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**INTEGRATED DEVELOPMENT OF PHARMACEUTICAL INDUSTRY  
IN THE SYRIAN ARAB REPUBLIC**

DU/SYR/92/008

SYRIAN ARAB REPUBLIC

**Technical report: Findings and recommendations\***

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

*Based on the work of Mr. Gábor Szepesi,  
STC on pharmaceutical raw materials/quality control*

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\* This document has not been edited.

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## ***INTRODUCTION***

Project number DU/SYR/92/008/11-08 aim to assist and strengthen the Syrian pharmaceutical companies adopting the basic GMP requirements and introducing of standards for pharmaceutical production. It includes the following most important topics:

1. To assist and strengthen the management of the pharmaceutical companies to improve the system of procurement of pharmaceutical raw materials in order to obtain high quality products at reasonable price.
2. To assist the management to improve the storage conditions of raw materials in compliance with GMP.
3. To assist and strengthen the quality control laboratories.
4. To assist the management for proper order and use of raw materials at the formulation processes.

These four main activities, however, can be reformulated for two basic problems as mentioned below:

- 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.

This project was part of a general project DU/SYR/92/008 entitled "Integrated Development of Pharmaceutical Industry in the Syrian Arab Republic" and at the same time three consultants were in mission, Dr. G. Szepesi (writer), Mr. J.T. Brown and Mr. J. Clark. The writer worked separately with the other two consultants, but the valuable discussions with them presented a great help for the writer.

## ***SUMMARY***

This abstract is collected to summarize the most important findings and recommendations of the UNIDO's consultant on the project DU/SYR/92/008/11-08 dealing with the assistance to improve the system of procurement of pharmaceutical raw materials in order to obtain high quality products at reasonable price, as well as with strengthening the quality control laboratories for the characterization and standardization of quality of raw materials.

### **A. Procurement of raw materials and problems related to this topic**

Working principles and concepts of the consultant can be characterized as follows:

1. Firstly, to formulate the problems as precisely as possible /diagnosis/.
2. Secondly, to find the reasons and their consequences /findings/.
3. Thirdly, to find the solutions, and to give the necessary tools for solution /recomr:endations/.

#### *1. Problems*

##### 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.

*II. Reasons and their consequences (see Table 1 for details)*

The most important problems, 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 are not adequately handled (in-house expiry date and retesting date system does not work).
2. QC do not work: effectively work due to lack of qualified persons and instruments.
3. QA is not established yet.

Table 1

Problems	Reasons	Consequences
Problems 1/a/, and 1/b/	QC does not effectively work, lack of qualified persons and necessary instrumentation	Quality and grade of raw materials are not adequately characterized
	Vendor is rather selected according to price of raw material, then the quality as the vendor selection is based on the tender price	The quality is highly dependent on the selected vendor
Problem 2.	Lack of good technological background	Quality requirements related to formulation technology is not incorporated into the Analytical Test Specifications.
	Lack of good analytical background	Special purity tests related to the stability of the raw materials are not incorporated into the Quality Test Specification
	Stability tests are not adequately performed due to the lack of qualified persons, instruments and information	Decomposition of raw materials and formulated products under the given storage conditions are unknown
Problem 3/a/	Tenderization of purchasing raw materials	Companies are forced to order much higher amount of raw materials than the actual requirements
Problem 3/b/	QA is not functioning	Storage conditions are not considered, when the raw materials are used for production.
	QC is not effectively work	Expiry quality is unknown.
	In-house expiry date and retesting date are not used and not labelled	No reliable information available until the raw materials can be used for production. Raw materials can easily overrun their latest applicability date for production.



### *III. Recommendations and too's*

#### 1. Purchasing raw materials

The recommended system includes two basic 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 in 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 services of a UNIDO consultant specializing in this field as well as in the field of stability testing is highly recommended.

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

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

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

#### 4. QA/QC problems

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

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

## **B. Assistance of QC laboratories**

Through the writer's visit at the National Drug Quality Assurance and Research Laboratories, a well established and organized laboratory has been found. As a whole, the Laboratory works according to the current GCLP rules, and equipped with the most important instruments necessary for supervising of quality of imported raw materials and production of the pharmaceutical industry.

Only few problems have been experienced.

### *I. Sterility test*

The presently existing laboratory for sterility testing is unsuitable to prevent accidental bacterial contamination, therefore significant improvement in air conditioning, changing room, material handling, etc. is absolutely necessary and highly recommended.

### *II. Standard operating procedures*

The most important SOP's are available. The introduction of the following SOP's has been recommended and advised:

1. General SOP /SOP for preparation of SOP/
2. SOP for arrival and documentation of reference standard materials
3. SOP for storage and handling of reference standard materials

### *III. Research and development program for pharmaceutical companies in Syria*

The necessary instructions for the different programs have been given.

### *IV. Instruments*

The laboratories are furnished with the most important highly sophisticated separation techniques, such as GC, HPLC, as well as with the equipments for the establishment of the physical state of the raw materials (DSC, particulate counter, IR-spectrophotometer, etc.).

In the future the introduction of one relatively new technique, *high-performance capillary electrophoresis*, is highly recommended, due to its capability for:

- separation of high molecular weight compounds (e.g. dextrans, proteins and polypeptides).
- separation of optical isomers including enantiomers.
- separation of active compounds in complex biological matrices (bioavailability studies).

## **RECOMMENDATIONS**

### **A. Procurement of raw materials**

1. To stop the presently existing purchasing system using tenderization for all imported raw materials in the public sector.
2. To introduce the direct partnership concept including vendor selection and certification, as well as vendor partnership.
3. To introduce the JIT (Just in Time) and MSR (Minimum Stock Requirements) concepts to rationalize the warehousing system at the pharmaceutical companies.

### **B. Quality control/Quality assurance units**

#### **I. Standardization of quality and grade of raw materials**

1. To extend the Quality Test Specification 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 in the use of the formulated products.

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

2. Due to lack of suitable analytical background at the companies working in the public sector, including qualified personnel and instruments, a suitable UNIDO project to assist the management and QC laboratories in the field of industrial analytical investigations (separation methods, physical testing methods, etc.) through the services of a UNIDO consultant specializing in this field as well as in the field of stability testing is recommended.

This UNIDO project for development and validation analytical methods and stability testing is recommended both for the National Drug Quality Assurance Laboratories, and pharmaceutical companies working in the public and private sectors, as well.

Recommended post title:

"STC on development and validation of analytical methods suitable for characterization and standardization of qualities of raw materials and finished products - stability testing, types, applications and methods"

## II. Instruments - equipments in the QC laboratories

1. Regarding the pharmaceutical companies to furnish the QC laboratories with the necessary number of highly sophisticated instruments (such as HPLC) is recommended.
2. Regarding the National Drug Quality Assurance and Research Laboratories whose presently existing laboratory *dedicated for sterility testing* is unsuitable to prevent accidental bacterial contamination, a significant improvement in air conditioning, changing room, material handling, etc. is absolutely necessary and highly recommended.
3. Regarding the National Drug Quality Assurance and Research Laboratories, the introduction of one relatively new technique, *high-performance capillary electrophoresis*, is highly recommended.

## III. QA unit

The introduction of QA function at the companies working in the public sector (in the private sector QA is functioning) is absolutely necessary and recommended.

### **C. Warehousing system for raw materials**

1. The introduction of in-house expiry date-retesting date system at the pharmaceutical companies in Syria is highly recommended. The necessary instructions have been given. Important analytical task has to be taken to establish the *expiry quality* of the raw materials.
2. Introduction of appropriate documentation in the raw material storage rooms, such as
  - material receiving card,
  - BIN card.

Necessary instructions have been given.

### **D. Problems related to the formulation processes**

1. Standardization of the quality of raw materials with special regards to the given production technology.
2. In the hazardous area (particularly in the antibiotic production areas) more rigorous clothing rules should be developed.
3. The movement and number of workers in the hazardous area should be regulated.

4. In the course of products, where technological process(es) depends on the quality of supplied raw material, the production technology should be evaluated as a function of the physical state of the raw materials.
5. Prescriptions of safety and environmental protection regulations for all procedures should be developed with special emphasis on processes used in the antibiotic production areas.

**SYSTEM FOR BUYING RAW MATERIALS  
VENDOR CERTIFICATION PROGRAM**

The quality of the raw materials (QRM) used for the production of various pharmaceuticals has a great importance, because of the following:

- the quality of the finished product could be a function of QRM,
- the pharmaceutical technology to be applied may also be influenced by QRM,
- expiry date of the raw materials is highly dependent on QRM,
- expiry date of formulated products would be influenced by the age of raw materials, etc.

The primary aim of each pharmaceutical company when purchasing raw materials from outside sources is to order raw materials:

- in the best quality,
- under the best conditions,
- for the best price.

To achieve this main goal, the following considerations should be taken into account:

1. The quality of the product has a primary importance. However, the QRM has to be in accordance with the used pharmaceutical technology. If various formulated products are manufactured from the same raw material, the best quality is equivalent to the quality that can be used for all formulations (quality of worst case formulation), with the exception of sterile products, when extra requirements must be put into the quality test specification (sterility, pyrogenicity).
2. Best conditions include the optimum conditions for:
  - batch size,
  - packaging size,
  - expiry date,
  - transportation,
  - others, such as sending presample to be represented for the batch, sample to be jointed to the batch for analysis (sterile products), etc.
3. Best price means the lowest price for which the best quality, under the best conditions could be available, but it is not equivalent to the lowest price itself.

**A. System for purchasing raw materials considering the presently existing situation in Syria**

The presently existing system for purchasing raw materials significantly differs for public and private sectors in Syria. In the private sector all decisions are made by the companies. Direct contact exists between the customer and vendor which can mostly solve the problems discussed in this subsection, or these problems do not exist for the private customer companies. For this reason the topic is mainly focused on the companies working in the public sector using a centralized, tender-based purchasing system.

*I. Findings*

1. Presently existing purchasing system in Syria in the public sector

The presently existing system in Syria centralizes the purchasing of raw materials. Technical Committee belongs to the Ministry of Health (marked as MOH in the material) collects all ordering, the basic tender conditions and quality requirements, and based on these data tenderizes all items of the public pharmaceutical companies (marked as user). This system suffers from several disadvantages, such as:

- highly bureaucratic, long procedure.
- can lead to wasting time which forces the users to order higher quantities for a longer period of time (approx. 2 years).
- increasing the risk of unstable materials will overrun the latest date for their applicability for production of formulated products.
- the price concept will surely dominate, losing the priority of the quality concept, which is very dangerous.
- the consistent high quality of the raw materials might be lost, the quality of the raw materials could be a function of the vendor offering the lowest price, even if the quality of the raw material will satisfy the requirements in each case.
- the system is very rigid, does not give possibilities for prompt ordering or changing the ordered quantities, etc..
- the high inventory level increases the production and analysis costs, may lead to high inventory for years, if the sales figure of the finished product is reduced from one year to another, and as a whole will lead to an unnecessarily increased demand for foreign currency.
- storage rooms will be filled up with materials, which can lead chaotic situation in the warehouse, together with the high risk of mixing materials.
- the after sale service of the manufacturing companies in most cases cannot be used, etc.



## 2. Quality of purchased raw materials

Majority of raw materials is ordered according to USP and/or BP pharmacopoeias, in several cases the former editions (USP XXI, XXII, BP80, 88) are indicated as quality sources.

In some cases additional tests relates to the particle size and bulk density of the ordered raw materials and are included in the specification, but no strict requirements are built into the analytical test specifications. Particle size distribution is not mentioned in the specifications.

The most important problem is that the quality and purity of the raw materials, which are required to manufacture the finished products with good quality at the end of their shelf lives are not clarified and defined. If the pharmacopoeia(s) do not include specific tests for purity testing, no tests for the determination of the impurities, and mostly the decomposition products are included into the analytical test specifications, therefore the decomposition products present in the raw material upon delivery are not determined and limited.

## 3. Expiry date - retesting of the raw material closed to the expiry date

This topic is discussed in detail in a specified subsection. Here, only the most important findings and problems are summarized.

- a. The quality of the raw materials required at the latest date when it can be used for production (in-house expiry date) is not clarified and defined. Raw materials are retested at the time of their expiry date, and the investigations are the same at the arrival of the raw materials, therefore, in many cases the results do not give reliable information about the applicability or non-applicability of the raw materials after longer period of time, which means a high risk of their use for production.
- b. Retesting date is also not defined for the raw materials especially in the case of sensitive materials, it leads to a high risk to overrun the latest date until this material can be used for production.
- c. Expiry date (and in many cases the manufacturing date also) is not indicated in the label of the packaging units of the raw materials as well as in the release labels. This situation is very dangerous, because can result the overrun of the expiry date of the raw materials.

## 4. Storage conditions - storage rooms.

- a. Most storage rooms are not air conditioned or ventilated (only the room where antibiotics are stored has ventilation, but neither the temperature, nor the humidity of the room are monitored). The storage conditions could significantly deviate from that one given by the manufacturer.
- b. All storage rooms are crowded with raw materials. No quarantine area is separated for the not released materials, rejected materials, materials under testing are stored together with the released materials without any physical separation, which can lead to mixing of batches and materials.

- c. First-in-First-out principle (FIFO) cannot be adequately followed, because the raw materials are not positioned (no position number system is used), and the release of the raw materials does not happen according to increasing batch numbers of the same raw material.
- d. Since the storage rooms are crowded with raw materials, no separate place or space for receiving, cleaning and sampling of the packaging units of raw materials.

## *II. Recommendations*

Considering the above mentioned problems and difficulties, a basic change in the purchasing system is recommended, which can eliminate the problems mentioned above.

### 1. Recommended purchasing system

The system which is recommended incorporates two basic principles:

- to allow the user companies directly purchasing the raw materials from the supplier (direct partnership concept).
- to use the JIT (Just-in-Time) and MSR (Minimum Stock Requirement ) concepts at the ordering and purchasing.

The direct partnership concept includes the following considerations:

- vendor selection,
- standardization of the quality and grade.
- age of the product, expiry date
- labelling instructions
- optimum batch size and packaging size.
- vendor certification and partnership
- correlation between pricing and quality

### 2. Using Just-in-Time and Minimum Stock Requirement concepts

In general, *Just in Time concept* is linking and overlapping operations to be separated in time and space, which are parallel and/or consecutively running to improve productivity, to reduce set-up times, inventory levels, etc.

The *Minimum Stock Requirement concept* includes the application of two basic principles:

- to minimize the stock of the raw materials to be stored in the storage rooms waiting for its application, and simultaneously

- to keep the suitable stock of raw materials, which is necessary to prove the consistent and continuous production of formulated products

In practice, the minimum stock is corresponding to about a quantity of raw material to be required for 2 to 5 month production of the finished product.

How these concepts work in life?

For demonstration of JIT and MSR concepts the following example is shown.

The user company produces a formulated product (named as SZEPESEI 50mg tablets) using a raw material (named as GABOR), which is purchased from a vendor.

Table 2

Composition of SZEPESEI 50mg tablets, 20x  
Batch size 2,000,000 tablets/batch, 100,000 box/batch

	per Tablet	per Batch
GABOR	50 mg	100.0 kg
Starch	40 mg	80.0 kg
Lactose	50 mg	100.0 kg
PVP	7 mg	14.0 kg
Talc	2 mg	4.0 kg
Magnesium stearate	1 mg	2.0 kg
Total	150 mg	300.0 kg

No.	QUESTIONS	ANSWERS
1	What is the sales figure of SZEPESEI 50mg tablets for the given period of time /mostly for one year, and how the sales figure can be splitted into smaller periods mostly to quarters?	1.000.000 box year 200.000 box I quarter 300.000 box II quarter 250.000 box III quarter 250.000 box IV quarter
2	What is the actual inventory level for SZEPESEI 50mg tablets?	200.000 boxes
3	What is the minimum required stock for SZEPESEI 50mg tablets considering the continuous delivery?	100.000 boxes
4	What is the total production time including packaging and QC for one batch of SZEPESEI 50mg tablets /100.000 boxes/	2 weeks
5	What is the split of production of SZEPESEI 50mg tablets for quarters considering the present inventory level and minimum stock requirement, and the sales figure, as well?	100.000 box I quarter 300.000 box II quarter 250.000 box III quarter 250.000 box IV quarter
6	Which demands of quantities of GABOR can be fitted to the sales figures determining the required quantities for:  - a year - a quarter	900,0 kg 100,0 kg I quarter 300,0 kg II quarter 250,0 kg III quarter 250,0 kg IV quarter
7	What is the actual inventory level for GABOR?	300 kg
8	What is the minimum requirement of stocks for GABOR, which can be available in each time?	min. 200 kg
9	Estimated time period between ordering and delivery of GABOR?	1 month
10	What is the minimum quantity which should be ordered considering the price of GABOR	min 200 kg consignment
11	How many GABOR should be ordered considering the MSR concepts for  - a year - a quarter	800,0 kg no I quarter 300,0 kg II quarter 300,0 kg III quarter 200,0 kg IV quarter
12	For the year demands splitted into quarters what is the date to send the request for offers	in February
13	Considering the time required for delivery and JIT concept, in which time the material should be ordered purchasing date, that the materials should be available in time?	in March 300,0 kg in June 300,0 kg in September 200,0 kg in December 300 kg /for the next year
14	Proposed date for delivery?	300,0 kg in April 300,0 kg in July 200,0 kg in October 300,0 kg in January next year

Quarterly changes in the inventory levels and stocks for GABOR and SZEPESI 50mg tablets are collected in Table 3 considering JIT and MSR concepts.

**Table 3**

	GABOR /kg/	BP*	SZEPESI 50mg tablets /boxes/
<b>Actual inventory levels**</b>			
initial	300		200.000
at the end of March	200	1	100.000
at the end of June	200	3	100.000
at the end of September	250	3	150.000
at the end of December	200	2	100.000
<b>Excess stock level***</b>			
initial	100		100.000
at the end of March	0		0
at the end of June	0		0
at the end of September	50		50.000
at the end of December	0		0

\* batches produced

\*\* actual inventory level= (recent inventory level + in coming material - quantity of raw material used for production)

\*\*\* excess stock level= actual inventory level - minimum stock requirement

The example shown here is very simplified. Only the raw material /GABOR/ was calculated.

When a real calculation can be made, it can be performed for:

- all active raw materials listed in the composition
- for all ingredients listed in the composition
- for all direct packaging materials (aluminium foil, hard PVC foil, plastic or glass vials, glass bottles, rubber stoppers, aluminium caps, tubes, etc.)
- for all printed or not printed indirect packaging materials (labels, boxes, package inserts, collecting boxes, cartoons, etc.)
- for other materials used during the production, but not listed in the composition (organic solvents, oil, etc.)

A recommended program for purchasing all materials can be seen in Table 4.

***Table 4***  
***Program for purchasing raw materials considering the JIT and MSR concepts***

Materials	Quantity required for one batch	Number of batches produced in a given period of time	Quantity required for this period	Actual inventory level	Minimum stock requirement	Quantity to be ordered	Request for offer	Date of purchasing	Proposed date for delivery	Arrival date	Responsible person
Raw materials 1. 2.											
Ingredients 1. 2. 3. 4. 5.											
Packaging materials 1. 2. 3. 4. 5. 6.											
Other materials 1. 2.											

Generally speaking, if all considerations collected in the Table 4 have been taken into account, the customer company exactly knows:

- the quantity of raw materials to be needed to buy from a vendor within a year, and also the sequences of the quantities to be ordered for a given period of time.
- the actual inventory levels will be closed to the minimum stock requirements of the materials, which results safety for the production, fast change of raw material batches in the storage rooms avoiding all expiry date problems, good conditions for storage, significant decrease in the amount of different raw materials present in the same time in the room.
- the latest purchasing date, when the ordering should be made.
- significant decrease in the risk of mixing raw materials,
- the system provides good conditions for FIFO
- significant decrease in the warehousing and analysis costs.
- save money for the customer company, etc.

The next step is to select a suitable vendor for the program demonstrated in the Tables above.

### 3. Vendor selection

Pharmaceutical raw materials can be available from three main sources:

- the company, which is producing formulated products manufactures the active raw materials (not existing in Syria),
- the company, which is producing formulated products purchases the raw materials from a manufacturer,
- the company, which is producing formulated products purchases the raw materials from a dealer, or broker.

As the first possibility cannot be further considered, as no raw material manufacturer exists presently in Syria, therefore, the remaining two other possibilities should be evaluated.

#### *a. Purchasing raw material from a manufacturer*

**Purchasing raw materials from manufacturers has a great priority, however, this statement is true only, if the raw material is purchased from a good manufacturer.**

It is very important to note that the **manufacturers** (only the manufacturer, not the broker) **have many responsibilities** relating to the raw material to be offered for sale:

- raw materials do not contain any contaminant(s) which can be hazardous for the patients, and/or may not change or modify the pharmacological effect of the formulated product(s) produced from it.
- the quality and grade of the raw material is suitable for production of pharmaceuticals.
- QRM will be satisfactory until the end of the expiry date, if the material is stored under the prescribed storage conditions.

**(i) How to characterize a good manufacturer?**

- The company is authorized to produce the raw material in question and GMP approved by the local health authority.
- The quality of the raw material satisfies the all requirements enables to use it for a longer period of time.
- Its production scale is suitable for manufacturing the required quantity of raw material in time.
- The production is consistent providing high quality. The formulation process will not be a function of quality of the supplied raw material.
- No quality or quantity claims occur at any of the shipment.
- Delivery dates are kept accurately.
- The batch size and the size of the packaging units can be easily fitted to the batch size of the formulated products.
- The containers used by the manufacturer have good quality, are well-closed, can protect the material from the environmental effects, including partial damages from outside forces.
- The containers are adequately labelled, the label contains all the data prescribed by the user company.
- Detailed Certificate of Analysis is attached to the consignment, containing all analytical data to be important to decide the quality of the supplied raw material.
- The company provides a good after sale service.
- Great flexibility in quantity and time (prompt delivery).



- The company expresses its readiness for inspection, to demonstrate the production, quality control and warehousing facilities, as well as their documentation system.
- The company could be a certified vendor in the future and ready for a long term contract with the user company (vendor partnership).

These are the most important features of a good manufacturer.

- (ii) The next problem is, how a manufacturer from a developing country could be considered, because the price of these companies mostly are much lower compared to other suppliers. How the GMP status of these companies should be evaluated?

The answer for this question is not easy, because in these countries (for example China, India, South Korea, etc.) several excellent companies satisfying perfectly all GMP requirements can be found. These companies, however, are ready for inspection (bad companies are not ready). The best recommendation is to inspect or audit them in branch, (inspection is made by the expert of the user company together with the local [Syrian] health authority), or asking an independent expert of GMP for inspection prior to the first ordering. Advantageously, the General Manager or Commercial Director of the user company is also a member of the inspection team, because, if the result of the inspection is good, the business discussion and contracting can be performed promptly.

Without any information, however, to purchase raw materials from a developing country is a high risk and cannot be recommended. This statement relates especially to the broker (dealer) companies, selling raw materials from this source.

- (iii) What is the most important features of a "not good" manufacturer?

- the quality of the supplied raw material is closed to the borderline (the manufacturer cannot provide high quality material).
- the physical state of the raw materials (particle size, particle size distribution, bulk density, etc.) varied from batch to batch, even if the criteria applied for the test are satisfied in each case (the manufacturing process is not consistent),
- the batch is not homogenous, inhomogeneity occurs within one container (sedimentation, discolourization of the surface, etc), or between containers for example each sample satisfies the quality test requirements, but the analytical results of the samples taken from different containers are varied within a broad range (unification of several batches without or with not adequate homogenization procedure, giving a new batch number, manufacturing date and expiry date for the raw material),

- visible particles can be found in one or more containers (this is the most frequently occurring problem) problems with manufacturing process, or with the application of the GMP rules.
- delivery dates are not accurately kept.
- some packaging unit contains less material, as indicated in the label.
- the packaging units are not adequately labelled, etc.

*b. Purchasing raw materials from a broker /dealer/ company*

The next question to be answered is the following: can we purchase anytime raw materials from broker (dealer) companies?

The answer is definitely yes, however, the following considerations should be taken into account:

- only from well-known, reliable broker company, the raw materials would be purchased.
- not only the origin of the manufacturing country, but the manufacturer also can be identified.
- high quality material is offered for sale.
- consistent quality of another raw materials has recently been obtained from the broker company,
- labelling instructions are accurately kept, etc.

*c. Purchasing policy and practice*

What is the good purchasing policy and practice for a user company with respect to vendor selection?

- Very sensitive (S0 group) and sensitive (S1 group) raw materials should be bought only from good (advantageously certified) manufacturer, even if the requested quantity is small. Only exception is, if the raw material is not available from that company, in this case the raw material can be bought from a broker company under specific conditions:
  - the broker company must certify in writings that the age of the product is identical with that one indicated in the label,

- the broker company can prove that the original manufacturer is a GMP approved company,
  - the broker company is ready to send presample characteristic to the batch(es) for request,
  - broker company is able to attach original copy of detailed /!!!/ Certificate of Analysis for each batch, indicating not only the test results, but also the methods used for the tests, and for request the broker company is ready to provide detailed description of the test methods including analytical service, if it is necessary,
  - in the label detailed and clear storage conditions are given,
  - in case of a quality claim the raw material will be immediately replaced with a new one originating from a good manufacturer,
  - consistent, high quality will be supplied for future deliveries,
  - if it is necessary, the broker company is ready to get the necessary information regarding impurities, their identification and determinations for request, from the manufacturer.
  - for request of user company, the broker company is ready to organize vendor audit at the manufacturer, etc.
- Raw materials belonging to group S2 (moderately sensitive materials) would be mainly purchased from good manufacturer. However, if the purchased quantity of the raw material is small, or good manufacturer cannot be found in the market, the raw material(s) can also be purchased from a good broker company as characterized above.
  - Raw materials belonging to group S3 (not sensitive materials) can be purchased from both sources. Selection of the vendor company should be made according to the basic principles, namely which company offers,
    - the best quality,
    - under the best condition,
    - for the best price.

*d. Vendor selection for a new raw material*

Vendor selection for a new raw material can be made even in development stage of the formulated product(s).

The most important manufacturers of raw materials can be found in specified books.

- The first step is to select as much manufacturer for the raw material in question as possible, and requesting samples from minimum three independent batches for analysis, together with the Certificates of Analysis.
- The following step is that all samples are very carefully tested according to the vendor specification, and by selective, stability indicating analytical methods, which are recently developed or can be found in the literature. If no method has been found, the method development and validation performed by the user company has a primary importance to accurately determine the QRM and to establish the purchasing quality.
- The samples of the best two, advantageously three vendors are subjected to extreme treating conditions (fast stability testing), to differentiate between the different vendors through the quality of the samples sent for analysis using the stability indicating analytical methods.
- Based on the results of the fast stability testing, as a first approximation, the apparently best vendors for further evaluation can be selected.
- Trial batches of formulated products are prepared in pilot scale from the raw materials bought from all selected vendors, and both the quality of the finished products and the formulation technology are evaluated with respect to the QRM.  
  
Buying raw materials in relatively small quantities shall provide information about the estimated price level of the selected vendors. However, these data can serve only as a guide, these are not suitable for a real evaluation.
- If no significant differences between the selected vendors with respect to the QRM and its effect on the formulation technology, further differentiation should be made on the basis of the contracting conditions, such as packaging size, batch size, age of the product, expiry date, after sale service, delivery time, and on that of the price of the raw materials.
- Based on the results of differentiation made between the selected vendors, the best two vendors are finally selected for supplying raw materials.

Selecting minimum two vendors for purchasing raw materials and dividing the yearly required demand of the raw material among them is a basic policy of each customer company, because it has several advantages (for the start a ratio of 80% to 20% or that of 70% to 30% is a good compromise and recommendation).

For example, if the QRM of one of the vendors is continuously decreasing, or some discrepancies with the purchased materials were found, one can turn immediately to another vendor. If the delivery dates are not accurately kept due to the problems of the production of raw materials, the missing quantities can be purchased from another vendor. It is also important, if one of the vendors wants to increase the price of the raw material, the supply ratio can be changed immediately buying higher quantity from the second vendor and less quantity from the first one.

This is one of the best ways to harmonize the QRM, the other conditions and price of the raw materials.

It is also advisable to have a long term contract (at the start half year, later on minimum one year contract can be considered as optimum) with the selected vendors, with respecified quantities and delivery dates. This means a good base for a future vendor certification and partnership, which can significantly increase the productivity, and cost-effectiveness of the customer company.

#### 4. Standardization of the quality and grade

Standardization of QRM is discussed in details in a specified subsection. Here only the most important conclusions are summarized.

- a. GMP requires consistent high quality of the formulated products produced from imported raw materials. It absolutely requires the standardization of the quality and grade of raw materials. Therefore, to establish the purchasing quality of each raw material is a primary aim to satisfy this requirement, demanding well organized, highly qualified analytical work and instrumentation. Each quality control laboratory should be furnished with equipment capable for the application of highly sophisticated analytical methods, and with well trained, qualified staff. According to the experience of the writer it cannot be found at the pharmaceutical companies in Syria, therefore, an expert mission supported by UNIDO sending a consultant to be highly qualified in this field and the field of stability testing is recommended.

HPLC equipment can be found at Thameco (presently the equipment does not work) and Dimas. The number of HPLC equipment is too small, additional equipment(s) are absolutely needed to perform the all tests (mostly stability tests) which are required.

- b. Reliable standardization of the quality and grade can be done by certification of the vendors. Therefore, vendor certification program should be started at the pharmaceutical companies as soon as possible.
- c. Standardization of quality and grade of raw material is absolutely required to effectively apply the JIT and MSR concepts, therefore as a whole, this is the basis for a good purchasing system.

#### 5. Vendor certification and partnership

Vendor certification means the highest level in the contacts and connections existing between customer (user) and vendors (manufacturers). Since the manufacturing companies of raw materials play very important role in the normal life of each quality oriented user company, it is an evident ambition from the side of user companies to collect more and more information about the vendors. During the course of time, many changes may occur in the vendor's operation, which changes may affect the quality of the raw material (e.g. changes in the manufacturing process or personnel). It is a basic requirement that the user company would be informed about these

changes in time. Only a good partnership between the user and vendor should avoid the problems related to the operational changes of the vendors. In addition, the good partnership has additional benefits in regards to quality, such as

- reinforcement of the quality objective,
- problem solving (the vendor is the most competent partner to solve smaller or bigger problems, which are not considered substantial enough, and connected with the quality of raw material),
- awareness of quality changes, which can be requested both by the manufacturer or user,
- new opportunities (e.g. new testing methods, or process improvements which may be available for the user, etc.),
- sampling (testing assessment ) additional benefit for the better characterization of the quality of raw materials.

Vendor certification is a long procedure, which consists of the following steps:

a. Collection and evaluation of all available information on the vendor.

- if the vendor is unknown for the user company, no any commercial connection exist with the vendor. The vendor's catalogue, the materials included in it, and their quality to be indicated are the possible source of information.
- if the vendor is known for the user company, another raw material(s) has been recently purchased, the following data serve as possible source of information:
  - quality of the purchased product(s).
  - quality problems, claims, and their arrangements.
  - level of certificates of analysis,
  - technological problems with purchased material(s).
  - batch to batch variability,
  - consistency in quality and delivery, etc.
- if the vendor is known for the user company and the same raw material has recently been purchased, the following data serve as possible source of information
  - the same as above,
  - quality of the raw material purchased by the vendor compared to other vendors.
  - documentation, provided by the vendor.
  - quality of containers, packaging materials used at the transportation.
  - expiry date,
  - warranty conditions.

b. Verification of the purchasing quality through the full tests of minimum three batch samples.

**Requirements:**

- the quality of all samples would be in full conformity to the stated and certified quality.
- the batch to batch variation should be as small as possible, supporting the consistency of the manufacturing process,
- the quality of the raw material would be minimum equivalent to the quality of other competent vendors.

**c. Vendor audits**

In the user and vendor partnership, this is probably the most important, but the least frequently performed, understood, or appreciated step. Vendor audits are normally performed to evaluate a potential new source, to monitor ongoing quality on a routine basis, or to investigate a specific quality problem(s) being experienced.

In respects to vendor certification all three audits have a distinguished role. But the first one (potential new source audit) has a priority.

In the course of potential new source audit, the quality level desired is clarified prior to the actual procurement is started, and the following most important parts of the vendor's operation are inspected and evaluated:

- Factory and buildings
- Manufacturing process
- Warehousing system, receipt of materials,
- Calibration, validation and their levels,
- Process and in-process control,
- Packaging and transportation,
- Documentation,
- Standard operating procedures,
- Job descriptions,
- Quality Assurance,
- Quality Control,
- Handling of claims, re-call system

- d. Purchasing the first batch of raw material to be sufficient for production of minimum three batches of finished product(s), and confirmation of QRM of the raw material through the quality of finished products produced from the purchased raw material.

If the quality of the finished product is satisfactory, the vendor will be put into the list of the raw material suppliers.

**e. Validation (certification) of a vendor**

**Requirements:**

- quality acceptance of minimum three consecutive batches of the raw material following the first batch.
- batch to batch variation calculated for the minimum four batches is negligible, proving the capability of the vendor to deliver consistent quality.
- the results of vendor audit is positive.
- vendor shows consistency in delivery,
- no any problem occur with the production technology of formulated products.

**Important notes:**

- vendor certification is **PRODUCT SPECIFIC**, not vendor specific, the certification relates only to the raw materials in question, not to the all products of the vendor,
- vendor certification is automatically withdrawn, in case of any quality claim.

**f. Analytical tests of raw material(s) supplied by a certified vendor**

In the course of a certified vendor four different levels of analytical tests can be distinguished:

- Full test : Its frequency is determined in the Analytical Control Plan to be jointly accepted in advance or in case of the results of abbreviated test require.
- Abbreviated test: Only the most important tests (identification, assay, purity test, loss on drying, etc.) are performed, which are characteristic to the QRM.
- Only identification test: If the result of trend analysis proves the consistent high quality of raw material only the identification test is performed. Release is made on the basis of the detailed Certificate of Analysis of the vendor using a selective (UV-, IR-spectroscopy) analytical method for identification.
- Extended analytical test: Besides the full analysis of the raw material, the analytical investigations are extended with additional tests not to be included in the Analytical test Specification. This test is performed, in case of any quality claim, if the quality of the raw material purchased from a certified vendor shows correlation with the not acceptable quality of the finished



product, and/or the QRM starts to continuously decrease, etc.

**g. Control Plans**

Important part of vendor certification is to establish control plans, such as:

- Analytical Control Plan: The Analytical Control Plan randomising the batches to be controlled by full tests yearly (e.g. each fifth batch, but minimum 2 year)
- Vendor Audit Plan: One vendor audit in each 2 years is generally applied.

**h. Vendor partnership**

Vendor partnership is based on the continuous good contact between the user and a certified vendor. Many benefits should be obtained for a user company from this type of partnership. The vendor can significantly contribute to solve several problems at the user company.

Only two very advantageous properties of vendor partnership are emphasized here:

- vendor can considerably contribute to the introduction and continuous use of JIT concept,
- the after sale service of the vendor company, which can be advantageously applied in the development program of the user company.

**6. Correlation between pricing and quality**

The price concept, and its criticism was mentioned several times in this material. It has to be noted that the low price itself does not mean automatically low quality, as the high price, high quality. Which was seriously emphasized in many places of the material is the quality preference, independently from the price of raw material. In addition to the price problem mentioned in the materials the following considerations are worth mentioning:

- a. The low price or high price does not mean anything without mentioning the quality of the raw material which is bound to the price. Without knowing the required purchasing quality, it is very difficult to differentiate among the qualities of raw materials, and only in a later stage - at the production - will be clear that the low price was a very high price (reprocessing cost is added), and vice versa.
- b. Besides the quality of the finished product produced from raw materials available for different prices, several additional factors relating to the cost of production should also be taken into consideration:

The production cost includes material and immaterial costs, as well. The most important elements of the production cost of a bulk pharmaceutical can be summarized as follows:

- cost of raw materials
- cost of other materials (ingredients, solvents, etc.)
- the yield of the production.
- production time relates to one batch (all time-related proportional costs of the plant, such as salaries of the workers, costs of supplying systems, etc.).
- cost of analysis, etc.

In case of any default in the quality of the product, the batch can be reprocessed, leading to extra costs, such as.

- reprocessing cost.
- reprocessing time.
- cost of loss in yield.
- extra analysis cost, etc.

The cost of analysis is increasing at each pharmaceutical company. To work with materials which can be several times reanalysed should mean an unnegligible contribution to the production cost. Therefore, the cost of raw material(s) is only one element of production cost. When a calculation is performed, the contribution of additional elements to the production costs can also be considered, and for example, if in using one raw material, the yield of the production is found higher than with another one (no reprocessing is necessary), it is highly possible that the first raw material is cheaper independently from the actual differences in price.

It is demonstrated in a very simple example. The raw material used can be purchased from three different vendors for three different prices. The difference between the prices of the vendors is 20-20% (120-100-80%). The ex-work price of one batch of formulated product, e.g. tablets is calculated for an average yield of 97%, and it is 100 units/tablet. To simplify the example at this calculation the proportional costs of non-productive areas are not considered. The average production cost of the tablets calculated for this yield is 50 units/tablet. In general, it is a good approximation that the contribution of the cost of the raw material(s) to the total production cost is about 20% (approx. 10 units/tablet).

If every additional cost is the same, by using the first raw material (cost is about 11 units/tablet, production cost will be 51 units/tablet, the yield of 97% (average yield) has been obtained. Using the raw material purchased from the second supplier (its price is cheaper than the first one with 20%, but more expensive compared to the price of the third supplier) raw material cost is about 9 units/tablet, production cost is 49 units/tablet, a yield of 95% has been found.

In case of the third supplier (its price is the lowest, the raw material cost is only 7 units/tablet, production cost is 47 units/tablet), however, the yield is only 90% due to the non-calculated difficulties experienced during the production.

The calculated profit in the first case will be:  $100 - 51 = 49$  units/tablet, while in second case this value is  $100 \times 0,95 / 0,97 - 49 = 48,9$  units/tablet, and in the third case it is  $100 \times 0,90 / 0,97 - 47 = 45,8$  units/tablet. This very simplified example shows that the vendor which provides the lowest price is the most expensive vendor, and the vendor, who offers the raw material for sale for the highest price is the best vendor.

c. It has to be noted, that the price of the same vendor should also change in time, due to several factors, such as:

- ordered quantity is too small.
- requested age of the product is changed (freshly prepared material is more expensive, than the older one),
- in case of special requests (e.g. size of packaging units, mode of transportation, etc.),
- in case of extra requests (prompt delivery, higher quality, larger quantity, etc.),
- it is a single order, or the shipment is part of a long-term contract, etc.

Therefore, a good pricing policy is a very complex topic, considering many different factors. A great advantage of vendor partnership is, which was discussed above, that with long term contract the price of a good quality raw material should be significantly decreased, and if the user company has a minimum of two certified vendors for the same raw material, the stabilization of the price is also minimum, but in many cases significant decrease in the price can be achieved. The consistent quality of the raw material provided by a certified vendor surely means the lowest price for which the raw material can be purchased.

#### 7. Age of the product, expiry date

The topic is discussed in details in a specified subsection. However, two basic principles should be added to the principles mentioned there.

- the purchased material would be freshly manufactured, however, it is a nonsense requirement that it would be manufactured in the time of shipment, as stated in the tender material. Between the manufacturing time and delivery date minimum one month will be spent due to the analysis time, packaging, organization of the shipment, etc.
- the age of the product at the time of delivery would be variable according to the expiry date (in-house expiry date) of the raw material. It is a good approximation that the age of the product in the time of delivery should not be more than three months for very sensitive (S0) and sensitive (S1) raw materials, and maximum 6 months for the others. Establishing the purchasing quality for each raw material and using the buying system recommended here, it gives enough safety for the customer company that the raw materials can be used for the production without any risk and problem.

#### 8. Labelling instructions and correlation with the storage conditions

a. Data should be indicated in the label (label text).

The following data should be indicated in the label of each packaging unit:

- pharmacopoeial name of the raw material.
- quality of the product: Indication of the pharmacopoeia ( without indication of the edition, which automatically means the latest edition, or the latest edition should be given), or if special quality is required. "according to the buyer specification No....."
- batch or lot number
- manufacturing date
- expiry date
- storage conditions under the given expiry date is valid
- number of an individual drum relating to the total number of drums (e.g. 1/12, 2/12.....12/12, if the batch contains 12 drums)

**b. Storage conditions**

The basic principle is that the storage conditions must be minimum the same as indicated in the label.

If the user is not able to provide the prescribed storage conditions, the expiry date (in-house expiry date) of the raw material should be reduced (see specified section).

If the storage conditions are not indicated in the label and Certificate of Analysis, the material should be rejected (rejected labels put into the containers and the raw material should be moved to quarantine area). [If the manufacturer for the immediate request of the user, accurately gives the storage conditions, the raw material should be released and the storage conditions, expiry date /in-house expiry date and retesting date/ must be indicated in the release label.]

If the storage conditions are indicated only in the Certificate of Analysis, the user has to inform the manufacturer immediately, and the raw material remains in the quarantine area until the written instructions arrive. After arrival, the storage conditions will be indicated in the release label based on the instructions given by the manufacturer.

If the storage conditions are not unambiguously and clearly indicated in the label:

- it has to be checked immediately in the Certificate of Analysis, and if it contains, the storage conditions are allocated in the release label.
- if the Certificate of Analysis does not contain the necessary information, then the vendor has to state it in writing (user company immediately turn to the manufacturer to specify exactly the storage conditions), and after the necessary information is available, put into the release label, otherwise the material should be rejected.

Not clear statements:

- normal conditions
- ambient temperature.

- protected from humidity, etc.

These determinations should be replaced with exactly written instructions given by the vendor and it has to be indicated in the label!

**Important:** manufacturing date, expiry date, storage conditions to be indicated only in the Certificate of Analysis cannot be accepted. **Written instructions from the manufacturer** are absolutely necessary, and **must be indicated in the label for release.**

Storage conditions given by the manufacturer are also important to check the protection of the raw material during the transportation (checking the shipping advice). It is extremely important when the raw material is transported by ship.

c. Relabelled materials

Due to the high risk of relabelling raw materials which have much older manufacturing date, or several smaller batches have been unified may lead to much difficulties in the stability of raw material and/or in the formulation process, **the relabelled materials must be automatically rejected.** Relabelling materials is against the GMP rules, and excluded from the procedure used for packaging raw materials.

**9. Optimum batch size and packaging size**

Batch size and packaging size of the purchased raw material is also important, even if it is not primarily an important factor. If the batch size is too small (e.g. one batch of formulated product can be produced from more than one batch of raw material) can cause difficulties at the production, unnecessarily increases the loss of material and analysis cost, therefore it should be avoided. Similar problem occurs, if the packaging size is too small, increasing the loss at the weighing, and the number of samples should be tested. If the packaging size is too big, it leads to the dispensing of raw materials in the warehouse, which can also be avoided.

As a consequence of this problems, the batch size and packaging size of the raw material should be in accordance with the batch size of the formulated product(s). In case of a certified vendor, mostly it can be easily solved.

**10. Required documentation from the vendor - role of Ministry of Health in the recommended purchasing system.**

Required documentations and actions prior to the shipment in case of the vendor belonging to new potential source.

**a. The raw material is known and used in the country**

- **GMP approval from the local health authority (in case of PIC countries, the summary of the last GMP inspection performed by the local health authority should be submitted, because all companies producing pharmaceutical raw materials in these countries are necessarily GMP approved) - receiver MOH,**
- **positive Vendor audit performed jointly by the Syrian health authority and user company, if the vendor has not recently supplied any raw material to Syria - actions of MOH and user company,**
- **samples and Certificate of Analysis from the raw material for quality evaluation - receivers MOH and user company,**
- **submission of additional data for request, regarding quality, purity or stability - actions are performed by and receivers user company and MOH.**

**If the documentation and samples are acceptable, the vendor is put into the list of raw materials suppliers - actions performed by MOH**

**b. The raw material is firstly used in Syria**

- **Master File containing all important information for manufacturing, analysis, stability, toxicology, pharmacology, etc. should be submitted - receiver MOH**
- **samples, Analytical test specification, Methods and Certificate of Analysis should be submitted - receiver MOH**
- **Vendor Audit - performed by only MOH!!!**

**If the documentation and samples are acceptable, the vendor is put into the list of raw material suppliers - actions performed by MOH.**

**c. Required documentations and actions prior to the shipment in case of a registered vendor**

- 1. The raw material is known and used in the country  
Same as in para a.1., but GMP approval and Vendor audit are not necessary.**
- 2. The raw material is firstly used in Syria  
Same as para a.2.**

**d. Required documentations and actions with the shipment in case of registered vendors**

- 1. Prior to delivery (information to be sent by fax)**

- Shipping advice containing information about packing (number of containers, boxes, palettes, label design, transportation company, due date of delivery) - receiver user company
  - copy of Certificate of Analysis - receiver user company
  - copy of Invoice - receiver user company
2. With the consignment
- Custom documents - receivers original MOH, copy user company
  - Packing list - receivers original MOH, copy user company
  - Invoice - receivers original MOH, copy user company
  - Certificate of Analysis - receivers original user company, copy MOH
  - Certificate of origin - receivers original MOH, copy user company

### 11. Role of MOH in the recommended purchasing system

The recommended purchasing system is based on direct partnership concept, however the role of MOH remains further important.

One of the most important tasks of MOH is to put the vendor to the list of raw material suppliers. All vendors which wish to export raw materials into Syria would be registered, audited (if necessary) and regularly controlled.

However, the vendor selection and contracting with the selected vendor(s) are the task and responsibility of the user company.

Using the recommended system the responsibility line is not broken. It will be moreover clearer, and passes the responsibilities to the correct places, to the MOH controlling the vendors and putting them to the list of raw material suppliers, and to the user company to select the best vendor offering the raw material in the best quality, under the best conditions, for the best price.

## **STANDARDIZATION OF QUALITY OF RAW MATERIALS (QRM)**

The most important considerations are as follows:

- 1. Pharmacopoeial requirements should be considered as minimum requirement.**
- 2. Additional tests for characterization of raw materials should be included into the Quality Test Specification in the following cases:**

- if the stability of the finished products is less than 5 years [unstable products (expiry date is 2 years or less)], moderately stable products (expiry date is 3 years).

Two tests limiting the trace impurities should be present in the raw material are mostly required from stability reasons:

- metal traces
- chromatographic purity (determined mainly by HPLC), with special emphasis on the test for decomposition/degradation products.
- if the technology used for the production of the finished product requires. Physico-chemical characteristics of the raw materials are accurately defined, such as:
  - particle size and particle size distribution,
  - bulk density,
  - polymorphic form
  - visible particles which can affect the appearance of the finished products (the material must be free from any of the visible particles, testing method has been passed to National Drug Quality Assurance and Research Laboratory).

- 3. Additional tests are included into the Quality Test Specification relating to the safety of the use of formulated products produced from the raw materials, such as:**

- trace solvents (hazardous solvents) used for the synthesis and should not be present in the sample, such as chlorinated hydrocarbons, acetone, methanol, benzene and benzene derivatives, etc..
- trace metals (hazardous metals) used as catalysts during the synthesis, and the test is not included into the pharmacopoeial tests,
- impurity profile listing the unknown impurities present in the sample and occurring in higher amount than 0.3%.



## EXPIRY DATE - IN-HOUSE EXPIRY DATE - RETESTING DATE

(Correlation between the expiry date of raw material and finished product)

### A. Definitions and explanations

Expiry date of raw materials is one of the most frequently misused and misunderstood term. To demonstrate, that confusion exists in this area, two generally used versions (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 QRM satisfies all the requirements of quality test specification, which is maximized as 5 years. This expiry date is indicated in the label and/or certificate of analysis. 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 the raw material and indicated in the label and/or the analytical certificate serves only as a guide, QRM is retested after certain period of time and if the QRM satisfies all the requirements of the analytical test specification the material can be further used for finished product production and with several retesting of the QRM the expiry date 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 the finished product having definite expiry date, too. If the QRM satisfies the requirements of an analytical test specification, it does not mean that the quality of the finished product will be good at the time of the end of its shelf life, it only means that the quality of the finished product at the time of manufacture will be satisfactory.

If we also consider that from one raw material, more different types of formulated products should be prepared such as tablets, capsules, powder, ointment, eye drop, injectables, etc., the problem is more complex, because the expiry date of the given raw material should be a function of the type of formulation, may lead to different expiry dates of the same raw material to be used for production of various formulations.

If we are to be more accurate with the term of expiry date, the following considerations should be taken into account:

1. The expiry date of formulated products is ABSOLUTE AND PRODUCT SPECIFIC, can be changed only by changing the registration document of a finished product (in most cases based on the favourable results of the previously started stability testing, the expiry date can be extended for a longer period of time). Therefore, the expiry date of the

finished products has a **PRIMARY IMPORTANCE**, when the QRM from which it is produced is considered!

2. The expiry date of the raw materials as term is **PRODUCT SPECIFIC**, not batch specific, cannot be varied from batch to batch, but the expiry date of a raw material may vary from manufacturer to manufacturer.
3. *The expiry date of raw materials given by the manufacturer* is the latest date until the QRM satisfies all the requirements of its quality test specification, if the material is stored under the stated and prescribed storage conditions. The maximum value of expiry date is 5 years. It protects the manufacturer from claims related to the not acceptable quality of the finished product due to the not properly stored raw materials or to the not adequately performed formulation process.

It is very important that the manufacturer (only the manufacturer, not broker) has many responsibilities relating to the raw material to be supplied:

- raw materials must not contain any contaminant(s) which can be hazardous for the patients, and/or may change or modify the pharmacological effect of the formulated product(s) produced from it,
  - the quality and grade of the raw material is suitable for production of pharmaceuticals.
  - QRM will be satisfactorily until the end of the expiry date, if the material is stored under the prescribed storage conditions.
4. *The in-house expiry date of raw materials given by the customer (user)* gives an indication of the latest date to use it as raw material in the production, when it is stored under the storage conditions of the user's warehouse, which is not necessarily identical with the conditions indicated in the label and/or certificate of analysis.

Therefore, the in-house expiry date is shorter than the expiry date, and influenced by:

- possible deviations in the storage conditions from that one given by the manufacturer of raw material, and may affect on the stability of the raw material in question.
- stability and life shelf of the formulated products produced from the raw material stored under the prescribed storage conditions,
- composition and/or formulation technology used for production of the formulated products (possible source of decomposition, if either the composition or the technological process is changed, the in-house expiry date of the raw material should be reconsidered),
- other effects, such as changed amount of raw material in the packaging unit, changed protection from humidity or light, etc.

5. **Retesting date of the raw materials given by the user**, is the date when the raw material must be retested prior to the in-house expiry date. Analytical data of the retested material serves for confirmation of the validity of in-house expiry date for the batch in question.

By retesting of QRM prior to the in-house expiry date may provide the following information:

- the batch(es) in question can be further used or not used for production,
- for the batch(es) in question the in-house expiry date can be extended or not,
- the in-house expiry date of the raw material can be generally reduced or extended.

It is an important rule that the batch(es) must be retested at the retesting date independently from the fact that the material will be used until the in-house expiry date or not.

## **B. Analytical background**

The good analytical background for making decision for the acceptability or rejection of the batch in time of its arrival and retesting, and from the point of view of QRM it is absolutely necessary and has a primary importance.

Precise determination of in-house expiry date of raw material considering the shelf lives of the finished product mostly requires the application of highly sophisticated separation methods, such as HPLC.

To develop and validate stability indicating assay and purity testing methods require special skill and expertise, and belong to the responsibility of each QC laboratory. However, the separation of the impurities itself is not enough. The method(s) should be capable to distinguish between the:

- by-products formed during the synthesis (its amount will not change, or decreases in time),
- degradation products formed during the synthesis and formulation technology, as well,
- decomposition products formed during the storage of raw material and formulated product(s), as well.

The methods and requirements should be incorporated into the in-house analytical test specification (not necessarily passed to the vendor), and can be routinely used for the determination of QRM. In case of unstable or moderately stable raw materials and formulation products, the application of these methods offers an excellent tool to determine the reliable in-house expiry dates until the raw materials can be used for production without the failure of producing finished products with no adequate shelf lives.

### **C. How the in-house expiry dates and retesting dates can be estimated and/or determined**

As mentioned above, the estimation and/or determination of in-house expiry dates and retesting dates have a great importance. No general rules or guidelines can be found in the literature. The principles and practical advices written in this material serve as a guidance and most of the problems related to the expiry date of raw materials can be easily avoided by using the *Just-in-time concept*.

#### **I. Estimation of in-house expiry date and retesting date of raw materials**

If a pharmaceutical company buying (importing) raw material for its production, and it has no reliable analytical data for the stability of the raw material (and/or finished product) the latest date until the raw material can be used for production (in-house expiry date) can only be estimated.

To do this, first the expiry date of the raw materials from the manufacturer and the expiry date of the formulated products from the user of the raw materials are considered.

In respect to their in-house expiry dates and retesting dates, the raw materials can be divided into three groups:

Group "A": unstable raw materials (their expiry date is 2 years or less).

Group "B": moderately stable raw materials (their expiry date is 3 years).

Group "C": stable raw materials (their expiry date 5 years).

Similarly the finished products according to their expiry dates can be also grouped into three groups:

Group "X": unstable formulated products (their expiry date is 2 years or less).

Group "Y": moderately stable formulated products (their expiry date is 3 years)

Group "Z": stable formulated products (their expiry date is 5 years).

The next step to prepare the possible combinations are outlined in the following Table 5.

GROUP	CHARACTERISTICS	COMBINATION	REMARK
S0	VERY SENSITIVE TO STORAGE CONDITIONS AND TIME	A-X, A-Y, B-X	decomposition product should be minimized at the ordering of raw material
S1	SENSITIVE TO STORAGE CONDITIONS AND TIME	B-Y	decomposition product should be limited at the ordering of raw material
S2	MODERATELY SENSITIVE TO STORAGE CONDITIONS AND TIME	A-Z, B-Z, C-X	decomposition product should be tested
S3	NOT SENSITIVE TO STORAGE CONDITIONS AND TIME	C-Y, C-Z	no special care of decomposition product at ordering raw material

Recommended in-house expiry dates and retesting dates of raw materials for the groups of combinations are as follows:

GROUP	EXPIRY DATE	IN-HOUSE EXPIRY DATE	RETESTING DATE*
S0	2 years /A/	10 months	8 months
	3 years /B/	10 months	8 months
S1	3 years /B/	18 months	14 months
S2	2 years /A/	18 months	14 months
	3 years /B/	24 months	20 months
	5 years /C/	36 months	30 months
S3	5 years /C/	48 months	36 months

\*Retesting date is simply calculated, by taking 80% of the in-house expiry date

In respect to the recommended in-house expiry dates and retesting dates, these data cover two different cases.

1. Different raw materials belonging to groups "A", "B", and "C" are used for the production of only one type of formulated product. (Each raw material has only one combination).

In this case no problem for establishing the in-house expiry date (retesting date) for the raw materials, because these data can be simply obtained from the Table.

2. The same raw material is used for the production of different types of formulated products belonging to the groups "X", "Y" and/or "Z".

In this case the same raw material (for example it belongs to group "B") should have the same expiry date (3 years), but three different in-house expiry dates (retesting dates), 10 months (S0), 18 months (S1) and 24 months (S2).

Which date should be used as in-house expiry date?

The simplest solution, if we dedicate the expiry dates according to the formulations ("X", "Y" and/or "Z"), and we indicate both three in-house expiry dates on the release label.

However, this solution may lead to confusion.

Better solution, if the worst case is considered, and only the in-house expiry date (and retesting date) of B-X combination /or B-Y combination, if it is the worst case/ is indicated in the release label. After retesting the material it can be decided, that the in-house expiry date of B-X combination can be extended to the in-house expiry date of B-Y combination /or B-Z combination, if B-Y combination is the worst case/. If the in-house expiry date can be extended a new release label indicating the new in-house expiry date (and retesting date) is prepared and labelled. If the in-house expiry date cannot be extended, in the time of in-house expiry date a new release label is prepared indicating that the material can be used only formulations belonging to groups "Y" and "Z", and it is not allowed to use for the preparation of product belonging to group "X". If both three types of formulated products are prepared from the same raw material the procedure can be continued as described above.

## II. Determination of in-house expiry dates /retesting dates/ of raw materials by the aid of stability testings

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 reexamination 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 .

**Table 6**

<b>CONDITIONS</b>	<b>ACCELERATED STABILITY TEST</b>	<b>RE-EXAMINATION STABILITY TEST*</b>
<b>Samples</b>	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
<b>Testing period</b>	initial, 1 month, 2 months, 3 months, 4,5 months, 6 months	1, 2, 3, /4 and 5/ years after production
<b>Treating conditions</b>	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
<b>Analytical tests*****</b>	IR- and UV-spectra appearance colour of solution /solubility/ /pH/ /bulk density/ loss on drying /optical rotation/ decomposition products assay	<b>Formulated products</b> according to the analytical test specification + decomposition products + assay <b>Raw materials</b> 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:

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

If the results obtained for the all batches to be tested are similarly changing in time (decomposition rates for the all 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 those 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.

2. 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).

3. 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 basis for grouping 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 can be much more accurately described. Calculating the average decomposition rates both for the raw material and finished product, the minimum requirement for purity and assay 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 (see later subsection).



Thirdly, from the 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.

4. 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)

a. **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 such as 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 below.

Table 7

All batches satisfy the all 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 7 and that 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.

## b. 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 I g concentration in time) for each treating conditions.

In the knowledge of the *expiry quality of raw materials* (see the recent subsection for its definition and determination) 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 between the 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 mind 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, 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.

## D. 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 for production. However, the knowledge base available in the time of retesting is very important to make further decisions.

1. 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 results obtained are close to that 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 time period 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, and 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 time period 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.
2. 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 in 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.

3. 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, NO POSSIBILITY EXIST TO OVERRUN THE EXPIRY DATE OF THE RAW MATERIAL GIVEN BY THE MANUFACTURER, IF IT OCCURS, THE ONLY POSSIBILITY 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).

#### **E. 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.

1. 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.

2. **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 changed, but the user decides a change in the storage conditions, which allows to extend the in-house expiry date of the raw material.**

**F. Recommended necessary actions for the introduction of in-house expiry date and retesting date system at the Syrian pharmaceutical companies**

1. **Recommended immediate actions**

(a) **Team formation**

**A team can be formed from the following persons:**

- **one person, who is responsible for the all quality matters inside the company (QA director or equivalent person)**
- **one person, who is responsible for quality control and quality development inside the company (QC manager)**
- **one person, who is responsible for the production inside the company (Technical or Production Manager)**
- **one person, who is responsible for warehousing (Head of storage rooms)**
- **one person, who is responsible for the purchasing inside the company (Commercial Director)**

**This team works together until the system is introduced.**

**Leader of this team, who is responsible for the system introduction: QA director or equivalent person**

**(b) List of raw materials**

**List of raw material is prepared including all materials used for the production.**

**Responsible person: Technical or Production Manager**

**(c) Classification of raw materials**

**Based on the list prepared above the raw materials are classified according to their stability /expiry date given by the manufacturer/ into Group "A", "B" and "C".**

**Responsible person: QC manager**

**(d) List of formulated products**

**List of formulated products produced from each raw material is prepared.**

**Responsible person: Technical or Production Manager**

**(e) Classification of formulated products**

**Based on the list prepared above the formulated products prepared from the same raw material are classified according to their stability (group "X", "Y" and "Z").**

**Responsible person: QC manager**

**(f) Establishment of in-house expiry date and retesting date for each raw material**

**Based on the classification of raw materials and formulated products combinations are prepared and the raw materials are classified according to their sensitivity (S0, S1, S2 and S3). After classification the in-house expiry dates and retesting dates are established for each raw material.**

**Responsible person: QA director or equivalent person**

**(g) Evaluation of the storage conditions.**

**In each storage rooms where raw materials are stored the conditions can be evaluated. Most important principles are:**

- temperature fluctuation, and deviations from the required one**
- humidity protection**
- light protection (only, if it is necessary)**

**Deviations from the required conditions must be reported for each room.**

**Responsible person: Head of storage rooms**

**(h) Re-evaluation of in-house expiry dates and retesting dates.**

It is based on the evaluation data of storage conditions.

Responsible person: QA manager or equivalent person

**(i) Listing the raw materials according to their estimated in-house expiry dates and retesting dates.**

All raw materials are listed according to their sensitivity groups (S0, S1, S2 and S3), and within one group according to their in-house expiry dates and retesting dates.

Responsible person: QA manager or equivalent person

**(j) Listing the raw materials according their storage rooms**

The list of raw materials are further divided according to the storage rooms, where the materials are stored. Each storage room has separate lists of raw materials stored in this room for S0, S1, S2 and S3 sensitivity groups indicating the in-house expiry and retesting dates for each listed raw material.

Responsible person: Head of storage rooms

**(k) New design of release label**

The recently used release label can be replaced with a new one, in which all important information relating to in-house expiry date and retesting date must be indicated.

Responsible person: QA manager or equivalent person

**(l) Evaluation of the present situation in the warehouse.**

All batches of raw materials stored in the different storage rooms have to be evaluated with respect to their expiry date, in-house expiry date and retesting date.

Responsible person: Head of storage rooms

**(m) Classification of raw materials according to their applicability.**

The materials can be classified into four groups:

- Group 1. raw materials which overrun the expiry date given by the manufacturer
- Group 2. raw materials which overrun the estimated in-house expiry date, but are below the expiry date
- Group 3. raw materials which reached or overrun the retesting date but, the storage time is below the estimated in-house expiry date
- Group 4. raw materials which have not reached the retesting date

Responsible persons: QA director or equivalent, QC manager and Head of storage rooms

**(n) Decisions about the raw materials classified above.**

Group 1. turning to the manufacturer

- Group 2: sampling and retesting immediately  
 Group 3: sampling and retesting  
 Group 4: relabelling with the new designed label indicating the in-house expiry and retesting dates

Responsible persons: all member of the team

(o) Analysis

The samples are tested according to the valid analytical test specification and qualification is made.

Responsible person: QC manager

(p) Decision about the applicability of the raw materials to be tested.

Based on the test results decision should be made about the applicability of the raw materials to be tested.

Responsible persons: QA director or equivalent, Technical or Production manager

(r) Labelling of the raw materials to be tested with the newly designed release or rejected labels

Based on the decisions above, all packaging units should be relabelled with release or rejected labels.

Responsible person: QC manager

(s) Quarantine

Materials belonging to Group 1, and rejected materials from any other groups should be removed from the storage rooms to quarantine area.

Responsible persons: QA director or equivalent person and Head of storage rooms

2. Recommended development actions

(a) Evaluation of analytical test specifications

The analytical test specifications of raw materials should be evaluated with respects to their capability to characterize the QRM to be needed for production. Firstly materials belonging to group S0 and S1, in a later phase group S2 and S3 are evaluated.

Responsible persons: QA director or equivalent person, Technical or Production manager, QC manager

(b) Modification of analytical test specification I.

If the analytical methods are available the specification is evaluated with respect of the formulation technology used for production. The specification can be extended with the tests which are



important to have consistent quality for the formulated products. If not enough data are available, the raw materials can be sampled and tested to establish the necessary analytical criteria.  
Responsible persons: QA director or equivalent person, Technical or Production manager, QC manager.

**(c) Application of the new analytical test specification at ordering of raw materials**

The raw materials having new analytical test specification including the case where the tests are the same, only the limits have been changed should be only further used at ordering.

Responsible person: Commercial director

**(d) Developing stability indicating methods.**

Stability indicating methods should be developed and validated for the raw materials where it is important (materials belonging to group S0, S1, first).

Responsible person: QC manager

**(e) Starting with re-examination stability tests**

Re-examination stability testing should be started in that case, if the stability indicating analytical methods are available. Stability testing plan must be prepared, and retained samples should be taken both from the formulated products and the corresponding raw materials.

Responsible persons: QA director or equivalent person, QC manager

**(f) Starting with the accelerated stability tests.**

Accelerated stability testing should be started in that case, if the stability indicating analytical methods are available. Stability testing plan must be prepared, and samples should be taken from the raw materials stored under the applicable storage conditions.

Responsible persons: QA director or equivalent person, QC manager

**(g) Establishment of purchasing quality and expiry quality, modification of the analytical test specification II.**

Based on the results of stability testings, the purchasing and expiry quality of raw material should be established, and criteria can be formulated.

Responsible persons: all member of the team

**(h) Application of the new analytical test specification at the ordering of raw materials**

The raw materials having new analytical test specification including the case where the tests are the same, only the limits have been changed should be only further used at ordering.

Responsible person: Commercial director

**(i) Re-evaluation of the in-house expiry dates and retesting dates of raw materials.**

Based on the stability testing data, the in-house expiry dates and retesting dates of raw materials

should be re-evaluated. If the expiry dates and retesting dates are changed, each packaging unit of all batches of these raw materials stored in the storage rooms should be relabelled indicating the new in-house expiry dates and retesting dates on it. In the list of the products allocated in the different storage rooms, where these raw materials are stored the in-house expiry dates and retesting dates must be corrected.

Responsible persons: QA director or equivalent person, Head of storage rooms, QC manager.

**(j) Expiry dates of the finished product**

By the aid of the results of re-examination stability tests using the stability indicating methods to be recently developed, the stability of the finished products should be re-evaluated. In that cases, when the results predict a longer shelf lives for the products, automatically the expiry dates cannot be changed. It can be supported with accelerated and long term stability testing results (please note that the results of 6 months accelerated stability tests with formulated products enable maximum predicted shelf lives of 2 years, not more, results of 1 year accelerated stability test may predict the shelf lives for maximum 3 years!). In that cases, if the results predict a shorter shelf life, than it is stated, immediately the formulation technology must be changed, and possibly a new composition providing higher stability must be developed, or the analytical test specification of the raw material used for the production should be tightened.

Responsible persons: Head of research laboratory, QC manager, QA director or equivalent person, Technical or Production manager

**G. Standard operating procedure for in-house expiry date and retesting date**

Beside the well known items of a standard operating conditions, such as objective, scope, personnel and training, their responsibilities, the following important points should be included into the SOP of in-house expiry date and retesting date:

- (a) Determination of in-house expiry date and retesting date, their possible extension, or shortage.
- (b) Validity of in-house expiry date and retesting date correlation with the storage conditions.
- (c) Grouping raw materials according to their in-house expiry dates.
- (d) Indication of in-house expiry date and retesting date in the storage rooms.
- (e) Labelling instructions for release label.
- (f) Written information about the raw materials to be close to their retesting dates, frequency of the information, person who is responsible for issuing this information, receiving source.
- (g) Sampling instructions for retesting, responsibility for sampling.

- (h) Evaluation of the results obtained for the retested sample, responsibilities for the further use of the material for production, possible extension of in-house expiry date of the specific batch of the raw material, relabelling instructions.
- (i) Quarantine rules for the batches of the raw material to be rejected or the expiry date is overrun.
- (j) Purchasing raw materials considering their in-house expiry dates.

## **WAREHOUSING SYSTEM**

### **A. General situation at the companies working in the public sector**

General situation at the public sector companies can briefly summarize as follows mentioning only the most important deficiencies:

- The storage rooms are filled up with raw materials.
- No separated space exist for sampling, sampling rules are not adequate.
- No quarantine area exist for the rejected materials.
- Dispensing of raw materials is made in the storage rooms without air protection and special care.
- No indication exist about the materials stored in the room.
- Materials are not positioned.
- Documentation is confusing.
- Labels are not adequately filled and allocated.
- No SOP's for the arrival, quarantine, sampling, storage and cleaning of storage rooms.

### **B. General situation at the companies working in the private sector**

General situation at the majority of the private sector companies to be visited complies with the current GMP rules.

- Receipt of the material is good and well documented.
- Suitable quarantine area exist to receipt the raw materials after arrival.
- For sampling suitable space is available.
- Storage rooms have the necessary space for receive raw materials after release.
- The raw materials are positioned.
- Only predispensing is made in the storage rooms, dispensing of raw materials is performed in: the production area.
- SOP's are available.
- Documentation system is acceptable, etc.

### **C. Immediate actions to be performed at the public sector companies**

Considering the presently existing situation at the public sector companies, the following immediate actions are necessary to improve the GMP status of the storage rooms:

1. 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.

2. To improve the documentation system.

The following basic documentation should be used in the warehouse:

- Material receiving card.
- BIN card.
- Sampling chart.

3. 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.

4. 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.

5. 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.

I. Sampling rules

Basic sampling rules are as follows:

1. 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.
2. The expiry date of the retained samples is: expiry date of raw material + 1 year
3. In respect to sampling, the ordered raw materials can be divided into three groups:
  - a) Materials, which are not allowed for 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.
  - b) 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.

c. **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 the 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.

4. 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.
5. 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.

## II. 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

### *1. 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 responsible 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

## 2. *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.

## 3. *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  
 dispensing 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 will arrive and placed into the storage room. all the data will be written in an empty row 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.

4. 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

### III. Inspection check-list for controlling the arrival, sampling, storage, delivery, predispensing and dispensing of raw materials.

#### 1. Receipt of raw materials

- Is there suitable space to receipt and clean the packaging units of raw materials?
- Does receiving inspection check incoming raw materials to requirements of the purchase order, specification and material weights?
- Are the released raw materials properly segregated from materials awaiting testing and disposition?
- Are records kept that track the date of receipt, batch number and vendor?
- Is the Material Receiving Card filled adequately. SOP for filling the Card is available?
- Is there SOP for receiving components?
- Is the visual control including control of labels properly documented?

#### 2. Sampling

- Is there an acceptable area for sampling?
- Are approved sampling procedure is used?
- Is the SOP corresponding to sampling available?
- Is the randomising rule kept for taking samples?
- Is the SOP containing the necessary information for labelling the samples?
- Is the sampling made by trained and qualified person?
- Is the received raw material adequately labelled after sampling?
- Is the cleaned stick available for the sampling area?
- Are the frequency and procedure for cleaning sampling area adequate?
- Is there any air handling system in the sampling area?

### 3. Release/rejection of raw materials

- Is the analytical file number indicated in the Material receiving Card?
- Is the qualification of the raw material clearly stated and undersigned by a responsible persons?
- Are the size and content of the release/rejection label proper to indicate all necessary information?
- Are the release/rejection labels properly filled with data?
- Are all packaging units of the batch of the raw material labelled?
- Is the release/rejection made by responsible person?
- Are the all packaging units of the batch removed from quarantine area after release/rejection procedure?
- Are the rejected materials properly separated from the raw materials awaiting for testing and disposition?

### 4. Handling and storage of raw materials

- Are the raw materials properly handled and stored to prevent damage, contamination or loss?
- Are the Bin Cards properly filled for the released raw materials?
- Is the SOP related to fill the Bin Cards available?
- Are the released raw materials positioned and adequately segregated to avoid mix-up?
- Are the in-house expiry date and retesting date indicated in the release label?
- Is the storage room clean?
- Is the SOP for cleaning the storage room available?
- Is the cleaning procedure adequately recorded?
- Are the palletes in good conditions for using them?
- Is there FIFO system for raw materials?
- Are the FIFO principles adequately kept?
- Can the issuance of raw materials be followed through the Bin Cards?
- Are non controlled raw materials stored together with released raw materials?
- Is the retesting date adequately kept for raw materials?
- Is the hazardous raw materials suitably segregated from other raw materials?

### 5. Predisensing

- Is there any written instruction /SOP/ for predisensing raw materials?
- Is there suitable space separated from the stored materials to perform predisensing?
- Is there any air handling system in the area used for predisensing?
- Are the balances adequately numbered, calibrated and cleaned?
- Is logbook available for each balance?
- Are there written instructions /SOP/ for opening and reclosing the containers of raw materials batch?
- Is the predisensing performed by qualified person?
- Are there written instructions /SOP/ to avoid mix-up and contamination?

- Is there written instruction for clothing?

6. Receipt of raw material in the manufacturing area - Weighing

- Is the raw material identified in the manufacturing area?
- Is the raw materials recorded in the manufacturing area?
- Is dispensing area separated from the other places of the manufacturing area?
- Is there batch record for dispensing materials?
- Is the dispensing made into adequate containers?
- Are the SOP's of dispensing, cleaning of balances, filling batch records available?
- Is the cleaning made regularly?
- Are the balances adequately numbered, calibrated and cleaned?
- Is logbook available for each balance?
- Are the containers used for storage of dispensed raw materials cleaned and adequately labelled?
- Is the rest of the raw materials adequately handled after dispensing?
- Where it is stored?
- Are the all procedures related to dispensing safe, to prevent cross contamination, damage, loss of raw materials?

## ***QUALITY CONTROL LABORATORIES/QUALITY ASSURANCE***

### **A. Governmental control of pharmaceuticals**

Pharmaceutical companies in Syria belong to the direction of Industrial Ministry, however, the governmental control of pharmaceuticals belongs to the responsibility of Ministry of Health. Deputy Minister of Health coordinates all pharmaceutical affairs, but the present Minister of Health, Prof. Dr. M. IAD El-Chatti, has a daily contact with the directors of different departments, he is well informed about the situation of the pharmaceutical industry and distribution of pharmaceuticals.

A Technical Committee working under the direction of Deputy Minister of Health coordinates the registration, licensing, pricing, inspection and control of the pharmaceutical companies. This committee presently arranges the tender-based import of raw materials, too.

The above mentioned tasks are divided between four different directorates, such as:

- National Drug Quality Control Laboratories
- Pharmaceutical Affairs
- Drug studies
- National Drug Quality Assurance and Research Laboratories

#### **I. National Drug Quality Control Laboratories**

As the most important tasks of this Laboratory relate to taking samples from raw materials and to perform inspections at the pharmaceutical companies a continuous connection with this Laboratory dedicated for raw material handling was built up during the mission.

A joint inspection has been performed at UNIPHARM /private company/ to demonstrate the most important inspection principles.

An inspection check list has been collected for controlling the raw material handling. Sampling instructions have also been given taking samples from the imported raw materials /see recent subsection/.

#### **II. Pharmaceutical Affairs**

The most important actions of this Directorate relate for registration, licensing and pricing.

The recommended purchasing system including the questions of correlation between quality and price, and the role of Ministry of Health in the recommended system /see the text/ has been discussed with this Directorate in details.

### III. Drug studies

There was no connection with this Directorate during the mission.

### IV. National Drug Quality Assurance and Research Laboratories

Visiting the National Drug Quality Assurance and Research Laboratories a well established and organized laboratory has been found. On the whole the Laboratory works according to the current GCLP rules, and possesses the most important instruments to be necessitated for supervising of the quality of imported raw materials and production of the pharmaceutical industry.

Only few problems have been experienced.

#### 1. *Sterility test*

The presently existing laboratory for sterility testing is unsuitable to prevent accidental bacterial contamination, therefore significant improvement in air conditioning, changing room, material handling, etc. is absolutely necessary and highly recommended.

#### 2. *Standard operating procedures*

The most important SOP's are available, the introduction of the following SOP's has been recommended and advised:

- a. General SOP /SOP for preparation of SOP/ (see Annex 2.)
- b. SOP for arrival and documentation of reference standard materials (see Annex 3)
- c. SOP for storage and handling of reference standard materials (see Annex 3)

#### 3. *Research and development program for pharmaceutical companies in Syria*

The necessary instructions for the different programs have been given /see Annex 4./

#### 4. *Instruments*

The laboratories are furnished with the most important highly sophisticated separation techniques, such as GC, HPLC, as well as with the equipments dedicated for the establishment of the physical state of the raw materials (DSC, particulate counter, IR-spectrophotometer, etc.).

In the future the introduction of one relatively new technique, *high-performance capillary electrophoresis*, is highly recommended, due to its capability for

- separation of <sup>high</sup> molecular weight compounds (e.g. dextrans), proteins and polypeptides,
- separation of optical isomers including enantiomers,

- separation of active compounds in complex biological matrices (bioavailability studies).

#### 5. *Other activities*

The Laboratory performs, or will perform the following additional activities:

- organizing special courses for QC laboratories
- participation in international analytical investigations
- performance of bioequivalency studies (laboratory is now being built up)
- on going stability studies for finished product (only this type of stability tests are known and used in Syria)
- participation in WHO, and UNIDO projects

#### **B. Public sector companies**

QC laboratories are presently able to perform only the pharmacopoeial investigations. To establish purchasing and expiry qualities, to carry out the standardization of raw material qualities extending the specifications with additional tests, and to perform stability tests require special skill and expertise (qualified person), as well as to use highly sophisticated analytical techniques (such as HPLC). Due to lack of these required elements results in a poor level of QC activity, which can be solved within the shortest time.

QA is not presently functioning at the public sector companies. Most of the problems related to the raw material handling, expiry date problems, and storage room discrepancies can be led back to the lack of an appropriate QA unit requiring immediate actions from the managements of the companies.

#### **C. Private sector companies**

QC laboratories of the visited private companies are well equipped with the necessary equipments. However, the method validation practice is not sufficient, and only on going stability tests are performed /for problems see the text above/.

QA is in function, and working well.

#### **D. Recommendations**

##### 1. For all QC laboratories:

A UNIDO project for development and validation analytical methods and stability testing is recommended both for the National Drug Quality Assurance Laboratories, and pharmaceutical companies working in the public and private sectors, as well.

Recommended post title:

"STC on development and validation of analytical methods suitable for characterization and standardization of qualities of raw materials and finished products - stability testing, types, applications and methods"

2. For governmental laboratories:

- a. the presently existing laboratory dedicated for sterility testing is unsuitable to prevent accidental bacterial contamination, therefore significant improvement in air conditioning, changing room, material handling, etc. is absolutely necessary, and highly recommended.
- b. introduction of one relatively new technique, *high-performance capillary electrophoresis*, is highly recommended, requiring financial support from WHO (price of instrument is about USD 40.000-70.000 depending on the level of automation).

3. For public sector companies

- a. Immediate action(s) both from the government side and that of the managements of the companies are absolutely necessary to establish QA function employing a pharmacist qualified in this field.
- b. Level of instrumentation is necessary to perform the investigations needed for standardization of qualities of raw materials and finished products.



## ***USE OF RAW MATERIALS AT THE FORMULATION PROCESSES***

### **A. Private companies**

Situation at the private companies in respects of purchased raw materials and their use for formulation processes basically differs compared to public sector companies. Differences can be mostly led back to four main reasons:

1. In majority of the companies, the products are licensed, therefore the Quality Test Specifications of raw materials obtaining from the license partner contain all details connected to the formulation processes, stability of the finished products and safety of use the pharmaceuticals, as well.
2. Private companies are directly purchasing the raw materials used for the production from the preselected (or predetermined) vendor, and/or from the license partner considering the JIT and MSR principles. No expiry date problems occur.
3. The formulation technology /processes includes all safety and environmental protection instructions, and well define the use of the raw materials as it was given by the license partner to the company, the consistent, high quality of the raw materials, and the standardized formulation technology are able to provide reliable, good quality of the formulated products.
4. Process validation and monitoring including cleaning processes are regularly performed providing standard conditions for production.

### **B. Public sector companies**

#### **I. Findings**

The most important findings can be summarized as follows:

1. Dispensing of raw materials is performed in the storage rooms under nonperfect conditions. Only the weight control is made in the plant.
2. The quality of the raw material is not standardized, as was mentioned, it does not consider the requirements of technological processes applied for the production, therefore the production technology cannot be standardized, the technology and the quality of the formulated products may be a function of the vendor changing the quality from batch to batch or from consignment to consignment.
3. No regulations for safety and environmental protection of production areas manufacturing hazardous products (antibiotics) exist.

4. **Process validation and monitoring including the validation of cleaning procedures are not performed.**
5. **Clothing rules do not strictly regulate the protection of the workers and environment from antibiotic exposure.**
6. **No regular maintenance program has been developed for controlling the equipments used for the production.**
7. **Reprocessing is not controlled and well documented.**
8. **Changing rooms are far from the production areas, and not adequately constructed.**

## **II. Recommendations:**

**Most important recommendations can be summarized as follows:**

1. **Standardization of the quality of raw materials with special regards to the given production technology (see recommendations in the recent subsection - QC function).**
2. **In the hazardous area (antibiotic production areas) more rigorous clothing rules should be developed - QA function.**
3. **The movement and number of the workers in the hazardous area should be reregulated (QA function).**
4. **In the course of products, where the technological process(es) depends on the quality of supplied raw material, the production technology should be evaluated as a function of the physical state of the raw materials. Where it is necessary, the technological process(es) would be redeveloped requiring the establishment of research and development laboratory for pharmaceutical technology with the leadership of an experienced pharmacist. Necessary instructions have been given (Technical Director function).**
5. **Prescriptions of safety and environmental protection regulations for all procedures should be developed with special emphasis on processes used in the antibiotic production areas (mostly QA function).**
6. **Process validation and monitoring including cleaning processes should be started. Necessary instructions have been given, and special course dealing the practical aspects of process validation has been presented by the UNIDO's consultant (QA and Technical Director functions).**
7. **Reprocessing should be regulated and correctly documented (QA and Technical Director functions).**

8. **Dispensing of raw materials should be moved from the storage rooms to the production area (QA and Production Manager functions).**
9. **SOP's for the technological processes including cleaning processes should be prepared (QA and Production Manager functions).**
10. **Regular program for maintenance of the equipments should be prepared (QA and Technical Director functions).**
11. **Adequate changing rooms should be constructed (General Manager function).**

***LECTURES AND SHORT COURSES PRESENTED BY THE CONSULTANT***

1. "Quality of raw materials - expiry date" lecture presented in the meeting of Validation processes (Aleppo, 24-25 August 1995)
2. "Process validation - practical aspects" short course for Thameco employees (Damascus, 5 September 1995).

**PHARMACEUTICAL COMPANIES TO BE VISITED AND PERSONS TO BE CONTACTED**

**A. Pharmaceutical companies**

1. Thameco - Damascus
2. Thameco - Aleppo
3. DIMAS - Damascus
4. Alfa - Aleppo
5. Unipharma - Damascus
6. Avenzor - Damascus
7. MPI - Damascus
8. Shifa - Aleppo

**B. Persons**

Prof. Dr. M. IAD El-Chatti	Minister	Ministry of Health
Dr. Kaukab Al Daya	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
Dr. Rashid Mourajed	General Manager	DIMAS
Prof. Dr. Ally Haggag	Vice Dean	Tania Univ. - Egypt
Dr. Joumaa Al Zehouri	Professor	Damascus University
Dr. Maged Koudsi	General Manager	Avenzor
Dr. Ahmad Al Chibabi	General Manager	Alfa
Mr. M. Imad Maatouk	Deputy Chairman	Unipharma
Dr. Ramez Haddad	Managing Director	MPI

Z. Csizer/el  
22 February 1995

**JOB DESCRIPTION**

DU/SYR/92/008/11-08

- Post title**                    **STC on Pharmaceutical Raw Materials/Quality Control**
- Duration**                    **1 m/m**
- Date required**                **21 August 1995**
- Duty station**                **Damascus, Syria**
- Duties**                    **To strengthen the management of pharmaceutical raw materials from the procurement to their quality control, storage and use. More specifically the STC is supposed to carry out the following duties:**
1.    **Assist to improve the system of procurement of pharmaceutical raw materials in order to obtain high quality products at reasonable price. Since the quality consistency can be a major issue, introduce and develop a vendor certification system in The Arabian Medical Company (Thameco) that would also support Good Manufacturing Practices (GMP).**
  2.    **Assist to improve the storage conditions of raw materials in compliance with the GMP. Introduce a part numbering system.**
  3.    **Assist to strengthen the quality control laboratories with specific emphasis on the raw materials testing.**
  4.    **Assist to develop the proper use of raw materials at the formulation processes. Take into account the environmental and safety considerations.**
  5.    **Prepare a report on the above.**
- Qualifications:**            **Analytical chemist/pharmacist with extensive experience in the pharmaceutical industry particularly related to the procurement, storage, sampling and evaluation of the entire range of raw materials consumed by the industry in compliance with the GMP.**
- Language**                    **English**

**Background information:**

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

The various activities planned for the second year of the project and those which have been rephased from the first year of project implementation were discussed. Among others it was agreed that STCs on Drug Industrial Standards and SOPs would be required. Two STCs, one m/m each, will be recruited by UNIDO to advise on essential Pharmaceutical Industrial Standards and SOPs. In addition to these consultants it was agreed that a STC on Raw Materials/Quality Control should be recruited. The original TOR was revised as above by UNIDO. The consultant should cover the total scope of pharmaceutical raw material management/ handling from procurement to use.

**STANDARD OPERATING PROCEDURES FOR PREPARATION OF  
STANDARD OPERATING PROCEDURES  
(SOP's of SOP)**

**Code Number: 01.001.001.50**

**1. Objective**

This document serves as a guidance on how to prepare an SOP, including the detailed discussions of the following document sections:

- scope of the SOP's
- authorization to maintain, supervise and keep SOP's
- responsibilities for preparation, introduction and supervising of performances of SOP's
- personnel, their qualification and training who can prepare, supervise, issue, authorize, modify or withdraw SOP's
- code numbering system for SOP's
- structure and content of the SOP's
- information source to whom the material is circulated
- copy numbering system
- archivation
- Annexes

**2. Scope**

This material is valid for all parts of the company, where SOP is prepared, issued, supervised, authorized and documented, and receives all responsible persons who is authorized to maintain, supervise and keep SOP's.

**3. Authorization**

General manager of the company is the only person, who can authorize persons according to the responsibility chart to issue, authorize, modify or withdraw SOP's.

**4. Responsibilities**

Responsibility chart is prepared to clearly identify the responsibility, authority and relationship of all persons who manage, perform or supervise work affecting quality. Based on the responsibility chart of the company, the authorized persons nominate the persons, who

- can prepare,
- can supervise,
- can maintain, and
- can keep SOP's



## **5. Personnel**

The personnel, their qualification and training, who participate in the preparation, supervising, maintenance and modification of SOP's are nominated by responsible person(s). Job descriptions of the qualified persons should be attached to each SOP's

## **6. Code numbering system for SOP's**

The numerical code numbering system used for SOP's serves to identify any SOP's, according to their objective, content and availability. The code number consists of 10 digits.

The first two digits of code numbers relate to the objective of SOP's.

- 01 General SOP's
- 02 Quality Assurance
- 03 Quality Control
- 04 Qualification
- 05 Verification
- 07 Validation
- 08 Calibration
- 09 Monitoring systems - Environmental and process control
- 10 Equipments
- 11 Maintenance
- 12 Production
- 13 Materials
- 14 Warehousing
- 15 Housekeeping - cleaning rooms
- 16 Cleaning equipments
- 17 Environmental and safety regulations
- 18 Research and Development
- 19 Registration
- 20 Self inspection and audit
- 21 Job description
- 22 Labelling system
- 23 Release and rejection
- 24 Quarantine
- 25 Archivation
- 26 Soft-wares - validation

The next three digits relate to the content of the SOP's.

For example in Series 01

- 001 this SOP
- 002 documentation system
- 003 batch numbering system
- 004 batch record system
- 005 technological descriptions
- 007 responsibility chart
- 008 authorization
- 009 ...

or Series 14

- 001 Receipt of the material
- 002 Quarantine rules
- 003 Arrival number system
- 004 Sampling
- 005 Position numbering system
- 006 Material receiving card
- 007 Bin card
- 008 Storage conditions
- 009 In-house expiry date - retesting date
- 010 Inventory control
- 011 FIFO principle
- 012 Housekeeping of different rooms
- 013 Labelling instructions in the warehouse
- 014...

The next three digits relate to the area where the SOP is used and available.

The digits includes the section-department, where the SOP is used (first digit), and the subsection(s) to which the SOP specifically relates (second and third digits).

The subseries starting with zero, serves to identify the inter-relationship connections, when the

SOP's relate to more departments.

- 001 relates to all the departments and all subsection
- 002 relates to QA/QC
- 003 relates to QA/QC and production
- 004 relates to QA and production departments
- 005 relates to QC and production departments
- 007 relates to all production departments
- 008 relates to QA/QC and packagi. department
- 009 relates to QA and packaging department
- 010 relates to QC and packaging department
- 011 relates to QA/QC and warehouse

Subseries starting with 1, relates to the management

- 100 management
- 110 commercial department
- 111 trade office
- 112 purchasing department
- 113 sales office
- 120 economical department
- 130 technological department
- 140 department for research and development

Subseries starting with 2 relates to QA/QC departments.

- 200 Quality Assurance and Quality Control

- 201 Retained sample storage house
- 202 Packaging materials - etalons
- 210 Quality Control department
- 211 Chemical analysis
- 212 Microbiological analysis
- 213 Biological analysis
- 214 Quality controllers /supervisors
- 215 Qualification - Documentation

Subseries starting with 3 relates to the Production Departments

- 300 Production
- 301 Head of the production departments
- 302 Central weighing rooms
- 303 Washing room(s)
- 304 Storage room(s)
- 305 Quarantine
- 310 Tableting plant
- 311 Sieving room
- 312 Weighing rooms
- 313 Homogenisation room
- 314 Granulation room
- 315 Tableting room I
- 316 Tableting room II
- 317 Coating room
- 318 Granulation and coating liquid preparation room/s/
- 319 ...
- 320 Capsuling plant
- 321 ....
- 330 Solution preparation plant
- 331 ..
- 340 Sterile product production plant I (heat sterilized injection)
- 350 Sterile product production plant II (aseptic plant including lyophilisation)
- 360 Sterile product production plant III (infusion plant)
- 370 Sterile product production plant IV (sterile powder filling plant)
- 380 Sterile product production plant V (eye drop plant)
- 390 Ointments, creams and suppositories production plant

Subseries starting with 4 relates to Packaging departments

## 400 Packaging

Subseries starting with 5 relates to the Warehouse.

500 Warehouse

..  
.  
.

Last two digits serve to identify the date of issue and the number of modifications of SOP's.

50 means the SOP was issued in 1995 and this is the original version

43 means the SOP was issued in 1994, and this is the third revision

The code number of this document considering the code numbering systems is: *01.001.001.50*

## 7. Structure and content of the SOP's

Each SOP can be built up in a similar base, containing the following sections:

- objective,
- scope and limitations.
- Responsibilities,
- Personnel, their qualification and training.
- (safety regulations),
- (list of materials, equipments required for the purpose),
- detailed description of the activity,
- name of persons and positions who issued, supervised, authorized, and dates.
- number of copies.
- received by names and dates,
- validity and archivation of the SOP's,

in brackets: if it is necessary

## 8. Information source to whom the material is circulated (copy numbering system)

The responsible person, who issues the SOP, selects the persons to whom the material is forwarded. Each person receives a numbered copies, indicating the copy number/all copies. In the original copy the persons, their copy number, receiving dates and signatures are indicated.

## 9. Validity and Archivation

The basic documentation system contents the validity of each document and the rules of archivation. Validity of this SOP's without any revision is 2 years. Validity date of the revised version started from the date when the revision is issued. After the expiry date of validity, the materials (SOP's) should be revised and the former copies are withdrawn and archived.

## 10. Annexes

Responsibility chart of the company and Job description of the responsible persons are attached to this SOP.

**STANDARD OPERATING PROCEDURE FOR DOCUMENTATION AND STORAGE  
OF REFERENCE STANDARDS**

**Code number:**

**1. Objective**

In this SOP all the important rules relating to the documentation and storage of reference standard materials are included.

**2. Scope**

The SOP is valid to all the analytical laboratories using reference standards for the pharmacopoeial investigations.

**3. Responsibilities**

To control the adequate documentation and storage of reference standard material is the responsibility of QC Director.

The QC Director is authorized to nominate well-trained personnel responsible for the good performance of the works described here.

The Chief Analyst is responsible for training of the personnel and those members of the analytical laboratory, who are using reference standards during their daily work.

**4. Personnel**

Nominated from the laboratory staff, trained for the documentation and storage of reference standards.

**5. Arrival of the reference standards into the laboratory - receipt of the materials**

All reference standards arriving into the laboratory are firstly visually inspected, that the packaging is intact, unbroken and correctly labelled.

The following data are registered in the reference standard recording book

- name of the reference standard,
- produced and supplied by,
- number of Certificate of Analysis (if not available, write no).
- batch number or lot number (if not available, write no),
- laboratory arrival number,
- gross weight indicated in the label,
- expiry date (if not available: 2 years in unopened containers),
- position number
- storage conditions (if it is not stated in the label for sensitive materials in refrigerator, or in deep-freezer, for not sensitive materials below 25°C).

After recording the materials should be immediately placed into their storage place.

#### **6. Storage of reference standards**

For all reference standards a separate BIN CARD should be filled. The following data are recorded:

- name of reference standard
- batch number or lot number
- laboratory arrival number,
- expiry date, (in unopened container 2 years, if the container is opened, from this date the expiry date is maximum 1 year, depending on the arrival date, if it overruns the 1 year period, with that period of time the expiry date is shorter).
- storage place and its number,
- position number,
- number of temperature monitoring and calibration book,
- date of starting storage,
- quantity prior to delivery (gross weight),
- quantity prior to delivery (net weight, at the start the labelled quantity is indicated),
- date of request for use,
- name of the person, who requested,
- date of delivery,
- signature of receiver,
- returning date,
- quantity after receipt (gross weight),
- quantity after receipt (net weight),
- signature of receiver,

All reference standards should be stored under the prescribed conditions. The storage conditions (temperature and humidity) are regularly controlled with calibrated thermo- and hygrometers.

Only authorized persons should deliver reference standards from the storage place, which must be registered in the BIN CARD.

For the storage of working standard the same rules should be used, but these are considered in respects to expiry date as opened reference standards,

**STANDARD OPERATING PROCEDURE FOR HANDLING  
OF REFERENCE STANDARDS**

**Code number:**

**1. Objective**

In this SOP all the important rules relating to the handling of reference standard materials are included.

**2. Scope**

The SOP is valid to all the analytical laboratories using reference standards for the pharmacopoeial investigations.

**3. Responsibilities**

To control the adequate handling of reference standard materials is the responsibility of QC Director.

The QC Director is authorized to nominate well-trained personnel responsible for the good performance of the works described here.

The Chief Analyst is responsible for training of the personnel and those members of the analytical laboratory, who are using reference standards during their daily work.

**4. Personnel**

Only qualified persons (analysts) nominated from the laboratory staff, can deliver and handle reference standards.

**5. Handling of the reference standards into the laboratory**

If a reference standard is delivered and moved from its storage place, it can be recorded into the reference standard recording book.

After delivering a reference standard, the analyst must control the closure of the container, and can use the materials, if the closure surely satisfactory. If the closure is not adequate, the reference standard can be analysed, and its application is only permitted, if the quality of reference standard is not changed.

Reference standard must be weighed immediately after delivery, and the container should be closed back as soon as possible after weighings are performed. To achieve a good closure again capping procedure using aluminium caps must be used. The exact weighings are recorded separately that the net weight of the reference standard in the container should be established. In a separate label put into the container, the date of the weighings, the accurate weight of the material, and the signature of the person who performed the weighings must be indicated.

Reference standard must return into the storage place immediately after its use. The accurate date of the return should be recorded in the reference standard recording book.

The receiver must control the closure of the reference standard and can control the gross weight of the material.



***R&D in the pharmaceutical industry***

**1. Different types of R&D actions**

**Profile development**

The main target of the R&D actions is to develop a new product, to broaden the production profile of the company.

This is a long procedure until the new product is registered and marketed.

Responsible person for the redevelopment stage is the R&D Director collecting all the necessary information from literature and from other available sources, forming a team to solve the first development stage.

Most important actions in the order of development stages:

**(a) First development stage**

- Pre-preparation phase
- Procurement of raw materials to be necessary for the development
- Analysis of the received samples, preparation of Analytical Test Specifications
- Analytical development to develop and validate methods suitable for stability indication
- Starting with the development work in laboratory scale.
- Comparative stability testing for selection of the best composition
- Preparation of Analytical Test Specification for the formulated product
- Evaluation of the results, preparation of formulation technology in laboratory scale
- Decision making about the further steps.

**(b) Second development stage**

- Production of three trial batches in pilot plant scale, with the composition selected by the comparative stability test as best
- Accelerated stability test with the three batches
- Standardization of quality and grade of raw material(s)
- Bioequivalency studies, if it is necessary
- Selection of packaging materials
- Label design, instruction for use preparation
- Collection of registration documents and submission for approval to the health authority
- Preparation of technological description and SOP's

**(c) Third development stage (after registration, prior to receive the marketing permission)**

- Purchasing raw materials, ingredients, packaging materials for the first three batches produced in industrial scale
- Production of three batches
- Validation of the manufacturing process

- Starting with long term stability testing with these three batches
- Starting marketing activity
- Batch record formation
- Finishing the development

### Product development

The main target of the development work is to improve the quality of a finished product produced by the company, or to develop a new formulation.

Most important actions in the order of development stages:

(a) First development stage

- Preparation phase, including problem formulation, and selection of the possible solutions
- Analytical development to develop and validate methods suitable for stability indication
- Starting with the development work in laboratory scale
- Comparative stability testing for selection of the best composition
- Preparation or extend of Analytical Test Specification for the formulated product
- Evaluation of the results, preparation of formulation technology in laboratory scale
- Decision making about the further steps

(b) Second development stage

- Production of three trial batches in pilot plant scale, with the composition selected by the comparative stability test as best
- Accelerated stability test with the three batches
- Standardization of quality and grade of raw material/s/
- Collection of registration documents and submission for approval to the health authority
- Preparation of technological description and new SOP's

(c) Third development stage (after registration, prior to receive the marketing permission/

- Production of three batches in industrial scale
- Validation of the manufacturing process
- Starting with long term stability testing with these three batches
- Finishing the development

### Process development

The main target of the development is to improve one or more technological steps involved into the formulation process(es) to improve the quality of the finished product.

The most important steps of process development are as follows:

(a) First development stage

- Pre-preparation phase, including problem formulation, and selection of the possible solutions

- Analytical development to develop and validate methods suitable for stability indication, if it is necessary
  - Starting with the development work in pilot plant scale
  - Accelerated stability testing for selection of the optimum processing conditions
  - Preparation or extend of Analytical Test Specification for the formulated product, if it is necessary
  - Evaluation of the results, preparation of formulation technology in pilot plant scale
  - Preparation of technological description and new SOP's
- (b) Second development stage.
- Production of three batches in industrial scale
  - Validation of the manufacturing process
  - Starting with long term stability testing with these three batches
  - Finishing the development

## 2. Recommendations for R&D in Syria considering the present situation

### (a) R&D activity at the pharmaceutical companies

Considering the presently existing situation in Syria only the third type of R&D activity (process development) is recommended.

The first two types of R&D activities require to establish pharmaceutical technological laboratories with well trained and qualified personnel.

Third type activity is only recommended if the experimental work can be done in pilot plant scale using similar equipments.

### (b) R&D activity performed by advisory centres

Until each pharmaceutical company should develop its own R&D activity, perhaps it is better to solve the problems through advisory centres.

Two centres are necessary:

- one for analytical development including stability testing, and
- one for pharmaceutical technological development.

Each centre possesses the necessary equipments and technical staff suitable for the first (and probably the second) development stage.

Both advisory centres have highly qualified persons (pharmacists) with long industrial practice. The development work is started at the same time at both centres, and finished when the second development stage is completed. The third development stage is performed at the pharmaceutical company with continuous support and presence of the members of the advisory centres.

## **TEST METHOD FOR VISUAL INSPECTION OF FOREIGN MATERIALS**

### **1. Objective**

Raw materials should be tested for the presence (or absence) of foreign materials. The test is based on the dissolution of the materials in a solvent in which the material is readily soluble. Solution is filtered through a filter paper and the paper is washed with the solvent used for dissolution. After drying the filter paper is inspected for visible particles using 4-times magnification. The paper is compared to a blank paper prepared similarly without dissolved materials.

Acceptance limit can be established by using a standard for comparison of the material, which means the borderline for this test.

### **2. Method**

Weigh 0.1 to 0.2 g material into a test tube with mg accuracy. Pipet 2.0 ml solvent into the tube, and dissolve the material into the solvent by gentle heating and shaking in an ultrasonic bath for 15 minutes. After dissolution transfer the solution into a Whatman No. V. filter paper, and filter through the paper. Wash the paper 3 times 2 ml of the solvent, then dry the paper in a heating cabinet at 100°C for 15 minutes.

Similarly prepare a blank paper using only the solvent for filtration (4 times 2.0 ml).

If a standard for comparison is available perform the test with this material as described above.

### **3. Evaluation**

Evaluate each filter papers visually using magnification lens with 4 times magnification.

### **4. Limits**

No visible particles should be present in the filter paper compared to the blank, or the amount of the visible particles should not be more than that of the standard for comparison.