. Rajwa Gbeily	General Manager	Thameco
Prof. Dr. Ally Haggag	Vice Dean	Tania Univ. - Egypt
Dr. Ahmad Al Chibabi	General Manager	Alfa

Annex 4

EXPIRY DATES, IN-HOUSE EXPIRY DATES, RETESTING DATES AND THEIR RELATION TO STABILITY TESTING

(Lecture presented in Training Course III on QA/GMP concerning Sterile Pharmaceutical Manufacture held in Aleppo on 26-27 September 1996, and in the Seminar held in the Ministry of Health, Damascus on 1st October 1996)

by Gabor SZEPESI

1. Expiry Date of Raw Materials

Expiry date of raw materials is one of the most frequently misused and misunderstood term. To demonstrate the confusion existing in this area, two generally used version (two extremes) are introduced as example.

According to the first version, the *expiry date* given by the manufacturer of the raw material *is absolute,* and equivalent to the time period elapsed from the date of manufacture until the quality of raw materials (used the word of *QRM* in the followings) satisfies all the requirements of Quality Test Specification (QTS), which is maximized in 5 years. Until this date the raw material can be used for production, after this date the material should be rejected.

According to the second version, the *expiry date* given by the manufacturer of raw material *serves only as guide.* QRM is retested after certain period of time, and if the QRM satisfies all the requirements of QTS the material can be further used for production of the finished product, and with several retesting of the QRM, the *expiry date* of raw material can be extended over the period of time given by the manufacturer.

Both explanations are dangerous, the first version overestimates, and the second one underestimates the significance of *expiry date* given by the manufacturer.

The most important problem with these types of explanations is that these do not consider the fact that the QRM directly affects the quality of finished product (QFP) having definite *expiry date,* too. If the QRM satisfies the requirements of QTS, it does not mean that the QFP at the time of manufacture, and which is more important at the time of its shelf-life will also be satisfactory. If we also consider that from one raw material more different types of finished products should be prepared (such as tablets, capsules, powders, ointment, eye drop, injectables, etc.), the problem is more complex, because the *expiry date* of a given raw material should be the function of the type of formulation, and it may lead to different *expiry dates* of the same raw material to be used for the production of various formulations.

The *expiry date* of raw materials as term is equivalent to the time period elapsed from the manufacture of raw materials until the QRM satisfies all the requirements of QTS, if the material is stored in unopened container under the prescribed storage conditions.

The most important characteristics of the *expiry date* of raw materials can be summarized as follows:

- Certified by the vendor (manufacturer).
- Absolute, it can be extended only by the vendors (manufacturers).
- Product specific, not group specific or batch specific.
- May change from manufacturer to manufacturer.
- Highly influenced by the storage conditions in the user's warehouse.
- Highly influenced by the opening and reclosing processes of the original container in the uses warehouse.
- Not valid, if the material is transferred into another container(s) in the user's warehouse.

2. In-House Expiry Date - Retesting Date of Raw Materials

To overcome the above mentioned difficulties of the use of *expiry date* of raw materials in the user's warehouse, the following terms are applied:

In-house expiry date of raw materials, as term, is equivalent to the time period elapsed from the arrival time of raw material into the use's warehouse until the latest date to use it as raw material in the production of finished product, if the material is stored under the storage conditions of user's warehouse, which is not necessarily identical with the conditions indicated by the vendor (manufacturer).

The most important characteristics of in-house *expiry date* of raw materials can be summarized as follows:

- Given by the user (buyer).
- Product specific, not batch specific, but can be extended or shortened from batch to batch without changing the *in-house expiry date* of raw material in question.
- Can be extended or shortened on the basis of stability data for all batches.
- In each case it is shorter than the *expiry date.*
- Possible deviations in the storage conditions compared to that one given by the vendor (manufacturer) can be considered.
- Stability and shelf-life of finished products produced from the raw material can also be considered.
- Affected by the formulation processes and composition of the finished products produced from the raw material.

Retesting date of raw materials, as term, is equivalent to the time when the raw material must be retested according to its QTS to confirm the validity of *in-house expiry date* for the raw material

batch in question. (in general at the 80% of the time period of *in-house expiry date* is used as *retesting date).*

3. Estimation of In-house expiry date and Retesting date of raw materials

To estimate the *in-house expiry dates and retesting dates* of raw materials the *expiry dates* of raw materials (given by the manufacturer), and of finished products (registered at the registration) are considered.

The raw materials in respect to their *in-house expiry dates and retesting dates* can be divided into three groups:

Group "A": unstable raw materials *(expiry date* is 2 years or less)
Group "B": moderately stable raw materials *(expiry date* is 3 years)
Group "C": stable raw materials *(expiry date* is 5 years)

To demonstrate the above mentioned principles in Fig.1/A, dependence of decomposition (Log C_D) of raw material in time is shown for the three groups. (It has to be noted that this and the following Figures serve only for illustration of the problem, not a result of a real study, although in low decomposition range the Log C_D vs. time curve is mostly linear.) In the Figure the limit in the QTS for decomposition product(s) and the range accepted at the purchasing of the raw materials are also indicated.

Similar considerations can be made for the finished products as shown in Fig. 1 /B. The finished products in respect to their *expiry dates* can be divided also into three groups:

Group "X": unstable finished products (expiry date is 2 years or less)
Group "Y": moderately stable finished products (expiry date is 3 years)
Group "Z": stable finished products (expiry date is 5 years)

For the demonstration of the above mentioned cases, dependence of decomposition (Log C_D) of finished products in time is shown for the three groups in Fig. 1 /B.

The possible 9 combinations are illustrated in Fig. 2/A to Fig. 2/C, where the storage time of raw materials and production time of finished products are also indicated.

Investigating the various combinations, only the AX combination (unstable raw material and unstable finished product, **"worst case"**) is further considered.

In Fig. 3/A the Log C_D time curve of the raw material is shown (L_{RM} indicates the best quality, U_{RM} the worst accepted quality of the raw materials).

Fig. 3/B shows the case when AX finished product is produced from the raw material immediately after its arrival. The estimated shelf-life of the finished product is 2,5 years for U_{RM} and 3 years for L_{RM}, which is acceptable.

Fig. 4/A shows the case when production is made after one year storage of the raw material, considering also that the storage conditions should deviate from the one prescribed by the manufacturer. The estimated shelf-life of the finished product in this case is 2 years for U_{RM} and 2,5 years for L_{RM}, which is closed to the limit, but acceptable.

Fig. 4/B shows the case when production is made during the time of the *expiry date* of raw material (2 years), considering also that the storage conditions should deviate from the one prescribed by the manufacturer. The estimated shelf-life of the finished product in this case is only 1 year for U_{RM} and 20 months for L_{RM}, which is not acceptable, the QFP will be acceptable at the production, but expected shelf-life of the finished product cannot be assured.

The summary of the consequences is illustrated in Fig. 5. The *in-house expiry date* of raw material used for the production of AX finished product is 1 year (finished product with the expected shelf-life can be produced from the raw material), and the QRM on the time of *in-house expiry date* can be characterized with the *expiry quality(E)*. The QRM which can satisfy the expiry quality at the time of the arrival of the raw material into the user's warehouse is named as *purchasing quality* **(P)**, which terms will be discussed later.

Considering the above mentioned principles as well as the possible combinations shown in Figure 2., the *in-house expiry dates and retesting dates* of raw materials can be estimated by dividing the possible combinations into sensitivity groups as shown in Table. 1.

Table 1
Estimation of *in-house expiry date and retesting date* of raw materials

Sensitivityy groups	Mark	Raw mat.	Expiry date	Combi-nations	In-house exp. dat	Retesting date
Very sensitive	SO	A	2 years	***AX, AY***	10 months	8 months
		B	3 years	***BX***	10 months	8 months
Sensitive	S1	B	3 years	BY	18 months	14 months
Moderately sensitive	S2	A	2 years	AZ	18 months	14 months
		B	3 years	BZ	24 months	20 months
		C	5 years	CX	36 months	30 months
Not sensitive	S3	C	5 years	CY, CZ	48 months	36 months

AX, AY, BX and CX represent the *worst cases*

If one raw material is used for the production of more than one finished products, there are two different possibilities to indicate the *in-house expiry date and retesting date* in the label. The first possibility is to indicate the *in-house expiry date and retesting date* of the worst case. The second

possibility is to indicate separately the *in-house expiry dates and retesting dates* of each formulations. As the later case can lead to confusion, the first case is preferably used.

4. Determination of In-house expiry date and Retesting date of raw materials by the aid of stability testing

If stability indicating assay and purity testing methods have been recently developed (the methods are absolutely necessary for the determinations),a more precise determination of *in-house expiry dates (retesting dates)* can be performed. Generally five different types of stability tests can be distinguished:

- comparative stability test (not discussed here)
- **accelerated stability test**
- long term stability test (not discussed here)
- on-going stability test (not discussed here)
- **stability tests based on re-examination of previously prepared batches (re-examination stability testing)**

The most important characteristics of accelerated stability test and re-examination stability test to be used for the determination of *in-house expiry dates (Retesting dates)* of raw materials are summarized in the following Table 2.

Table 2
Stability tests performed for the determination of *in-house expiry dates and retesting dates* of raw materials

CONDITIONS	ACCELERATED STABILITY TEST	RE-EXAMINATION STABILITY TEST*
Samples	3 to 5 different batches of raw material in the stock	3 to 5 different batches of finished products produced 1, 2, 3 (4 and 5 years before testing and the raw materials from which they are produced
Testing period	initial, 1 month, 2 months, 3 months, 4,5 months, 6 months	1, 2, 3, (4 and 5) years after production
Treating conditions	refrigerator** (cool place) ** room temperature** ambient** 40°C/80%R.H.*** 50°C** (reflected light) ** UV-light - 10 hours) ***	samples stored under the given storage conditions

CONDITIONS	ACCELERATED STABILITY TEST	RE-EXAMINATION STABILITY TEST*
Analytical tests*****	IR- and UV-spectra appearance colour of solution (solubility) (pH) (bulk density) loss on drying (optical rotation) decomposition products	Formulated products according to the analytical test specification + decomposition products + assay Raw materials same as accelerated stability test

* Testing period is dependent on the expiry date of the formulated products
** only in closed container
*** both in closed and opened container
**** only in opened container
***** tests for decomposition products and assay - stability indicating methods in brackets: only, if it is important

From the results the following conclusions can be obtained:

(a) Batch to batch variability (data obtained from the accelerated stability tests)

If the results obtained for all the batches to be tested are similarly changing in time (decomposition rates for batches tested are practically the same at each tested conditions, and the rate constants are only function of the treating conditions), batch to batch variability is neglectable, and cannot be further considered, the average of the rate constants can be used for the calculations.

If it is not, only the rate constant obtained in the worst case can be further on considered.

If the results for the worst case significantly differ from that the ones obtained for the other batches, the requirements in the analytical test specification should be modified to be more rigorous, and the worst case batch can be left out from further considerations.

(b) Variation between manufacturers (data can be obtained from accelerated stability test and re-examination stability test of raw materials, as well)

If the samples are originating from different sources, it gives a possibility to evaluate the different manufacturers of the same raw material. Only manufacturer(s) would be considered in the future, which can supply consistent and good QRM. (It is important that in case of the re-examination stability test of raw materials, similar aged samples would be compared and evaluated.)

(c) Correlation between QRM and the quality of the finished products (data obtained from the re-examination stability tests)

Comparing the most important analytical data for the finished products and the corresponding raw materials (data obtained for decomposition product and assay) as a function of time elapsed from the production some important considerations can be drawn.

Firstly, the observed differences between the decomposition rates obtained for the raw materials and finished products should be the most important base for grouping of the raw material and finished product, as well. If the decomposition rate of the raw material is much higher than that obtained for the corresponding finished product, the *in-house expiry date* of the raw material must be relatively short (material belongs to Group "A", finished product to Group "Z"). In opposite situation, the raw material is stable (it belongs to Group "C"), and the formulated product is unstable (belongs to Group "X"), longer *in-house expiry date* can be stated. If the difference experienced for the decomposition rates are smaller or similar, considering the *expiry date* of the finished product as well as the results obtained for the samples of raw materials and finished product at the end of their shelf lives, it is relatively easy to determine in which group the raw material and finished product can be classified.

Secondly, based on the results obtained, the QRM needed at the time of production be much more accurately described. Calculating the average decomposition rates both for the raw material and finished product, the minimum requirement for purity and as values of the raw material can be calculated.

This is the most important quality requirement of raw material at the time of *in-house expiry date* and defined as *expiry quality*.

Thirdly, from batch to batch variability, the formulation technology with respect to its consistency, contribution to the decomposition, etc. can be evaluated. If the formulation technology is not sensitive to the quality changes of the raw material (for example for the deviation of the physical state of the raw material), the analytical test specification cannot be necessarily changed. But, if the formulation technology is a function of QRM, the actual specification should be modified, by extending it with additional tests, or by changing the existing limits.

(d) Determination of *in-house expiry dates Retesting dates* of raw materials (data obtained from accelerated stability test, and confirmed by the data of re-examination stability test)

First approximation

In the course of first approximation of *in-house expiry date* all important analytical data are considered including those ones which cannot be characterized by accurately given limits (appearance, colour of solution, etc.).

From the data obtained for accelerated stability test the *in-house expiry dates Retesting dates* of raw material can be determined, as shown in Table 3 below.

Table 3
Determination of *in-house expiry dates Retesting dates* of raw materials

All batches satisfy all the analytical requirements stored under all treating conditions*	**In-house expiry date stored the material under ambient storage conditions****
after 6 months	**36 months**
only after 3 months	**24 months**
only after 2 months	**12 months**
only after 1 month	**6 months**

* treatments in brackets are considered, if these are important
** no protection against humidity, temperature can fluctuate

The *in-house expiry dates* indicated in Table 3 and the ones obtained from the re-examination stability tests are compared and used only in that case, if the data are in agreement. If not, data obtained for the worst case are considered (see batch to batch variation).

If the raw material can be stored under different conditions than ambient (cool place, refrigerator) treatments at higher temperature(s) are omitted (50° C, if the raw material is stored in cool place, 40°C/80%R.H. and ambient, if the raw material is stored in refrigerator), and the *in-house expiry date* can be calculated from the data obtained for the remaining treatments similarly as given for ambient condition.

Second approximation

In the course of second approximation only the assay and purity testing data are considered and the decomposition rates are calculated according to the apparent first order kinetic (linear relationship between the change of lg concentration in time) for each treating conditions.

In the knowledge of the *expiry quality* of raw materials as well as that of rate constants for decomposition the *in-house expiry date* can be accurately calculated for all storage conditions to be applied.

From the calculated data, another important quality parameter, the minimum required quality at the time of arrival of the raw material defined as *purchasing quality*, can also be calculated.

Purchasing quality considers the worst case concept (it is established for the worst quality batch), as well as the applicable storage conditions for the raw material at the company, because it is calculated for this condition.

At the calculation, we generally apply a time period of 3 months elapsed betweent he manufacturing date and the arrival time of the raw materials to the warehouse. The quality requirements (assay and purity) extrapolated back to this 3 month period of time by using the rate constant obtained for the applied storage conditions, obtaining the *purchasing quality* of the raw material.

The third important parameter which can be calculated from the data of accelerated stability test is the dependence of the quality on the storage conditions. Comparing the rate constants obtained for different storage conditions the *in-house expiry dates* for these conditions can be calculated. We have to keep in our minds the *expiry quality* in each case is the same. However, the *purchasing quality* is a function of storage conditions, therefore, if the required *purchasing quality* established for the given storage conditions is not available in the market, without changing the *in-house expiry date* of the raw material, the QRM used for the production (*purchasing quality*) can be selected for the possible, but different storage conditions (for example cool place instead of ambient). Similarly, if we do not want to change the storage conditions and *purchasing quality*, and the *in-house expiry date* must be shortened to the date providing identical *expiry quality*.

These data serve to establish a good correlation between *purchasing quality,* storage conditions and *expiry quality,* which is the most important consequence of this study.

5. Possible extension of in-house expiry date based on the retesting data (IMPORTANT NOTE: THIS POSSIBILITY IS BATCH SPECIFIC, NOT PRODUCT SPECIFIC!!!)

Considering the principles mentioned above, there are certain possibilities to extend the *in-house expiry date* of a specific batch of the raw materials based on the *retesting data.* Since the QRM is retested prior to its *in-house expiry date,* the QRM experienced at the *time of retesting* should provide information for its further applicability to production. However, the knowledge base available in the *time of retesting* is very important to make further decisions.

(a) The *in-house expiry date* is only estimated, stability data are not available, stability indicating methods are not developed and validated at the *time of retesting*.

This is the worst case, and all considerations must be very carefully taken into account.

- If the QRM satisfies all the requirements of actual analytical test specification, and the obtained results are close to the one certified at the time of the arrival of the raw material into the warehouse, the *in-house expiry date* can be extended for this specific batch with the same period of time elapsed between *retesting date and in-house expiry date.* (This time period is added to the *in-house expiry date).*

- if the QRM is changed, but this change is not too big, and the QRM is far from the stated minimum quality requirement until the batch can be used for production, we

also estimate a good quality of finished product at the time of its shelf life, the *in-house expiry date* of the batch can be extended with the half of the period of time elapsed between the retesting date and in-house expiry date.

- if the change in QRM is significant at the *time of retesting,* the batch can be used until its *in-house expiry date.*

(b) *The in-house expiry date* is only estimated, stability data are not available, but stability indicating methods have been developed and validated at the time of retesting.

In this stage, the QRM can be perfectly characterized by using stability indicating methods, unfortunately no possibility exists to determine the QRM during the time of the arrival of the specific batch of raw material *(expiry quality and purchasing quality* are not defined yet).

(Please remember, the *expiry quality* is the QRM at the latest time of its possible application for production, *purchasing quality* is the minimum QRM to be required at the time of the arrival of the raw material to satisfy *expiry quality* of the raw material). Practically, the same decisions can be made as in point (a), but our decision is much more supported by analytical data obtained for the specific batch of the raw material.

(c) The *in-house expiry date* is only estimated, but minimum the re-examination stability testing data, and stability indicating methods are available at the *time of retesting.*

In this case the *expiry quality* is known, *(purchasing quality* is not known).

- If the quality of the specific batch of raw material characterized by the stability indicating methods is very good (far from the *expiry quality) the in-house expiry date* of this batch can be extended with double time elapsed between *retesting and in-house expiry dates,* but maximum to its *expiry date* stated in the label.

- If the quality of the specific batch is acceptable, it is not too far, but not too close to the *expiry quality, the in-house expiry date* can be extended with the time elapsing between *retesting and in-house expiry dates.*

- If the quality of this specific batch is close to the *expiry quality, the in-house expiry date* cannot be extended.

IT IS VERY IMPORTANT TO NOTE THAT NO POSSIBILITY EXISTS TO OVERRUN THE EXPIRY DATE OF THE RAW MATERIAL GI VEN B Y THE MANUFACTURER, IF IT OCCURS, THE ONLY POSSIBILITY IS TO TURN TO THE MANUFACTURER TO EXTEND THE EXPIRY DATE OF THE RAW MATERIAL!!!

(It can be done by the analysis of the specific batch of the raw material, sending a sample together with the certificate of analysis and exact description of the storage conditions to the manufacturer, asking its advice.)

6. Re-evaluation of in-house expiry date

(IMPORTANT NOTE: THIS POSSIBILITY IS PRODUCT SPECIFIC, NOT BATCH SPECIFIC!!!)

Basic requirements are as follows: the *in-house expiry date* is determined, all stability data including accelerated and re-examination stability tests as well as stability indicating methods are available.
In this case both the *expiry quality and purchasing quality* are determined and known. It is also important that retesting data of several batches of the same raw material using stability indicating methods for the characterization of the QRM at *retesting time* would be available.

The following possibilities could be considered for re-evaluating and extending a recently determined (estimated) *in-house expiry date* of raw material.

A. QRM enables to extend the in-house expiry date (re-evaluation is based on the retesting data of several batches of the same raw material when the purchasing quality and storage conditions are fixed).

- If the QRM characterized by stability indicating methods are below or close to *the purchasing quality* at the time of retesting, the *in-house expiry date* can be extended to the *expire date* of the raw material given by the manufacturer.

- if the QRM characterized by stability indicating methods at the *time of retesting* is changed, but this change is not so big, and the QRM is far from the *expiry* requirements, the *in-house expiry date* can be extended to 80% of the *expiry date* given by the manufacturer,

- if the QRM characterized by stability indicating methods at the *time of retesting* is close to the *expiry quality the in-house expiry date* cannot be changed.

- If the QRM characterized by stability indicating methods does not satisfy the *expiry quality, the in-house expiry date* can be reduced to the date when the *expiry quality* in the worst case can be achieved.

B. QRM does not enable to extend the in-house expiry date

When the QRM characterized by stability indicating methods at the *retesting time* does not allow to extend the *in-house expiry date,* there are two further possibilities for possible extension:

a. Re-evaluation is based on the retesting data of several batches of the same raw material when the *purchasing quality* is changed and the storage conditions are fixed.

In this case the analytical test specification is changed that the new *purchasing quality* should provide longer *in-house expiry date.*

b. Re-evaluation is based on the retesting data of several batches of the same raw material when the *purchasing quality* is fixed and the storage conditions are changed.

In this case the *purchasing quality* does not change, but the user decides a change in the storage conditions, which allows to extend the *in-house expiry date* of the raw material.

7. Expiry date of finished products, the most important characteristics

(Brief summary and conclusions)

- Expiry date of finished product is absolute and product specific (not batch or group specific).

- It is determined at the registration of the product, any change in the *expiry date* automatically changes the Registration Dossier of the finished product.

- Only little correlation exists with the *expiry date* of raw materials, because
  - in most cases the raw material is more stable than the finished product produced from it;
  - the *expiry dates* of finished product depends on the type of formulation and the formulation process itself;
  - different decomposition products are frequently formed.

BUT

- the raw material is not stabilized against hydrolytic decomposition, humidity, oxidation, microbial contamination, light, etc., therefore, in significant number of cases the raw material is less stable than the finished product.
- the assay and purity testing limits are different, for finished product the limits are higher than for raw materials.

—

Conclusions

(1) *Expiry date* of finished product cannot be changed, only if the Regulatory Authorities changes the Registration Dossier of the product.

(2) Manufacturers responsibility to provide such QRM which proves the expected shelf life of the finished product if it is produced within the *in-house expiry date* of raw material.

(3) Purity testing limits for finished products consider the acceptable purity of raw material, and decomposition occurs during the shelf-life of the finished product, as well.

Fig. 1/A: Expiry date for RAW MATERIALS

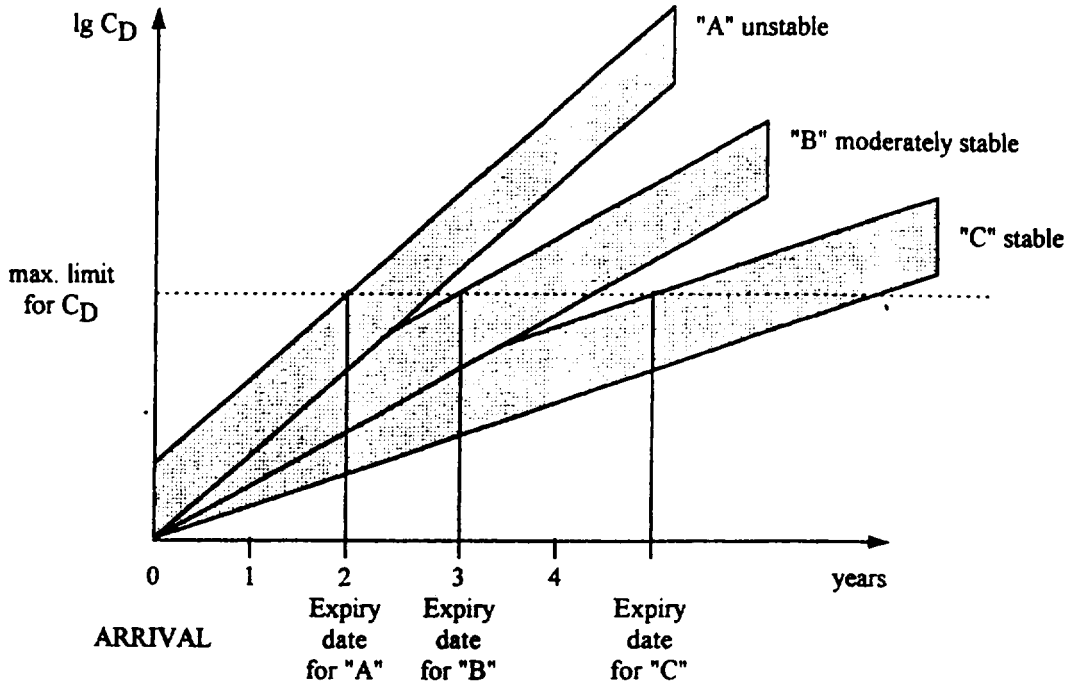


Fig. 1/B: Expiry date for FINISHED PRODUCTS

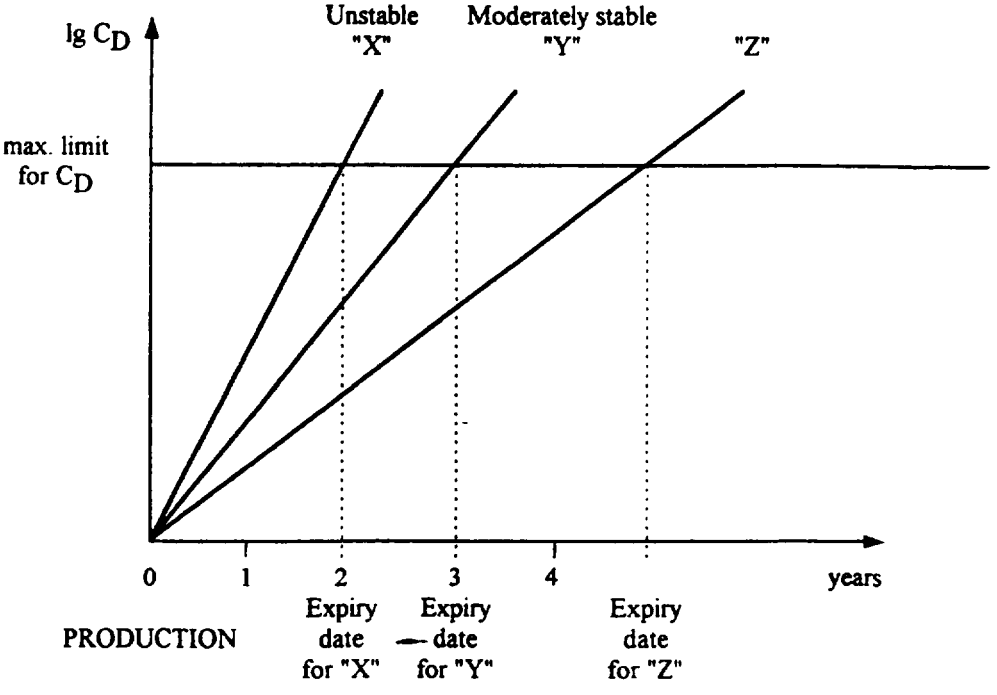


Fig. 2/A: COMBINATIONS

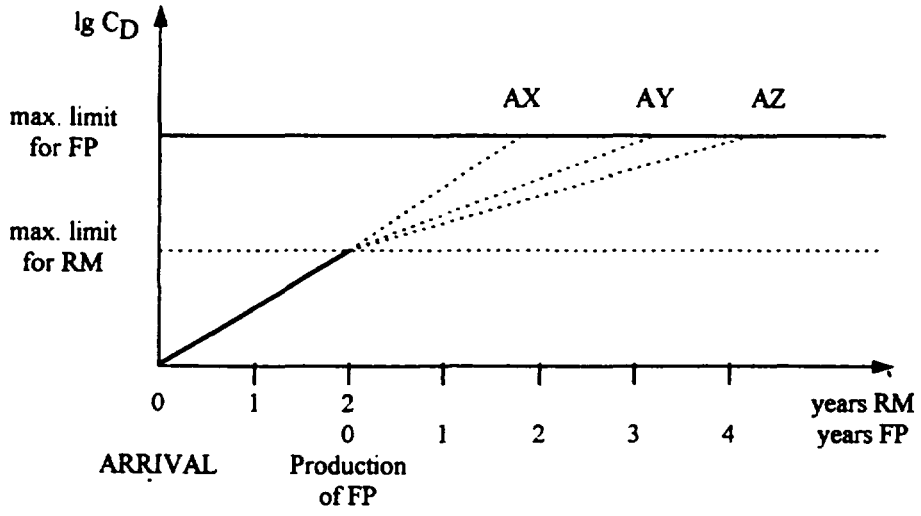


Fig. 2/B

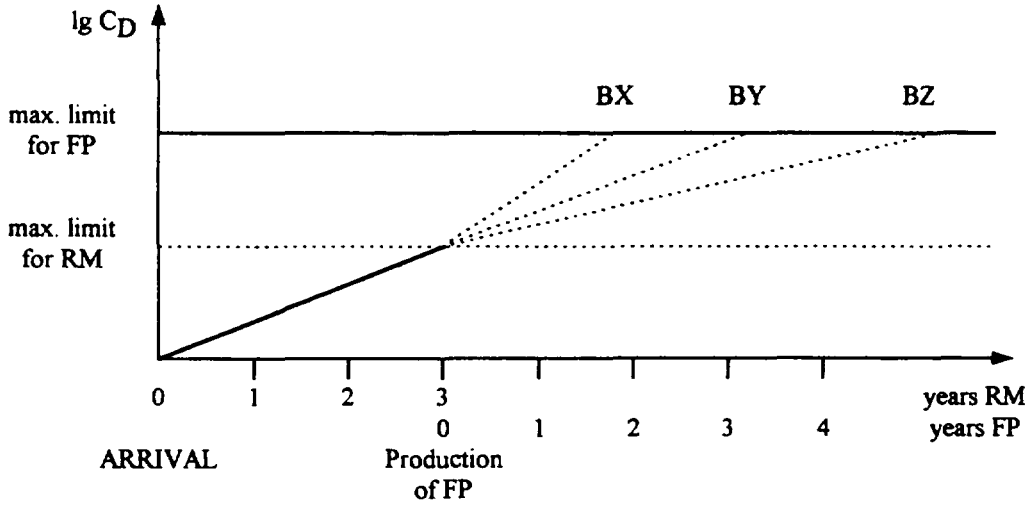
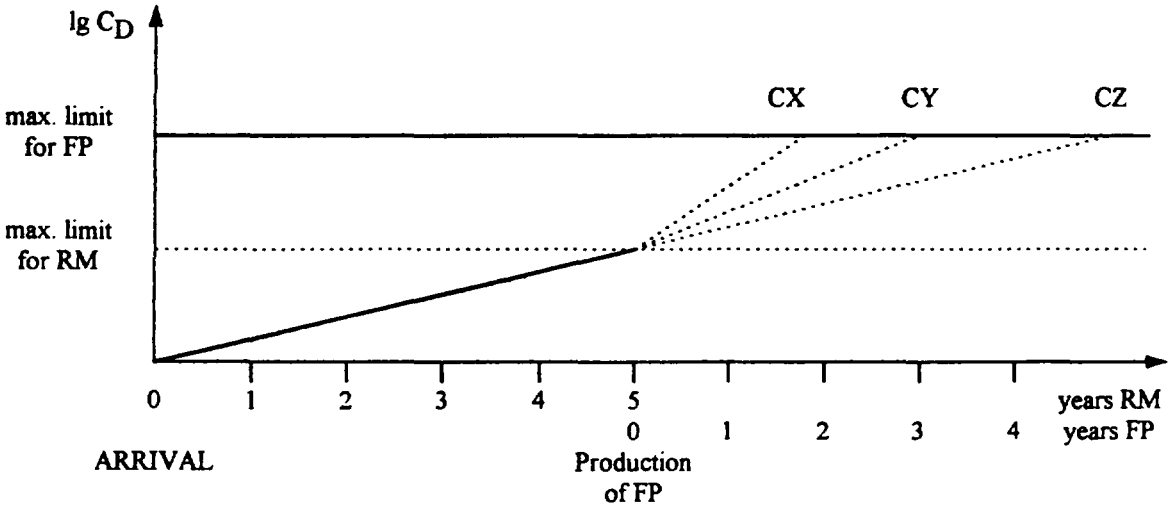


Fig. 2/C


lg C_D
max. limit for FP
max. limit for RM
CX
CY
CZ
0
1
2
3
4
5
0
1
2
3
4
years RM
years FP
ARRIVAL
Production of FP

Expiry date - in-house exp. date - RE-TESTING DATE

MODEL: AX (unstable raw material - unstable formulation) = "WORST CASE"

Fig. 3/A: CHANGE IN DECOMPOSITION FOR RM
in time (during the storage)

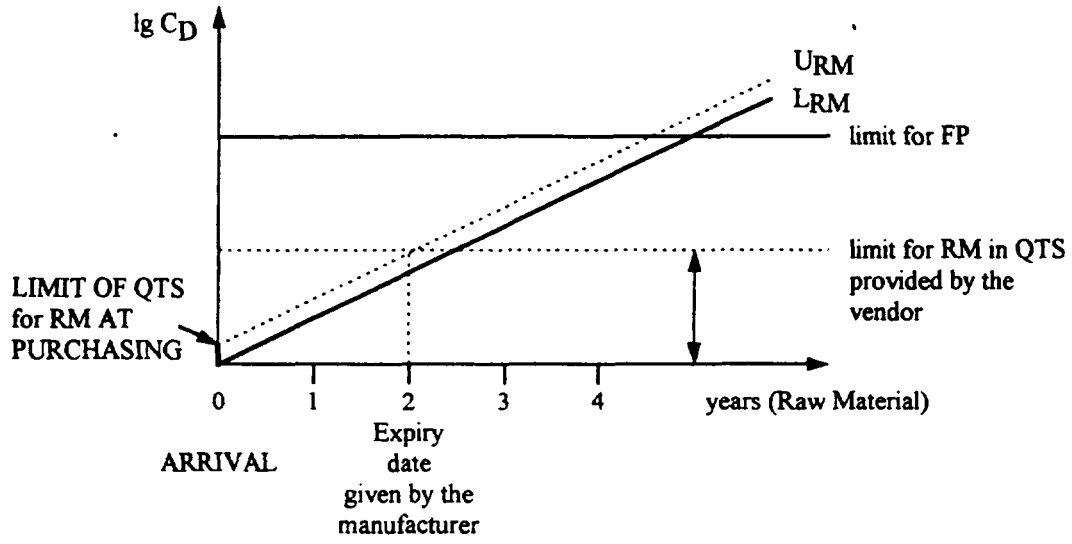


Fig. 3/B: Production of FP at the arrival of RM

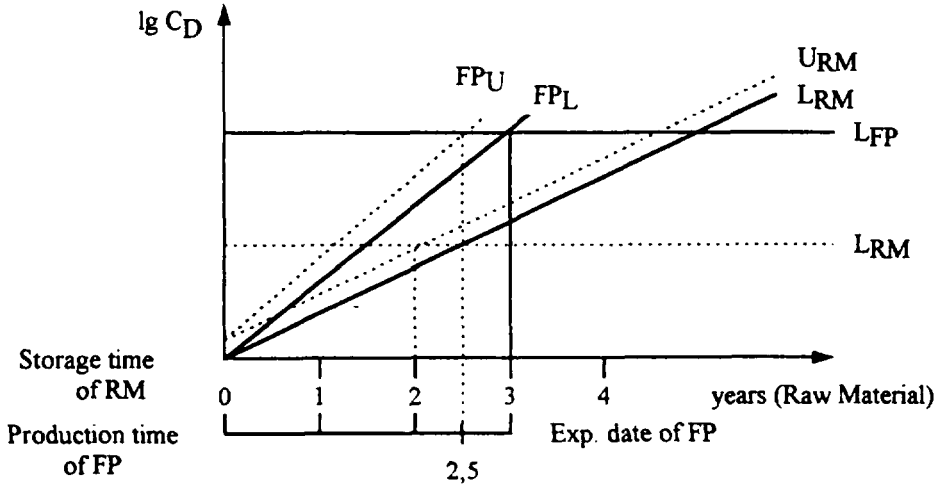


Fig. 4/A : PRODUCTION OF FP AFTER 1 year storage of RAW MATERIAL

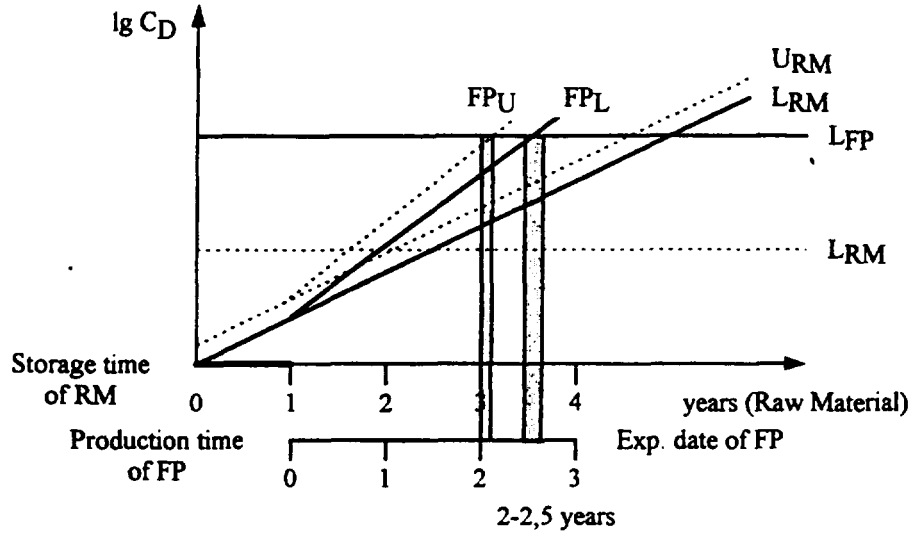


Fig. 4/B : PRODUCTION OF FP AT TIME OF THE EXPIRY DATE OF RAW MATERIAL

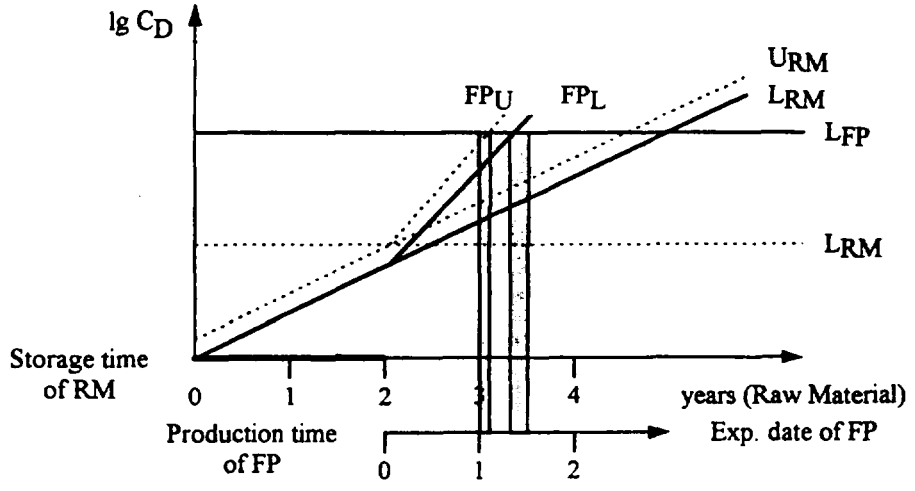
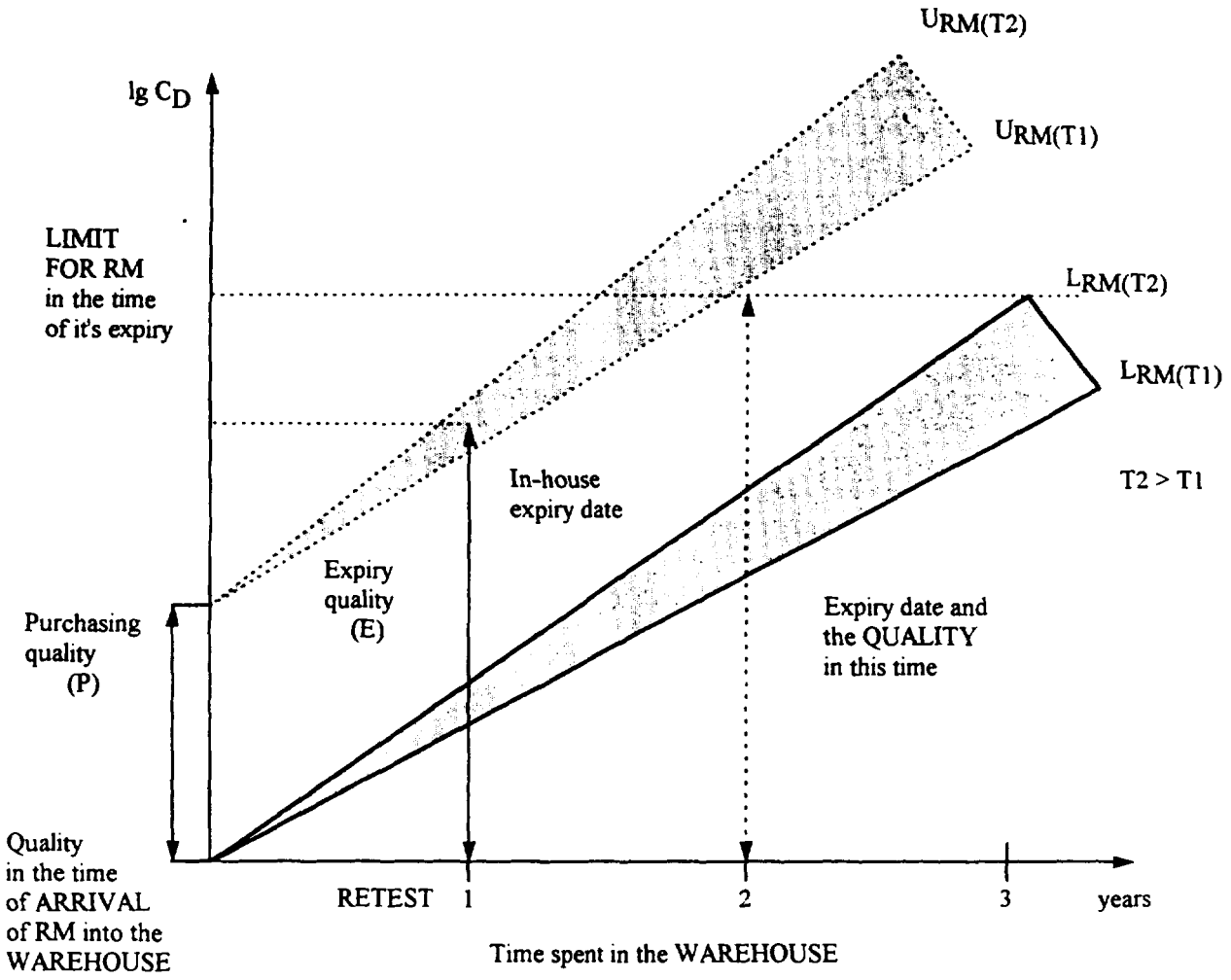


Fig. 5


URM(T2)
lg CD
URM(T1)
LIMIT
FOR RM
in the time
of it's expiry
LRM(T2)
LRM(T1)
T2 > T1
In-house
expiry date
Expiry
quality
(E)
Expiry date and
the QUALITY
in this time
Purchasing
quality
(P)
Quality
in the time
of ARRIVAL
of RM into the
WAREHOUSE
RETEST
1
2
3
years
Time spent in the WAREHOUSE

Annex 5

HYGIENIC CLASSES REQUIREMENTS AND RECOMMENDATIONS

(Lecture presented in "Training Courses III on QA/GMP concerning Sterile Pharmaceutical Manufacture" held in Damascus on 17-18 September 1996, and in Aleppo on 25-26 September 1996)

by Gabor SZEPESI

The philosophy governing the manufacture of aseptically prepared and thermally sterilised products is essentially the same, in spite of the fact that in practice the route to achieve the same aim differ for the two types of products.

This philosophy can be summarized as follows:

- to minimise the challenge to the sterilisation step
- thereafter to minimise the potential for recontamination.

The contamination risk associated with the two types of sterile products, however, is not the same, the risk with aseptic processing is at least 100 times greater than for terminally sterilised products.

The most important problem associated with the aseptic processing relates to the **PEOPLE** accounting for over 80% of all particulate contamination in the clean room and virtually all the microbiological contamination.

The key aspects to control and to assure acceptable product quality are summarized in Table 1.

Table 1

Key aspects	Terminally sterilised products	Aseptically prepared products
Sterilisation procedure	- Validation - Maintenance - Calibration	- Validation - Maintenance - Calibration - Filtration
Pack integrity	- to minimise post - manufacturing contamination	- to minimise post - manufacturing contamination
People	- **Training** - **Attitude**	- **Major source of contamination**
Materials	- Raw materials - Water - Containers	- Raw materials - Water - Containers
Environment	- To minimise particulate and microbiological challenge	- To minimise particulate and microbiological challenge
Processing time	-	To minimise microbiological risk

Methods to control the quality factors are as follows:

- validation
- documentation
- monitoring
- engineering maintenance
- in-process control
- staff training
- self-inspection

1. Principles and design of clean rooms

1.1. Clean room concept

The basic concept of clean rooms is to create a controlled environment:

- control of microorganisms,
- control of particles,
- control of temperature and humidity, etc.

The fundamental philosophy is to **protect the critical operation** where the contamination risk is the greatest, as shown in Fig.

The idea is simple, protection of the critical operation is performed in a "'**BOX**", as illustrated in Fig. 2.

1.2. Room air quality -Air filtration

It is evident that to protect the *Critical Operation* **High Efficiency Particle Air (HEPA) Filters** can be used, which ensures to remove 99,997% of particles less than 0,6u, and room to be free from microorganisms.

The air supply at over-pressure prevents contamination in-flow by outward flow of clean air.

By continuous air change in the box, any contamination is captured and removed.

The application of HEPA filters in the box protecting the critical operation is shown in Fig.3.

1.3. Entry of materials

The clean room is now ready to work, however, materials have to enter into the box. The following principles are used for the material transport into the clean room:

- Sterilise materials entering the box
- Autoclave (solutions, filling pumps, filters, etc.)
- Dry heat oven (glassware, etc.)
- Filtration (solutions)

- Supplying systems (water, compressed air, steam, vacuum, protecting gases, etc.)
- Disinfect large items
- Use double entry sterilisers

The clean room (box) in this stage is shown in Fig. 4.

1.4. Operator entry

As it was mentioned, the **PERSONNEL** is the most important source of contamination regarding clean room process.

The key elements to maximise the protection possibilities can be summarized as follows:

- Design of entry system.
  This concept includes the changing room facilities (HEPA filtered air supply both in the aseptic part and the white part of the changing room, sterile cleaning possibilities, air lock (double door with single operation) system, etc.
- Design of protective cloths.
- Operator training and self-inspection.

The clean room design now is shown in Fig. 5.

1.5. Outer defences

The background area surroundings to clean room:

- provides an area for preparation
  - filter assembly
  - component washing
  - machine parts assembly
- needs a controlled environment for successive clean up
- needs a separate black/white changing room

The final design of the clean room is shown in Fig. 6.

1.7. Design of the total facility

This overall approach includes the following considerations:

- Facilities for people preparation
- Facilities for equipment and component preparation
- Facilities for product preparation
- Interfacing equipment to clean rooms
- Transfer in and out of clean rooms
- Special relationships of one area to another

1.8. Design of the structure, surface and hardware

Table 2 summarizes the most important requirements regarding the clean rooms.

Table 2

ITEM	DESIGN
Surface	Smooth, impervious, unbroken, resistant to cleaning agent, ease of cleaning, continuous, durable, accessible, easy to maintain
Walls/Doors	No recesses, minimum of ledges, shelves, cupboards, no sliding doors, false ceilings to be sealed
Services	No surface pipes/ducts. Avoid sinks/drains where possible (if fitted cleanable traps/air breaks), In aseptic areas exclude sinks/drains in any form. Hand washing in the changing room only.
Interlocks	Air locks should not be opened simultaneously, interlock system or visual and/or audible alarm needed.
Conveyors	Not allowable in Class B areas (unless if it is part of a steriliser tunnel, etc.)
Air supply alarms	Warning system needed to indicate failure in air supply
Room shape	Keep it simple
Clean room hardware	Number, siting, type of diffuser to be used in the air inlet filters and their relative positions to air extraction points are highly considered

The basic approach is: **"DESIGN IT CLEAN - KEEP IT CLEAN"**

2. Standards for pharmaceutical clean rooms

2.1. Aseptic processing

Environmental standards for aseptic processing of medicinal products have been established by the regulatory authorities worldwide. In the USA "Guideline on Sterile Drug Products Produced by Aseptic Processing" published by FDA in 1987, in the European Community "The rules Governing Medicinal Products in the European Community, Volume IV. Good Manufacturing Practice for Medicinal Products" published in 1992, and its annex devoted to the manufacture of sterile products contain all prescriptions, guidance and recommendations relating to airborne particulate and microbiological contamination level and various activities associated with aseptic product manufacture. In Table 3 the comparison of the standards used by US and EC manufacturers can be compared.

Table 3
A) Aseptic processing

	Critical zone		Background room		Preparation area	
	Non-viable (0,5 U)	Viable	Particulate	Micro-organisms	Particulate	Micro-organism
USA	100/ft³	1/10 ft³	10,000/ ft³	-	100,000/ft³	25/10 ft³
	manned not more than one foot away from the work site	manned	manned		manned	manned

EC Guide (1992)

ITEM	Grade	Particles/m³		Organism/m³	Notes
		0,5u	5u		Conditions
Critical zone	A	3500	0	< 1	At all times (manned) Homogenous Air speed
Background room	B	3500	0	5	Unmanned After short Clean-up period
Solution preparation	C	350K	2000	100	Prior to sterile filtration
Handling starting materials	C	350K	2000	100	Weighing/Sampling etc.
Component preparation	-	-	-	-	Do not recontaminate after cleaning

The problem of US standard is that it relates only to airborne contamination, while in case of EC requirement with the exception of standards for Grade A environment (equivalent to critical zone determined by FDA) all environmental standards pertain to the unmanned state only, when product is not at risk of contamination.

2.2. Terminally sterilised products

Annex 1 of the EC Guide to GMP also provides environmental standards to the manufacture of terminally sterilised products in Europe. In the USA presently similar standards are not existing, only a draft document has been prepared in 1976. (21 CFR 212, Current Good

Manufacturing Practice in Manufacture, Processing, Packing and Holding of Large Volume Parenterals). Table 4 collects the Standards for comparison.

Table 4
B) Terminally sterilised products

	Critical zone		Background room		Preparation area	
	Non-viable (0,5 U)	Viable	Particulate	Micro-organisms	Particulate	Micro-organism
USA	100/ft^3	1/10 ft^3	10,000/ ft^3	25/10 ft^3	100,000/ft^3	25/10 ft^3
	manned not more than one foot away from the work site	manned	manned	manned	manned	manned

EC Guide (1992)

ITEM	Grade	Particles/m^3		Organism/m^3	Notes
		0,5u	5u		Conditions
Critical zone injectables	A	3500	0	< 1	At all times (manned) LAF required
Critical zone	C	350K	2000	< 100	At all times (manned) LAF required
Background room	C	350K	2000	< 100	Unmanned After short Clean-up period
Solution preparation	C/D	350K/ 3500K	2000 20K	< 100/ < 500	Where open process/ Where closed process
Handling starting materials	-	-	-	-	Not specified
Component preparation	-	-	-	-	Do not recontaminate after cleaning

Problems with the standards are similar to that one mentioned at Aseptic processing.

3. Validation of clean rooms

Validation of a clean room is a very complex procedure, as shown in Table 5.

Table 5
Validation of a clean room

Design validation	Plant validation	Validation of equipment	Validation of processes	Validation of product manufacture
-Surfaces -Doors/Walls - False ceiling - Services - Changing room including clothes and personnel - Drains - pipelines, etc.	- HVAC system - Water system - Steam - Pressurized air - Vacuum - Inert gases, etc.	- Autoclaves, - Hot ovens, - Sterilizing tunnels - Filters - Disinfection - Washing equipments - Filling (and capping) equipments	-Washing - Drying - Solution preparation - Sterilisation - Filtering - Filling - Capping - CLEANING equipments - Sterile cleaning - House keeping - Disinfection	- Bioburden - Media fills (Broth filling)

Validation, as a term (including all types of validations mentioned above) includes total physical and microbiological control of the manufacturing environments under manned and unmanned conditions. Validation involves four stages of qualification work as shown in Fig. 7.

- Installation qualification (IQ)
  Documentation of the installation of the equipment/facility to show that it conforms to the design specification.

- Operational qualification (OQ)
  Documentation of the installation of the equipment / facility to show that it operates correctly and within specific limits.

- Performance qualification (PQ)
  Documentation of the installation of the equipment / facility to provide a high degree of assurance that it will reliably and consistently operate/produce a product that will meet its predetermined specification and quality attributes.

- Monitoring
  To ensure that the working environment and physical conditions established during the validation study are valid and exist under continuous operation.

In another lecture detailed discussions of IO, OQ and PQ are given by the writer (Validation

of sterilizers), therefore, only the fourth aspect - monitoring - is mentioned here.

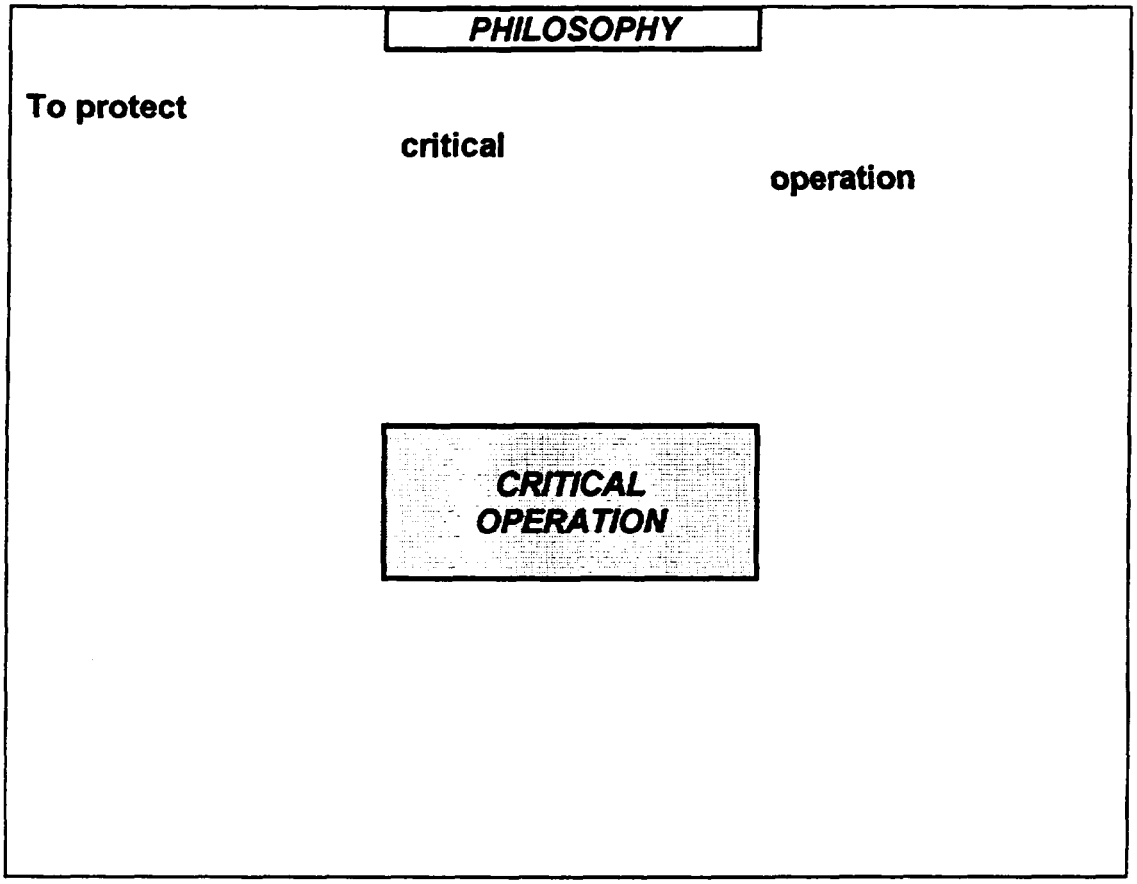
Summary of minimum recommended monitoring frequencies is given in Table 6.

Table 6
Recommended minimum monitoring frequencies

Parameter	Action	Method	Minimum monitoring frequency	
			Class A/B	Class C/D
Air pressure difference	Indication Check Record	Differential manometer	Continuous Hourly Daily	Continuous Hourly Daily
Installation leak test	Test and record	DOP or equivalent	Quarterly	Half-yearly
Particulate contamination	Test and record	Particulate counter	Daily	Daily
Pressure drop across HEPA	Test and record	DOP or equivalent	Quarterly	Half-yearly
Integrity of HEPA	Test and record	DOP or equivalent	Half-yearly	Half-yearly
WFI Water chemical	Test and record	USP/BP	Weekly	Weekly
WFI Water microbial	Test and record	USP/BP	Daily	Weekly
Viable particulate in the air	Test and record	USP/BP	Daily	Monthly
Viable particulate in LAF	Test and record	USP/BP	Continuous during the production	-
Hygienic monitoring - clothes	Test and record	USP/BP	Weekly	Quarterly
Hygienic monitoring - personnel	Test and record	USP/BP	Weekly	Quarterly
Hygienic monitoring - cleaning	Test and record	USP/BP	Weekly	Quarterly

Fig. 1.

1. CLEAN ROOM CONCEPT



Fig, 2.

1. CLEAN ROOM CONCEPT

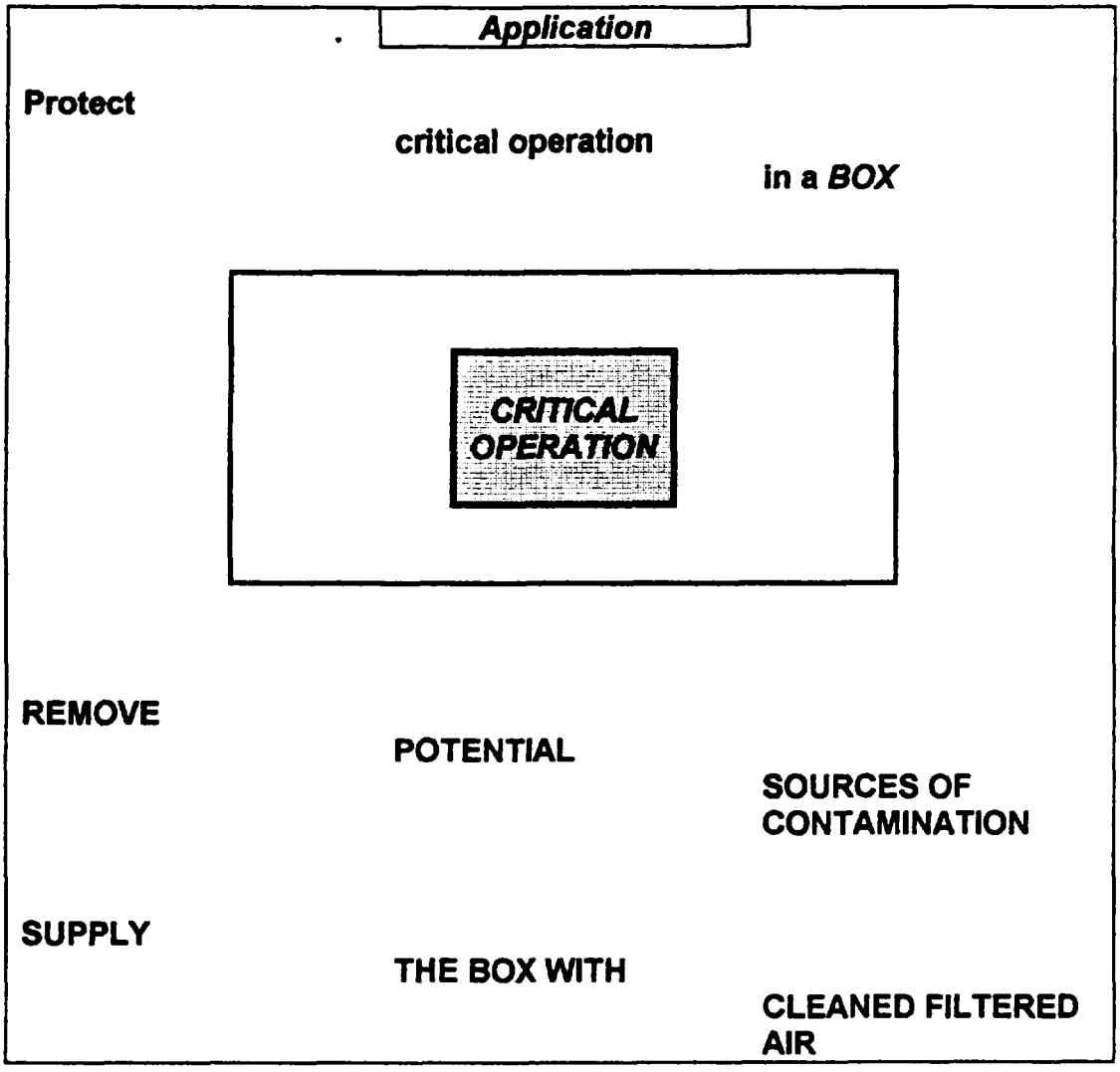


Fig.3.

2. Room air quality

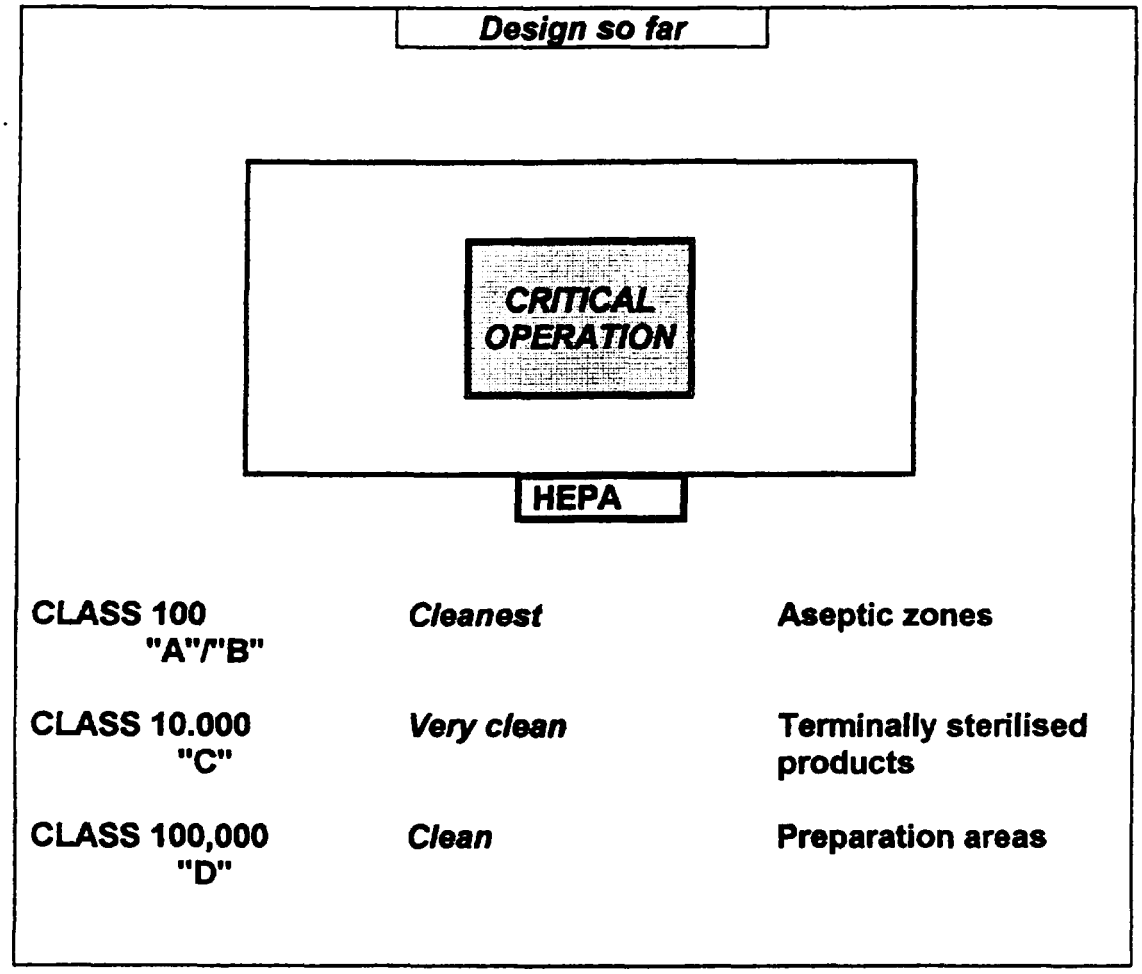


Fig. 4.

3. Entry of materials

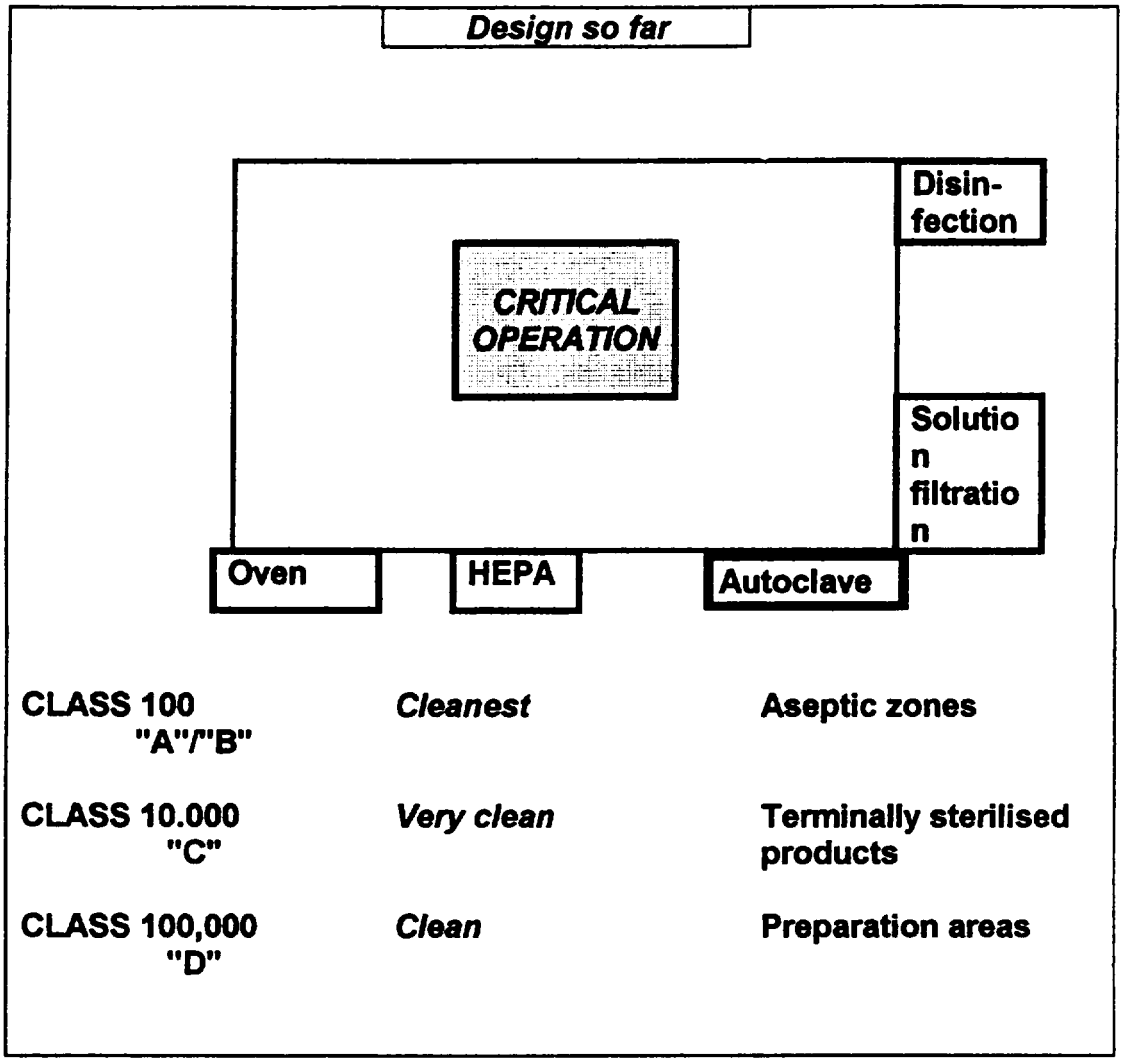


Fig. 5.

4. Entry of operators

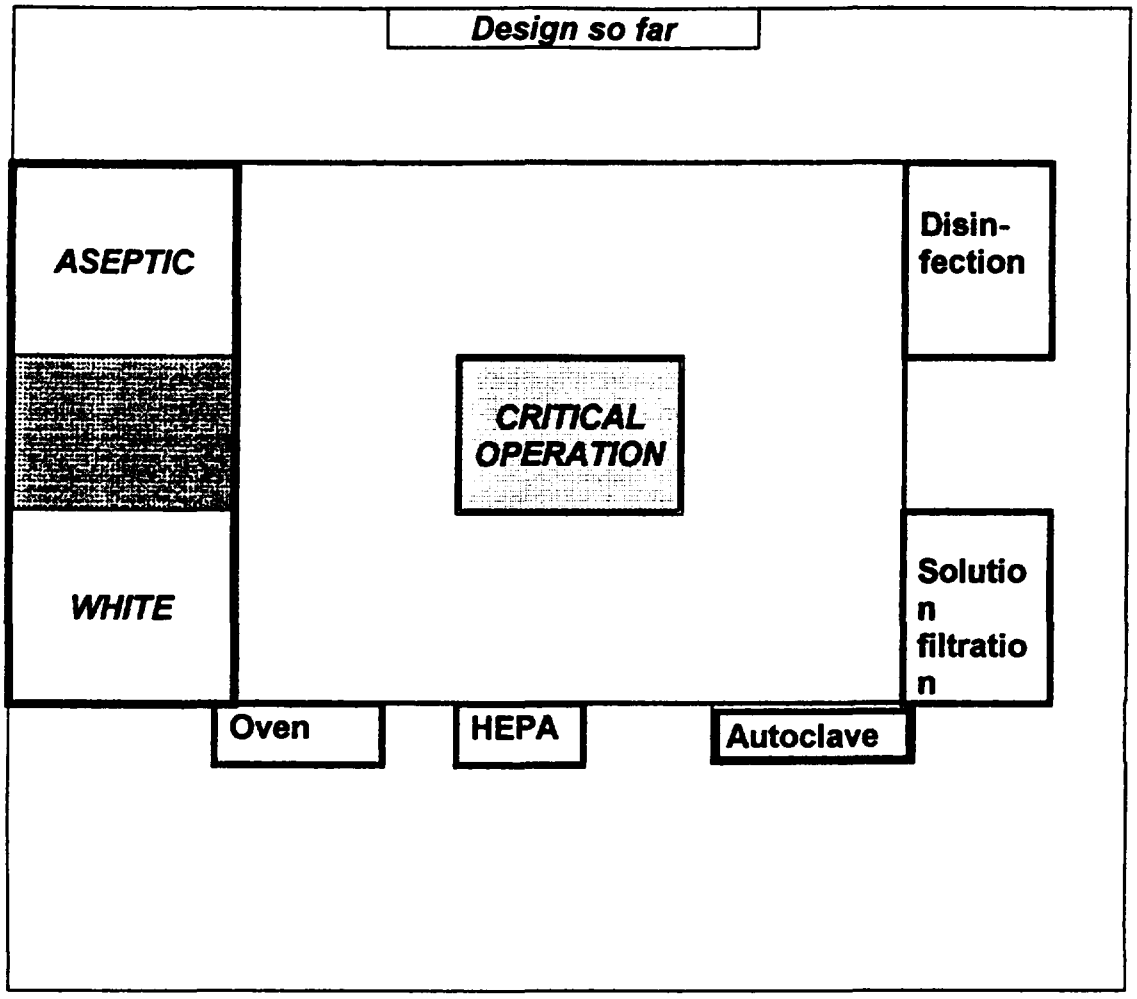


Fig. 6.

5. Outer defences

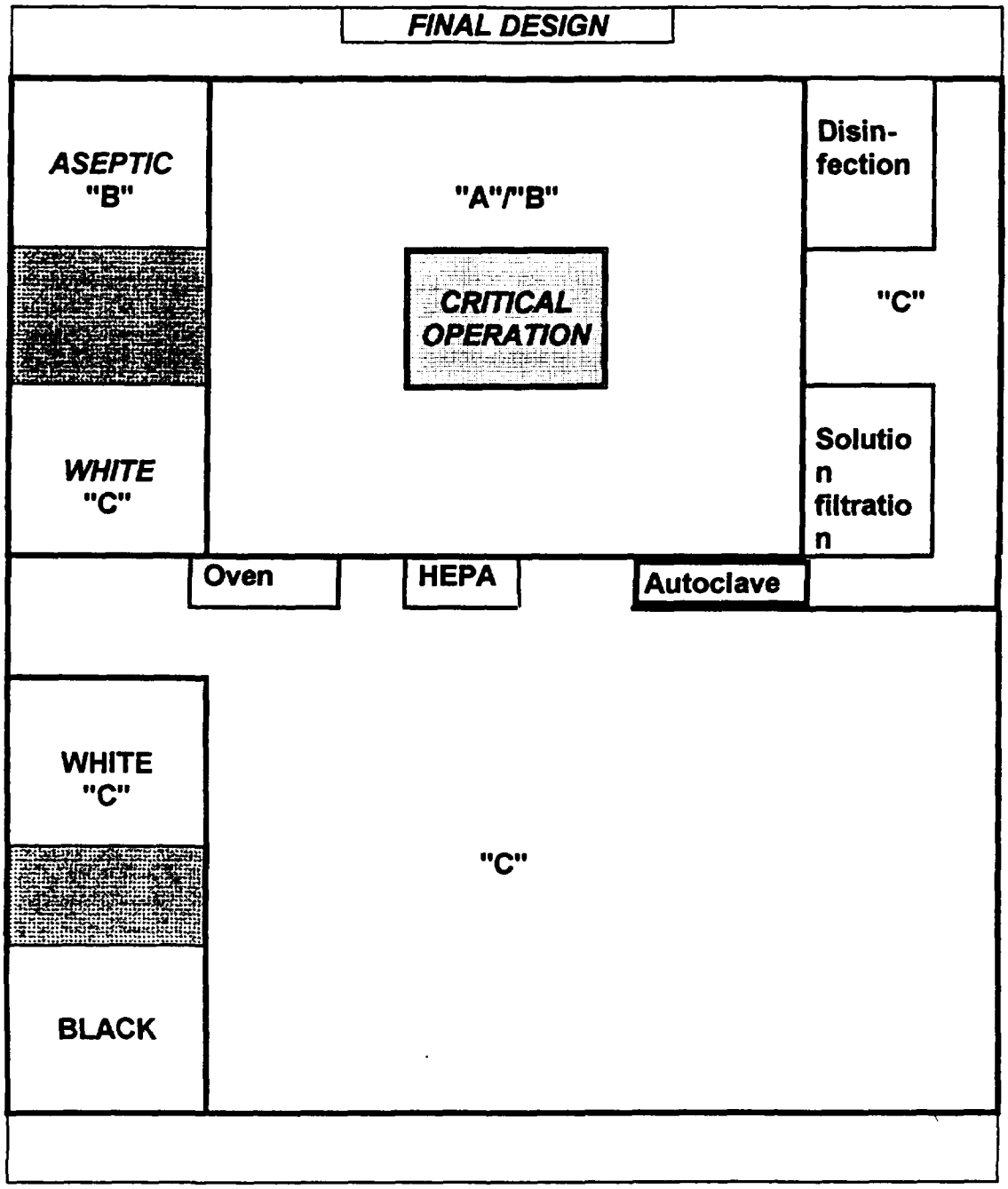
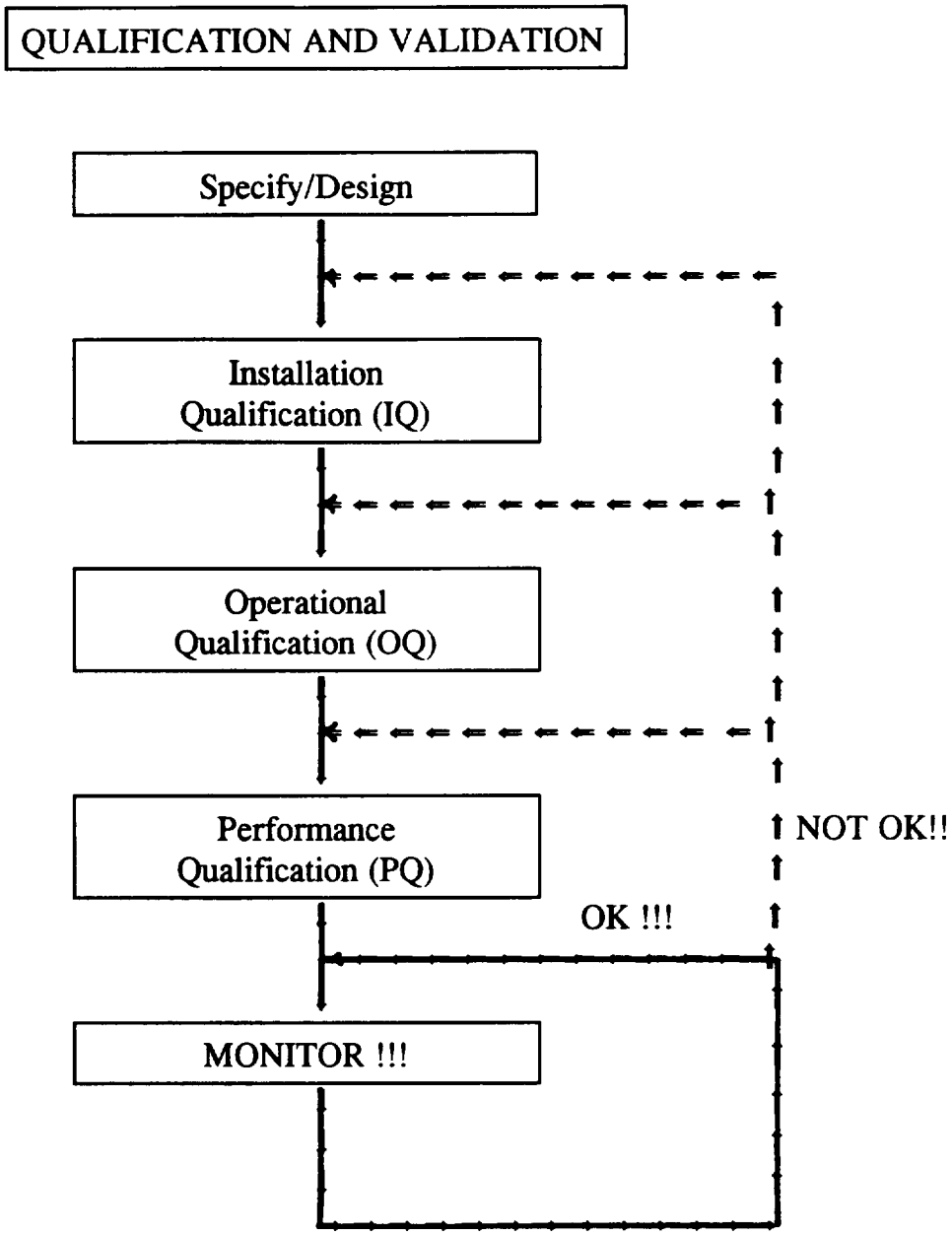


Fig. 7 **VALIDATION OF CLEAN ROOMS**



Annex 6

VALIDATION OF STERILISER (AUTOCLAVE/KINETICS OF MICROBIAL DEATH)

(Lecture presented in "Training Course III on QA/GMP concerning Sterile Pharmaceutical Manufacture" held in Damascus on 17-18 September 1996, and in Aleppo on 25-26 September 1996)

by Gabor SZEPESI

1. Moist heat sterilisation

Moist heat or steam sterilisation is carried out in a vessel into which saturated steam under pressure is introduced to achieve a temperature above 100°C.

1.1. Mode of killing

Steam contains two kinds of heat:

- sensible heat to be measured by thermometer,
- latent heat to be required to convert water to steam, and to be released when the steam is condensed.

Moist heat sterilisation kills the microorganisms by the transfer of sensible and latent heat leading to the coagulation of essential proteins in microorganisms and to their death. Heat transfer by preparing steam under pressure is more effective improving the lethality of the process.

1.2. Critical parameters

Critical parameters of moist heat sterilisation are as follows:

- temperature (higher temperature is more effective for killing),
- pressure (temperature and pressure together ensure the saturation of the steam required for efficient transfer of latent heat),
- time (longer exposure time with steam under pressure increases the killing effect).

Temperature in °C	Corresponding relative pressure in bar	Recommended time in min
115-118	**0,70**	**30**
121-124	**1,05**	**15**
126-129	1,40	10
134-138	2,25	3

- efficiency of air removal (if the temperature is achieved partly by conductive heating not by saturated steam (air pocket is formed), lethality of the sterilisation process will dramatically decrease.

Efficiency of the air removal is a function of two factors:
- material to be sterilised,
- design of the system.

Considering these two key factors, four basic types of moist heat sterilisation cycles have been developed as discussed in details below.

- gravity displacement cycles,
- fluid cycles,
- porous load cycles,
- air ballasted cycles.

1.3. Gravity displacement cycles (see Fig 1. for details)

Because the steam is less dense than air, the entering steam rises to the highest point, thus the air is displaced downwards, and exits the system at the lowest point, the condensate exits the system also at the lowest point.

The success of sterilisation depends on

- free circulation of steam,
- absence of entrapped air and condensate,
- correct loading of vessels.

This system is used mostly for unwrapped materials, utensils, e.g. machine parts, tubes, tools, etc., where the air removal is simple and easy.

1.4. Fluid cycles (see Fig.2 for details)

The system is similar to gravity displacement, but the air removal is supported by the use of vacuum. The vacuum is broken by entry of steam.

The application of liquid cycles is similar to gravity displacement, however, the reliability of the cycles is very much improved. This programme can be used for sterilisation of solutions, water in rigid sealed containers, etc.

1.5. Porous load cycles (see Fig. 3 and Fig. 4 for detail)

For more complex materials to be sterilised, such as long lengths of tubing, cartridge filters, clean room clothing, etc., more rigorous air removal technique can be applied including the application of repeated vacuum pulses which are broken by entry of steam. Each vacuum stage is followed by steam injection until the residual air is below 1 % (normally three vacuum stages are sufficient), and further vacuum stages will remove the air to very low level.

Vacuum pulses can be **sub-atmospheric** (the steam is introduced to just below atmospheric pressure), **super-atmospheric** (steam is introduced under higher pressure than atmospheric pressure, (e.g. British sterilisers), or in combination (e.g. Fedegari autoclave).

Effective air removal depends on

- design, wrapping and orientation of the components to be sterilised,
- integrity of the chamber under vacuum.

The control procedures are as follows:

- air leak rate test (the air do not enter into,,the chamber during vacuum stage)
- measuring the effectiveness of air removal (e.g. Bowie-Dick test)
- measuring the air in the steam (air detectors)

1.6. Air ballasted cycles (see Fig. 5 for details)

In case of less secure closure systems (such as vials) and flexible plastic containers the internally generated pressure should be much higher than the external pressure generated by saturated steam leading to damage of the containers during the sterilisation process. If the pressure difference would be eliminated by increased external steam pressure, the sterilising temperature will increase dramatically. Therefore, the best way to equalize the pressure difference by using air to raise the external pressure. To avoid the separation of the two gases (steam and air) leading to temperature variations within the chamber, fans are situated within the chamber to ensure good steam/air mixing at all times. The critical parameters for this air ballasted system are the steam/air ratio and the fan performance.

2. Steam quality and GMP issues for steam systems

As the steam quality has a direct influence on the products and components to be sterilised, clean steam must be used for sterilisation to avoid chemical contamination. The steam is generated from purified water by using specialized clean steam generator, and welded stainless steel piping is applied for steam distribution.

2.1. Critical Quality Specifications for steam

- chemical quality: condensate should meet Purified water specification,
- microbiological quality: condensate should be sterile and pyrogen free,
- physical quality: must be saturated (dryness value 0,90 to 1,05), and low content of non-condensable gases (lower than 3,5% v/v),
- capacity/pressure: high demand (no compromise is allowed regarding pressure or other quality requirements).

2.2. Design for steam systems

- supply water quality
- pressure
- materials of construction
- drawings

2.3. Installation

- control of components of system
- control of material of construction
- weld quality
- pressure testing
- calibration of key instrumentation
- drawings update (if necessary)
- passivization (if necessary)

2.4. Operation

- steam quality
  - chemical
  - microbiological
  - dryness
  - non-condensable gases
- pressure
- maintenance and calibration
- records of performance
- change control
- start up time for generators prior to steam use

Requirement of steam quality and the methodologies to be followed can be found in the following standards:

BS 3970
HTM 20/10

3. Qualification and validation

In order to have confidence in the reliability and consistency of moist heat sterilisation processes, it is necessary to qualify the equipment and validate the process.

During the qualification and validation studies we have to consider,

- the characteristics of the equipments, which would be controlled,
- type of control methods, which we are intending to use,
- to formulate acceptance criteria that the correct work of the equipment, or the suitability of the process for the intended application should be supported.

Three types of qualification work can be distinguished:

- installation qualification (IQ)
- operational qualification (OQ)
- performance qualification (PQ)

A more detailed discussion of qualification will be given in later subsections.

3.1. Acceptance criteria

Validation protocol should specify a sufficient number of replicate process runs to demonstrate reproducibility and provide an accurate measure of variability among successive runs. The test conditions for these runs should encompass upper and lower processing limits and circumstances including those within standard operating procedures, which pose the greatest chance of process and product failure compared to the ideal conditions, such conditions have become widely known as "worst case" conditions. However, "worst case" conditions do not necessarily induce product or process failure. The user (manufacturer) should carefully evaluate all factors that affect the product quality, and the key factors should be carefully defined in terms of their characteristics, such as physical, chemical, electrical and performance characteristics. Acceptable ranges or limits should be established for each characteristics, which are named as acceptance criteria.

Acceptance criteria can be divided into two major groups:

(a) General acceptance criteria

General acceptance criteria include the limits or ranges, or minimum requirements which should be considered in each case independently from the type of equipment or process.

(b) Specific acceptance criteria

Specific system or equipment may each have unique criteria which must be satisfied. These criteria refer to the specific system or equipment only, establishing confidence that the system or equipment is capable of consistently operate within the pre-specified variations of the conditions, and the process is effective and reproducible.

3.2. Installation qualification

Installation qualification shall demonstrate that the building construction including forming of the manufacturing areas, as well as the various systems and items of the equipment conform to their purchasing specifications, design drawings, user requirements as defined in the contract.

Main purpose: to confirm that we have what we ordered.

The installation qualification consists of a review of:

- Equipment specification
  - pressure gouges
  - timing devices,
  - temperature recording devices
  - valves, traps, etc.

- Ancillary Equipment specification
  - steam generator
  - air filtration system
  - vacuum pump

- Utilities required
  - power source
  - compressed air
  - cooling water

(a) General acceptance criteria for moist heat sterilisers

- The equipment and system must be installed according to the approved engineering documents and drawings (Master documents), including the following documentation and drawings:

  - Process and Utility diagrams
  - Engineering schematic diagrams
  - Piping and Instrumentation drawings
  - Equipment/System Specifications
  - Vendor supplied documents
  - Electrical drawings
  - Operational, Maintenance and Software documentations
  - Computer hardware documentation, where applicable

- All equipment, piping, wiring, instrumentation must be clearly identified, and their conformity to the description in the drawings must be confirmed.

- All electrical and instrumentation wiring shall be completed in accordance with the design documentation, and all loops must be functional.

- Instrumentation must be calibrated using approved written procedures and standards (where it is required and possible).

- Piping and equipment/system intended to operate under pressure or vacuum must be tested and certified.

- All piping and ducting systems shall have been cleaned to remove the all dust, particles, etc. formed during the construction and installation.

- Materials of construction shall be checked for conformity against the specification.

- All installed air filters and process filters shall be checked for conformity against the specification.

(b) Specific acceptance criteria for moist heat sterilisers

- Calibration of installed thermocouples and pressure control instruments must be performed and certified.

- The installation of the closed chilled water circuit for the vacuum pump cooling must be performed and certified.

- Sterile air filter shall be capable for in situ steam sterilisation.

3.3. Operational qualification

Operational qualification shall serve to demonstrate that the equipment or system operate as intended in the absence of materials.

The main aim is to establish assurance of consistent operation:

- instrument calibration,
- chamber pressure,
- jacket pressure,
- heat up, cool down rates,
- temperature hold,
- cycle timing,
- empty chamber heat distribution.

(a) General acceptance criteria

- All testing performed as part of OQ must be completed in accordance with approved protocols and written procedures.

- All automated sequences, interlocks, alarms, timers, counters, etc. must operate repeatedly as specified in the documentation and specification.

- Equipment and systems must function reliably under environmental conditions approximately those of normal use.

- All instrumentation (indicating and recording) must be calibrated or certified by the manufacturer.

- Draft SOPs shall have been prepared for the operation of each system or equipment. Critical instrument loops for systems shall be verified for proper operation.

- All safety valves, switches and other emergency systems shall be verified for proper operation.

- All required documentations for each system and equipment shall be available on site and shall be approved.

(b) Specific acceptance criteria

- The autoclave shall maintain a distribution temperature range of +/- 0,5°C throughout the expected operating temperatures, 100-102°C, 115°C, 121°C. The heat distribution study shall be performed with at least 6 calibrated thermocouples (or maximum 12 thermometers), which are independent from the installed ones for chamber monitoring, and regulation and located on different places of the trolley trays (corners, middle, bottom and upper trays, near to the condensate drains). The heat distribution study with the empty chamber shall be recorded by calibrated recorder independent from the installed one of the autoclave.

- The autoclave shall maintain a heat penetration temperature range of +/- 0,5 to 1°C under the testing and recording conditions as described above, but with loaded chamber. The thermocouples shall be fitted in test bottles and ampoules. The test bottles and ampoules shall be placed on the sterilisation trays as described above in order to represent the heat penetration characteristics in the whole chamber.

- The appropriate location of cycle regulation thermosounds placed in the reference bottles and representing the "coldest points" of the load must be verified. The sterilisation period must be started when the required sterilisation temperature has been reached at the coldest point of the load, determined during the heat penetration study.

- The flow rate, pressure, in- and outlet temperature throughout the closed chilled water circuit system for the cooling of the load shall conform to the vendor specification at the expected operating temperatures during the qualification studies of cycle runs. The cooling cycles (chamber/product °C and chamber pressure vs. time) must be recorded.

- Chamber vacuum leak rate shall not exceed 10 mbar/8 min and 50mbar/30 min

when the empty chamber is tested at 60, 80 and 100 mbar.

- The ampoule vacuum leak test cycle with loaded chamber including final rinse of the leak tested load shall conform to the specified cycle parameters: chamber pressure - vacuum (mbar), number and time period of vacuuming, load and chamber temperature, rinse water temperature, temperature of the load at the end of the cycle. It must be verified that the ampoule vacuum leak test program run both:

  - as continuation of the sterilisation of the load, and
  - individually, without previous sterilisation of the load.

  In this case the load temperature must not exceed 60 °C during the cycle run.

The cycle runs and parameters (pressure /vacuum/, temperature vs. time) should be recorded.

Verification of the door interlock operation must be done.

3.4. Performance qualification - Process validation

The performance qualification shall demonstrate that each system and pieces of equipment will perform its intended function as desired resulting in components, materials, products and results that conform to their established Quality Test Specification. Such performance shall include the documentation of parameters, measurements, conditions, etc. as specified in the design documents.

This study serves to demonstrate that the chosen cycle will reliably and consistently deliver the required time/temperature parameters throughout a given load/chamber and pipework combination.

This generally consists of:

- loaded chamber heat distribution study;
- equipment mapping study;
- heat penetration - cold spot studies.

(a) Loaded chamber heat distribution

- use maximum and minimum loads
- for each distribute thermocouples evenly throughout chamber (not touching solid surfaces)
- place one probe in drain or by vessel controller sensor
- deviation of individual probes from mean should not be greater than +/- 0,5 to 1°C

(b) Equipment mapping to determine:

- the coldest point in each item of the equipment (and hence the critical spot to place thermocouple)
- the most difficult item of equipment to sterilise (that item of equipment with the lowest heating coldest point)

(c) Heat penetration

To assure that the coldest item of equipment within a loading pattern will consistently be exposed to sufficient heat lethality (e.g. acceptable time/temperature combination):

- use maximum and minimum loads;
- position thermocouples at coldest point of slowest heating equipment;
- position slowest heating equipment at coldest part of the chamber (or, if unknown throughout the chamber);
- demonstrate the slowest heating equipment at coldest part of chamber receives sufficient heat lethality;
- repeat minimum twice to demonstrate consistency;
- if necessary, place microbiological indicator (strips containing 10^6 spores of a thermally resistant organism, such as Bacillus stearothermophilus) adjacent to thermocouples to demonstrate that the chosen sterilisation cycle will reliably kill a large number of resistant microorganisms.

(d) General acceptance criteria

- The critical processing steps for each system or piece of equipment shall be observed in at least three consecutive production scale trials.

- Critical operating parameters shall be independently measured and documented in each trial runs.

- All testings performed as part of PQ must be completed in accordance with the approved protocol and written procedures.

- Key parameters for each system or piece of equipment must be maintained within the limits specified in the design documentation.

- Systems assembled from a number of individual pieces of equipment must be shown to operate successfully as an integrated system.

- Equipment and system controls shall fulfils the functional requirements.

- System shall perform as intended with regard expected yields volumes, flow rates, cleanliness, sterility, particle and microbial contamination levels, etc., as described in the various documentations.

- Components, materials (including compressed air, steam and protection gases in contact with the product or internal surface of primary packaging materials and product lines) products, etc., processed by each system or piece of equipment shall confirm to appropriate in-process control of finished goods specifications.

- The PQ trials shall be performed using actual production materials, unless an individual protocol provides for the use of placebo or other materials.

- All materials and components utilized in the PQ activity must meet the corresponding Quality Test Specifications.

(e) Specific acceptance criteria

Typical programmes and acceptance criteria are included in the following Tables:

Cycle	Conditions	Temp.	Time	Pressure	Fo min-max	Other
Vial programme-1	121 °C /20 min, cooling with air and counter pressure	+/-1 °C	+/-1%	+/-10%	min:25 max:30	-
Vial programme-2*	121 °C /15 min, quick (forced) cooling with spraying or air and counter pressure to reach a product temperature of 100-105 °C	+/-1 °C	+/-1 %	10%	min:15 max:20	-
Ampoule programme-1**	121 °C/20 min. vacuum leak test final rinse of load	+/-1 °C	+/-1%	+/-10%	min:25 max:30	-
Ampoule programme-2**	115 °C/40 min vacuum leak test final rinse of load	+/-1 °C	+/-1 %	+/-1 0%	min:15 max:20	-
Ampoule leak test programme**	vacuum leak test final rinse of load	+/-1 °C	+/-1 %	+/-10%	-	-

* Air ballasted cycle
** liquid cycle

Cycle	Conditions	Temp.	Time	Pressure	Fo min-max	Other
Porous programme for aseptic clothes	fractionated prevacuuming, heating, sterilisation at 121 °C /20 min., vacuum drying 30 min.	+/-1 °C	+/-1%	+/-10%	-	-
Rubber stopper programme	time and pressure controlled prevacuuming, heating, sterilization at 121 °C /20 min., vacuum drying 60 min.	+/-1 °C	+/-1 %	+/-10%	-	KF water max 100 mg/stop
Utensil programme for machine parts, tubes, tools, glass and metal wares	fractionated prevacuuming, heating, sterilisation at 121 °C /20 min, vacuum drying 30 min.	+/-1 °C	+/-1%	+/-10%	-	-
Filter programme	prevacuuming, heating sterilisation at 121 °C /20 min, no vacuum drying	+/-1 °C	+/-1 %	+/-1 0%	-	-

3.5. On-going control and preventive maintenance

Validation of moist heat sterilisation cycles itself is not sufficient to guarantee satisfactory sterilisation on an on-going basis. Therefore, the continuous control of sterilisation is very important. This includes the followings:

- planned maintenance and calibration schedules,
- change control procedures,
- control of steam quality,
- strict adherence to validated loading patterns,
- critical review of cycle charts to ensure no deviation from validated cycle parameters.

Recommended routine testing and monitoring program is collected in the next Table:

Frequency	For each sterilisation cycle	Extra program for porous cycle
DAILY	- temperature (steriliser recorder, temperature recorder chart) - pressure (indicator gouges)	- Bowie-Dick tape test
WEEKLY	- Automatic temperature and process test	- Bowie-Dick tape test - Leak rate test
QUARTERLY	- Thermocouple test	- WEEKLY test - Air detector function test
YEARLY	- QUARTERLY test	- QUARTERLY test - Air detector performance test

The sterilisers will need their regular preventive maintenance. Most steriliser manufacturers provide a planned preventive maintenance programme, which is part of the Instruction Manual. The steriliser manufacturers will also carry out the quarterly, half yearly and yearly maintenance tests under guarantee during the first year of operation, which is the most useful training for the local engineering group to perform these tests later on. Here, only the daily and weekly performed tests are mentioned, because these tests shall be performed by the local staff from the start of operation.

The daily and weekly performed tests are collected in the following Table:

Frequency	Task
DAILY (User tasks)	- Clean all foreign matter from the chamber - Clean chamber drain filter - Clean door seal, inspection for door condition - Fill new chart to recorder, check pens are marking well - Examine sterilisation processing log for operation - Ensure the plant history record is kept up to date - Perform Bowie-Dick test
WEEKLY (Engineer task)	- Check the daily tasks have been carried out - Check door alignment and operation - Check manual door override for operational safety - Check operation of safety valves - Check operation of steam traps - Clean all strainers - Check operation of vacuum pump - Check the water level in the feed tank, and the operation - Check the oil level of the compressor - Check all pipes and connections for leaks - Lubricate door mechanisms - Check operation of all indicator lights - Carry out air leakage test - Carry out Automatic Temperature and Process Control test.

4. Specific tests for validation of moist heat sterilisers

4.1. Bowie-Dick (steam penetration) test

The ability of pre-vacuum type autoclaves to effectively remove air from the porous loads is checked by Bowie-Dick test. The test strip is placed into the centre of prepared package of textile material, and the package is placed into the chamber next to the vacuum exit. Using porous cycle the material is sterilised at 132-134 °C for 10 min.

If the air and non-condensable gases have not been sufficiently removed, the test strip indicates the malfunctioning of vacuum pump, pressure/vacuum control switch, or chamber air leaks into the load.

4.2. Heat distribution test

The main purpose of this test to:

- monitor the uniform heat distribution in the autoclave,
- establish the coldest point of the chamber,
- record the heating up and cooling down characteristics of different loads,
- verify the proper operation of cycle regulation instrumentations, starting the

sterilisation cycle when the coldest point reaches the sterilisation temperature,
- demonstrate the reproducibility of the approved cycles.

The theromocouples, thermometers, Browne tubes, etc. are placed into the autoclave under unloaded and loaded (use maximum and minimum loads) conditions. For the studies at least 6 calibrated thermocouples (or maximum 12 thermometers) located at different places of the chamber: comers, middle, bottom and upper trays, near to the condensate drainage to represent the distribution in whole chamber are used. The measured values shall be recorded by calibrated recorder. The coldest points are determined both for unloaded and loaded conditions.

4.3. Heat penetration study

The conditions and arrangements of the test bottles and ampoules are the same as specified at Heat distribution test, but the thermocouples shall be fitted in test bottles and ampoules. The appropriate location of cycle regulation, thermocouples placed into reference bottles representing the coldest point is examined regarding the start of sterilisation temperature. The F_o-value is calculated according to the following formula:

$$F_o = t \times 10[(T_1 - T_2) \times Z]$$

where

F_o = time-equivalent measured at the coldest point to reach the theoretical sterilisation temperature
t = the time interval until the temperature is measured
T_1 = the actual temperature
T_2 = theoretical temperature
Z = killing rate of microorganisms at the actual temperature (for autoclaves $Z=10$)

4.4. Determination of dryness value

The principle of the test is as follows:

- Mass of the whole assembly (flask and stopper) is measured (m_o) in kg
- Mass of the assembly with water filled into flask is measured (m_s) in kg
- Temperature of the water in the flask is measured prior to start sterilisation (T_1)
- Measure the temperature of the steam when the sterilisation cycle is started at the steam supply (T_3)
- Measure the temperature of the flask when it is between 80 and 85 °C (T_2)
- Weight the flask together with the stopper and rubber tube assembly (m_t)

Calculate the dryness value according to the following formula:

$$D = [(T_2 - T_1) \times (4,18/m_s - m_o/ + 0,24)]/L(m_t - m_{s)} - 4,18\ (T_3 - T_2)/L$$

where

L= latent heat of the steam at temperature T_3 (in kJ/kg)

4.5. Determination of the concentration of non-condensable gases

The method is based on the following principle. Air is perfectly removed from water which is filled into a burette. The steam is condensed and the non-condensable gases will displace the water from the burette. The volume of the water displaced from the burette (V_b) is compared to the volume of the water produced as condensate of the steam (V_c).

$$N\ (\text{noncondensable gases})\% = V_b/V_c \times 1\ 00$$

Fig. 1 GRAVITY DISPLACEMENT STERILIZING CYCLE

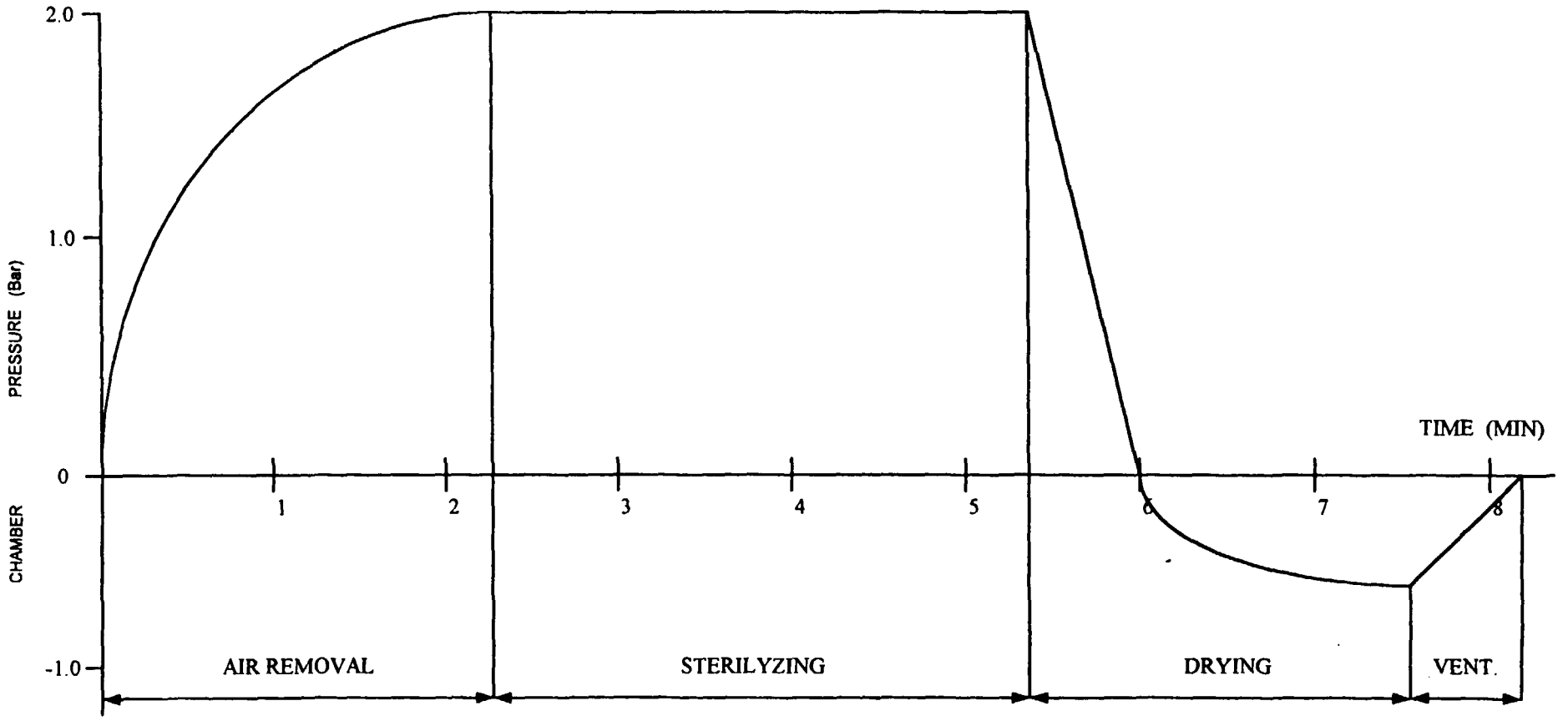
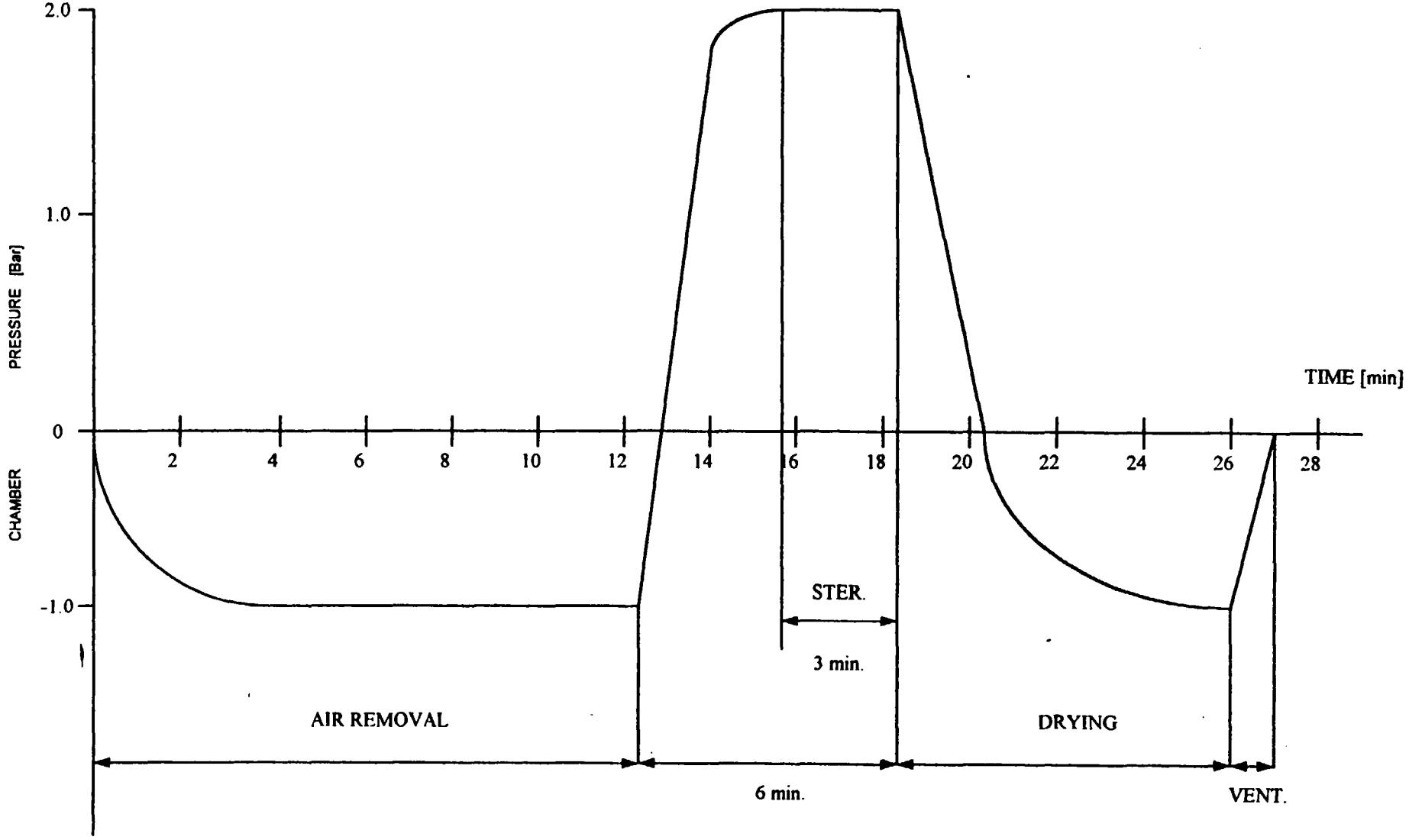


Fig. 2 HIGH VACUUM STERILIZING CYCLE



70

Fig. 3 POROUS LOAD STERILIZING CYCLE
(super atmospheric)

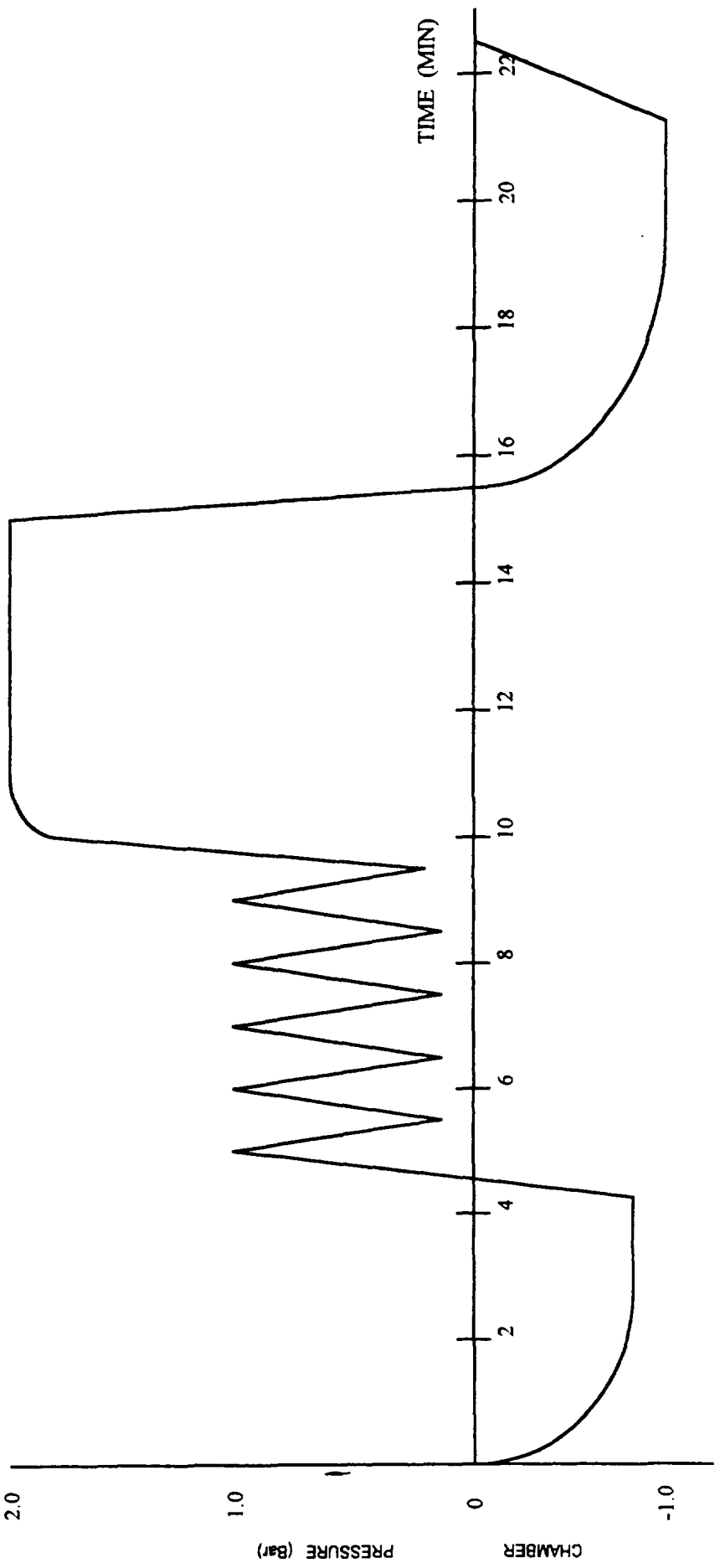


Fig. 4 FEDEGARI STERILIZING CYCLE

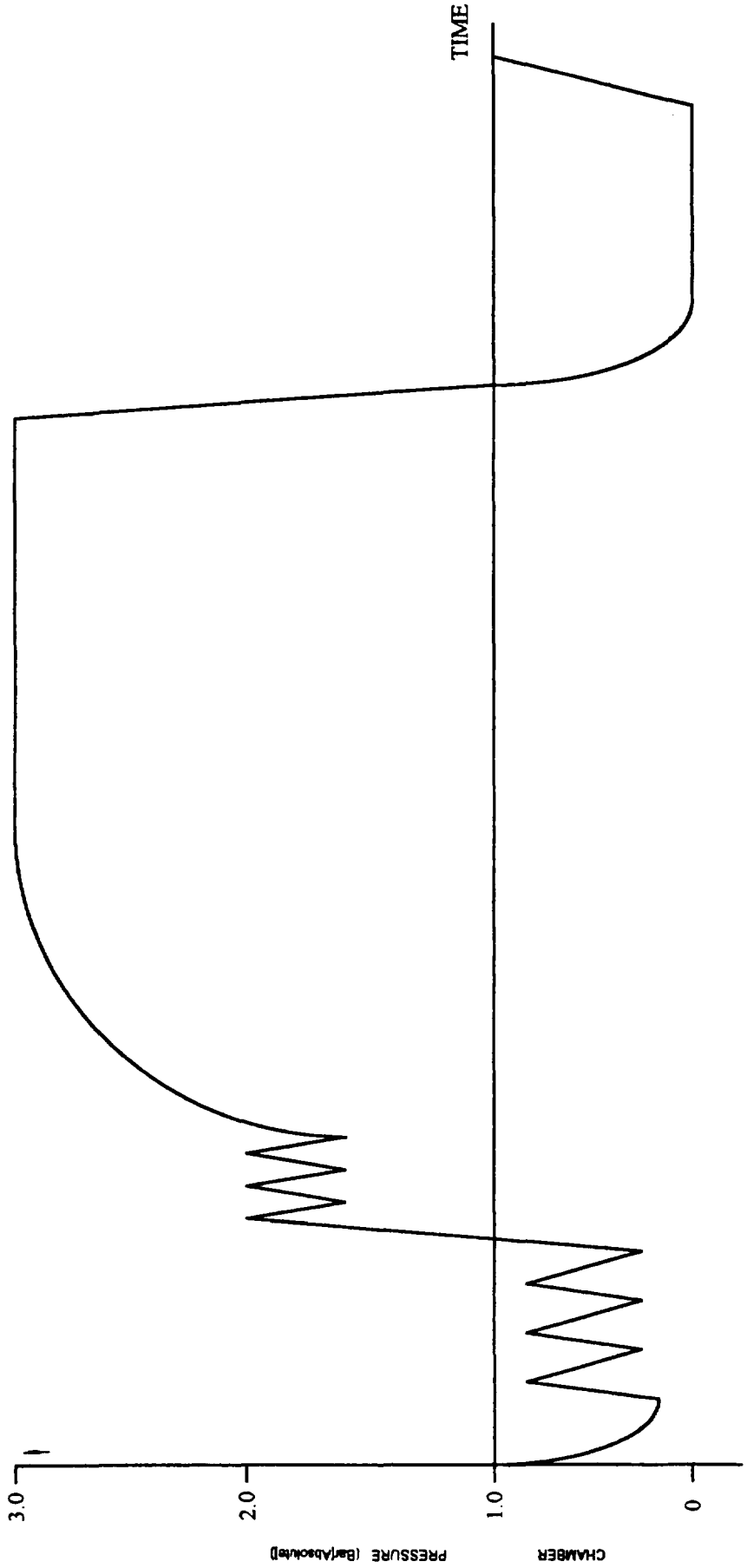


Fig. 5

AIR BALLASTED CYCLE