

PN-ABF-566

67106

EVALUATION OF PHARMACARE  
RAMALLAH, WEST BANK

A Report Prepared By PRITECH Consultant:  
DAVID H. BRYANT

During The Period:  
JANUARY 9 - 20, 1990

TECHNOLOGIES FOR PRIMARY HEALTH CARE (PRITECH) PROJECT  
Supported By The:  
U.S. Agency For International Development  
CONTRACT NO: AID/DPE-5969-Z-00-7064-00  
PROJECT NO: 936-5969

AUTHORIZATION:  
AID/S&T/HEA: 4/13/90  
ASSGN. NO: HSS 068-WB

**DAVID H. BRYANT**  
Regulatory Consultant  
Device, Drug and Food Industries  
12920 Old Columbia Pike  
Silver Spring, Maryland 20904  
Telephone: (301) 384-2124  
January 20, 1990

I, David H. Bryant, am a consultant in the area of production of pharmaceuticals in accordance with Current Good Manufacturing Practice as specified in Chapters 210 and 211 of the Code of Federal Regulations of the United States of America. I am an expert in this area based on my education and experience. I was employed by the U.S. Food and Drug Administration for 29 years. During this time I inspected a wide variety of industry regulated by this Agency. In 1974 I became the Director of Drug Manufacturing Review Branch in the Bureau of Drugs. My duties included assisting in the revision of the United States Code of Federal Regulations. This revision was published as a final order on September 29, 1978. The revised section of this Code was entitled "Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs". I made decisions as to the requirements of these regulations and was the primary person charged with the responsibility of deciding whether or not provisions of this Code had been violated by pharmaceutical factories in the United States. I have served as a consultant to the pharmaceutical industry since my retirement from the Food and Drug Administration in May, 1985.

I was employed by PRITECH, 1925 North Lynn Street, Suite 400, Arlington, Virginia 22209 as a consultant to provide a thorough assessment, with reference to Good Manufacturing Practices (GMP), of the manufacturing and production operations of the Pharmicare pharmaceutical manufacturing firm in the Ramallah area of the West Bank. I worked with management of Pharmicare during the period of January 9, to January 20, 1990. The yardstick by which I have judged the operation of this firm is the aforementioned United States Code since there is no formalized standard for this industry in the West Bank territory. I conclude that this firm would be allowed to continue operation in the United States if that were where it was located. Even though there were some deviations noted, none were so serious as to preclude the continuance of operations. If a Pass, Fail criteria were to be applied, this firm would Pass.

  
David H. Bryant

## REPORT OUTLINE

### I. SUMMARY DESCRIPTION OF THE SCOPE OF WORK (include changes made to initial SOW)

I performed an examination of Pharmicare's pharmaceutical manufacturing and production operations at the factory near Ramallah in the West Bank area based on the Current Good Manufacturing Practice regulations of the United States. There is no formalized standard such as this for West Bank firms. I made recommendations by identifying areas considered deficient and advising how corrections can be accomplished. I

identified two areas in which additional personnel should be trained. The staff of personnel are well trained. I advised the firm of seminar opportunities that could update knowledge of production. I could not suggest possible marketing links due to the restrictions placed on West Bank firms restricting sales.

### I. PURPOSE(S) OF THE PROJECT

The purpose of this assignment was to provide Pharmicare with an assessment of their production and manufacturing controls with respect to a recognized standard. I also recommended some changes and some improvements that need to be made.

### III. METHODOLOGY

I performed an inspection of Pharmicare utilizing the U.S. Code of Federal Regulations, Parts 210 and 211, as a standard. I suggested minor changes to management throughout the 10 days that I was in the factory and found management most receptive to these recommendations. The most critical deviations from GMP are identified in my narrative report under "Good Manufacturing Practice Deficiencies".

### IV. SUMMARY OF OBSERVATIONS AND FINDINGS

As is common with most pharmaceutical factories, even in the United States, deviations from GMP were detected. None of the deviations are so serious as to warrant the discontinuance of production. The area of greatest concern is with the facility as outlined in the narrative report.

Personnel are well trained and perform their assigned duties very well. Two critical positions need people trained as an alternate in the event of unplanned absences.

### V. MAIN CONCLUSIONS

This firm is operated by a knowledgeable staff who are interested in their jobs and the welfare of the factory. They are hampered somewhat by the restrictions in sales to the West Bank area. Facility needs are being addressed and if funding can be obtained, improvements recommended will be accomplished during the coming year.

### VI. PRIMARY RECOMMENDATIONS

The firm should add air handling and controls to the facility. Light fixtures should be replaced or at least covered to protect personnel and product. Raw material storage should be expanded as should finished product storage. Two critical positions have inadequate back-up to prevent possible shut down if either were absent for an extended period of time.

I, David H. Bryant, have completed my evaluation of Pharmacare, a small pharmaceutical manufacturing factory located in the Ramallah area of the West Bank. This evaluation was based on the United States Code of Federal Regulations, Parts 210 and 211, Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs. Evaluation was based on this set of regulations since there are no formalized regulations governing pharmaceutical manufacturing in the West Bank territory.

The aforementioned Code is divided into several sections of major importance in assessing whether or not pharmaceuticals are being produced properly with appropriate safeguards to assure the quality, purity and strength of the finished pharmaceutical offered for sale in the marketplace.

#### PERSONNEL

This manufacturing facility has a well educated staff of employees who are energetic and interested in their jobs. The success of the company seems to be a common goal. Management is involved in daily operations and fosters a healthy atmosphere for open discussions wherein problems can be solved through a joint effort. Personnel in key positions with their qualifications are as follows:

1. Subhi Khoury, Manager, has a B. A. in Pharmacy from The American University, Beirut, Lebanon. He has many years experience in pharmaceuticals.
2. Bassim Khoury, Assistant Manager, has a B. A. in Pharmacy from the University of Oklahoma, Norman, Okla. He has served in this capacity since the founding of the company in 1985. He has attended a number of training courses throughout Europe. He is knowledgeable and energetic and is progressive in approach to producing quality products.
3. Toula Serna, Computing Manager, has a Masters Degree in Computer Science. She has received hands on training in computer programming with several leading pharmaceutical companies in France. She is well qualified for this position.
4. Ayman Qadoumi, Quality Control Manager, has a B. A. in chemistry from BirZeit University. He has been with this company for three years and in this capacity for over one year. He is presently in the United States for training. He well qualified for his position.
5. Buthayna Salem, Assistant Quality Control Manager, has a B. A. in chemistry. She is presently receiving additional training in the United States.
6. Muna Yasmineh, Quality Assurance and Production Manager, has a Masters Degree in Pharmacy from Technical University of Germany. She is very knowledgeable and is capable of substituting for almost anyone in the area of production, quality control and quality assurance. In the absence of the quality assurance manager and his assistant, she is serving in the dual role of quality control and quality assurance with the aid of a student who will receive a degree in chemistry this year.

7. Khawla AbuHashish, Production Manager, has a degree in Chemistry. She is experienced in pharmaceutical production and is responsible for all weighing of ingredients and for implementing daily production plans.

8. Munther Barghouti, Maintenance Engineer, was educated in engineering in the Soviet Union. He has been with the factory for over three years. He is well trained and performs his duties with confidence.

BUILDING:

The factory is housed in a building constructed of natural stone. It is in a good state of repair. Two other tenants share occupancy of the building which is owned by the Betunia municipality. A food factory is located on the bottom floor beneath the offices of Pharmicare. The bottom floor beneath the kitchen and rest rooms is storage for the owners of the building. All production and storage are presently on the upper level of the building. The interior walls are either plaster or drywall finished with a high gloss paint to about 7 feet with ceiling and remaining verticle walls finished in a flat white paint

Floors are tiled and contain adequate drainage. All drains are trapped to block air borne odors and bacteria from creating a problem. The floors are slightly sloped to aid in cleaning. Ideally, drains in pharmaceutical factories are provided with an air break to preclude back-siphonage from sanitary sewers becoming a problem. However, all production and quality control functions are performed on the third level which should preclude this being a problem in the factory.

Lighting in the factory is adequate, however it is provided by surface mounted fluorescent fixtures with exposed glass tubes. These tubes might break and cause injury to workers as well as contamination of product. Light fixtures such as this can also provide areas where dust can collect that may also become a contaminant of product. These light fixtures must be shielded. Flush mounted fixtures which are shielded serve two purposes, i.e., removing both problems at the same time.

Wash rooms are adequate, clean and well maintained. They are located outside the production area. Anti-rooms are provided and lockers are present for employees to change into laboratory jackets or coats and head covers, leaving their outer garments in the lockers before going to production. Single use hand towels are not provided in the men's locker area. Hot air hand dryers were ordered for both locker rooms and one did not work. Single use towels should be provided until hot air is available for the men.

This building is without central heat or air conditioning. Heat in the offices and laboratories was provided by small electric space heaters. Temperatures in the production area were 3 to 11°C during this visit.

There is no air handling equipment in the production area. Dust extraction units attached to equipment assist in dust control but are inadequate to assure air quality control. Air handling equipment should be added and should be designed to aid in the removal of dust and provide humidity control which will improve production features of tablets, capsules and dry suspensions.

Space restrictions at the present time causes mixing and granulation operations to be done in the same room. To provide separate areas is to reduce the chance for cross contamination. As presently set up, only one operation is performed at a time to avoid mix ups and cross contamination. Cleaning of all equipment in the room is required after each use. Mixing and granulation should be done in separate rooms. Cleaning procedures address this problem at this time. Scheduling records did not reflect dual usage of this area at any time.

Raw material storage is cramped and should be enlarged to facilitate expansion. Enlargement of this area is planned with the availability of more space in the building. Finished product storage is too small. New plans under development will provide additional space for storage and distribution.

#### EQUIPMENT:

Equipment used in the production of pharmaceuticals is of design appropriate to the operations for which it is intended. It is suitably located to facilitate cleaning and maintenance. Equipment in use in production during this evaluation includes:

1. Tablet machine: This machine is of a standard type and is constructed of materials suitable for its intended use. It is in a good state of repair. A dust extraction unit is attached to this piece of equipment. A maintenance schedule is established and is posted along with cleaning instructions on the wall in the tablet room next to the machine. This machine is completely broken down and cleaned between products. Written procedures were followed during this visit.
2. Capsule machine: This machine is of an Italian manufacturer. It has a capacity equal to the need of this factory at the present time. With expansion the firm will either need another such machine or a model with a larger capacity. It is suitably constructed and easily cleaned. A dust extractor is added to this unit to aid in dust control. Cleaning and maintenance schedules are established, are posted by the machine and are followed.
3. Fluid Bed Dryer: This machine is adequate for its intended use and is well maintained. Cleaning and maintenance schedules are established and are followed.
4. Vari-mixer: Clean and adequate for its intended use and is well maintained according to schedule.

5. Liquid Mixer and two liquid fillers: These are suitable for their intended use at this factory. They are cleaned and maintained according to a written schedule.
6. Tablet coating machine: This machine is adequate for its intended use. Only one product is coated by this firm so this piece of equipment sees limited use. It was clean during this visit.
7. Blister machine: This machine is used for packing all capsules and tablets of various sizes. It is the most critical piece of equipment to production since all tablets and capsules are marketed in blister pack. It is well maintained and is adequate for its intended use.
8. Reverse Osmosis water: All water used in production is purified through this unit. It is maintained according to the suppliers recommended schedule and laboratory testing is routinely performed to assure the water quality.
9. Air Compressor: This piece of equipment is oil free and has a vapor trap to assure the quality of compressed air used in the factory. It is adequately maintained.
10. Scales: All batch sizes are small and all active ingredients are weighed on an electric scale of 4Kg capacity. That scale is checked for accuracy on a monthly schedule. Such a scale should be checked on a daily basis with a known weight standard. Inactive ingredients are weighed on a mechanical balance (platform scale) of 100Kg capacity. It is checked in its daily use. A small balance is used in the tablet room where tablet weights are made every 5 minutes during production. Tablet weights are checked every thirty minutes on a very sensitive laboratory balance. This balance should be checked with a known standard every day.
11. Computer: This firm is in the process of computerizing all of its operations. Master plans were developed and the computerization of operations began in July of 1989. D-Base III+ is being used. All master formulae are in the computer. All raw material inventory and control is now computerized. Testing timetables for the laboratory are in the computer. Raw material release by the laboratory is entered into the computer and use records are automatically reflected as to when used and in what batches. All finished product movement is computer controlled. Marketing and sales are in a separate computer which will be bridged to the main computer in the near future. The timetable provides for all production control to be in the computer before the end of 1990.

CONTROL OF COMPONENTS, CONTAINERS AND CLOSURES:

All drug components are computer controlled. Upon receipt the item is entered in the computer by the quality assurance manager and a quarantine label is printed and attached

to the container. A request for samples is entered, samples are drawn and a sampled sticker is attached to the container, and the samples taken to the lab. Samples are drawn according to a written procedure. Appropriate tests are performed according to written procedures. This meets the requirement of GMP. The computer maintains an inventory control and reflects the status of components available for use. All finished products are tested before release and all components are tested before use. All components must be tested at six month intervals until they are used up. This is a system instituted by the firm to always have current information on the condition of the raw materials. The computer system will not allow use of raw materials scheduled for retesting until such testing is completed and entered into the computer.

Storage of components, i.e., all active ingredients, containers and closures is neat and orderly, however additional space is desperately needed. Plans which are under review will provide more storage area. This is essential if this firm expects to expand. Storage for both supplies and finished product is in short supply under the present floor plan.

#### PRODUCTION AND PROCESS CONTROLS:

Production and process controls are not yet completely computerized. There are written procedures designed to assure that the drug products are properly compounded and tested before being released to distribution. All batches are formulated to provide not less than 100 per cent of the labeled amount of active ingredient. On weighing out ingredients are placed into production containers and are properly identified with adequate information to assure that they can be traced to the original container. The weighing operation is so established that controls are exercised wherein the person performing check weights does not have access to the original weights until the two weight sheets are compared with each other by quality control.

Equipment is properly identified and sampling and testing are performed in accordance with established procedures. Any reprocessing is with concurrence with the quality control unit and is closely supervised.

#### PACKAGING AND LABELING CONTROL:

Procedures have been established that will assure review and approval of labeling or packaging materials before they are released for use. All labels are roll labels and are adequately controlled in accordance with regulations under which this review is being performed. Each container is examined at the time of packaging in its final container. Each blister pack bears the expiration date of the product contained therein. Blister packs are packaged into boxes which bears the lot number, the manufacturing date and the expiration date.

This firm has established policy that restricts expiry dates on finished product to the expiry date on the active ingredient. Ample data has been generated through their stability testing to support a three year expiry date on most products in the container closure system which they market the product. I recommended that review of the policy be initiated with serious consideration given to changing to a three year expiry date from the time of manufacture regardless of the expiry date of the active ingredient. As this firm's labeling operations are conducted, only one product is labeled at a time. When blister packs are being inserted into boxes (the box contains most of the required labeling), a product information insert is included in the package. Boxes are stamped with the lot number, expiry date, and manufacturing date just prior to being filled. This greatly reduces the chance for mix-ups. It also serves to reduce the number of boxes that might have to be discarded for having already been printed with lot number information. Units are collected as samples and are examined by quality control to assure accurate labeling.

#### HOLDING AND DISTRIBUTION:

This firm presently has a separate computer system which is utilized for holding and distribution. It will be tied to the main computer system as the different phases of computerization of operations are completed. This computer system in use is limited to warehousing and distribution. Controls exercised by this firm at this time are such that no finished product can reach the finished product store without a label generated by the computer program utilized in production reflecting that it has been released by quality control.

An inventory card is prepared only after lots are received in the finished product store. On each withdrawal from a lot, the date, amount withdrawn, to whom sold, and the amount remaining in inventory are entered on the inventory card. Lots are controlled so that the first in is the first out.

As is the case with raw material storage, the finished product store is cramped for space. While storage is in an orderly manner, it is crowded. Plans have been made and drawings are under review for the expansion of this area. Management recognizes that to be able to expand, this firm will need additional finished product storage. I recommended that this firm consider the installation of rack storage to facilitate greater utilization of storage facilities. Such a system would require a small electric fork lift with which to load racks above floor level.

#### LABORATORY CONTROLS:

This firm has a well organized laboratory with the equipment necessary to perform the assays and tests established by reference manuals of methods and procedures on hand at the firm. The British Pharmacopeia and the United States Pharmacopeia are available and represent most of the tests methods utilized by this firm

Specifications, standards, sampling plans and test procedures have been established for the products manufactured by this firm. These address not only the finished product but also components, containers, closures, in-process materials and labeling.

On receipt, all components are sampled according to an established sampling plan. Each component has an established standard and assays and tests are performed to determine acceptability in accordance with these standards. Containers, closures and labeling are sampled and examined on receipt and records of their acceptability are maintained. Intermediates are sampled and tested, as appropriate, to determine acceptability for use in further processing.

Each batch of drug product is determined to be in conformance with final specifications prior to being released for distribution. This includes strength of each active ingredient. Testing is conducted in accordance with established specifications. Most products produced by this firm are manufactured elsewhere in Europe and the firm has purchased the formulae and tests methods utilized by the original formulator. This firm restricts production and marketing to products that are legally marketed elsewhere, and which will fulfill the needs of West Bank residents. Reserve samples are retained until one year after the expiration date of the product. There is ample sample retained to perform all the tests established for the product. Testing for stability attributes is performed at six month intervals for all lots up to and including three years after the date of manufacture.

Attached is a list of laboratory equipment available at this firm as of September 1989. Since that time an R.O. water unit has been added. An HPLC analyzer has been purchased but has not yet been delivered. The Quality Control Manager is presently in the United States receiving training in the use of this piece of equipment. This will add to the firms analytical capabilities.

#### RECORDS AND REPORTS:

Batch records are retained until one year after the expiration date assigned the product. Records relating to components, containers and closures are likewise retained. These records will eventually be stored in the computer but at the present, batch records are in hard copy.

I failed to determine whether or not a record of major equipment cleaning, maintenance and use is maintained. A record of use should exist and should include the date, time, product and lot number of each batch processed. If equipment is dedicated to one product, the cleaning, maintenance and use should be a part of the batch record.

Records for components are computerized and were found to be satisfactory.

Master records, i.e. formulae, production and laboratory controls are computerized. Batch records are not yet in the computer but are in the process of being added. Batch

production and control records reviewed during this visit were satisfactory. All production records are reviewed by quality control prior to release of the product. The assistant Manager must sign off on these records prior to product being released to the finished product store. Records reviewed satisfied this requirement.

Laboratory records are adequate. A proposed change, which will incorporate a copy of the method used as a part of the batch record will make the batch record more complete. Laboratory workbooks are bound and reflects the person doing the analysis, the analysis performed, the results of the analysis, the method used and the date and results of the analysis.

Distribution records reflect all necessary information to be able to effect recall if the need arises.

GOOD MANUFACTURING PRACTICE DEFICIENCIES:

Deficiencies detected during this visit were based on the United States standard. None of these deficiencies are so serious as to require suspension of operations. Generally, they can be easily corrected and are as follows:

1. The building lacks temperature, humidity and air quality controls. This can be corrected by the addition of air handling equipment in production areas. Heating and air conditioning would aid in controlling production problems created by humidity, heat and cold.
2. Single service towels were not provided in the male locker room. An electric hand dryer ordered for this area did not work and has been returned. Until such time as is necessary to get this dryer and get it installed, single service towels should be provided, one towel per employee.
3. Light fixtures throughout production are not shielded. Exposed glass fluorescent bulbs are surface mounted and not only do they pose a potential for contamination of product, they can also pose a hazard for employees. Light fixtures such as this can also provide areas of dust collection that are difficult, if not impossible to clean, thereby creating a potential source of cross contamination. These light fixtures must be either properly shielded or replaced with shielded fixtures. The preferred fixture is one that is flush mounted, i.e., recessed in the ceiling.
4. General cleaning schedules are sometimes not followed due to the absence of such personnel. General cleaning did occur on occasion during this visit but was accomplished while production was under way. This creates a potential for contamination of product. General cleaning should be scheduled either before or after production so that people not trained in production and quality control are not in the production area during production.
5. Electronic scales used in production are not calibrated prior to each use. Known weight standards should be used.

PRIMARY RECOMMENDATIONS:

1. Install air handling equipment, preferably a system that incorporates heating, air conditioning and humidity controls to reduce the possibility of air borne cross contamination and to control the environment in which pharmaceuticals are being compounded, packaged and stored.
2. Replace light fixtures in production areas with shielded fixtures to reduce the potential of glass contamination of product and to protect employees from injury in the event of a broken glass bulb.
3. Expand the raw material storage area, adding environmental controls to reduce potential cross contamination as well as an added element of protection for the components.
4. Expand the finished product store, adding rack storage to better utilize the storage space available. Purchase a small electric fork lift to facilitate storage on upper levels of the rack storage.
5. Adjust the workday of cleaning and maintenance personnel to avoid having persons not trained in pharmaceutical production and quality control present in production areas while production is under way. The maintenance engineer can reassemble and adjust equipment between changes in products being produced and after disassembly for complete cleaning without delaying production employees.
6. This firm should identify someone and give them the necessary training to be able to fill in for the computer scientist so that an absence of the computer scientist, for whatever reason, will not shut down operations if by chance something occurred to prevent the computers proper operation.
7. This firm should identify and train an additional employee in the cleaning and maintenance of equipment.
8. A candling light for use in examination of bottles of liquid products should be obtained. The use of a high intensity unprotected glass light bulb should be discontinued. The intense light is hard on the employees' eyes assigned the task of examination of the bottles and also creates an unpleasant glare for other employees in the area.
9. Obtain a copy of a Book of Methods, Association of Official Analytical Chemists, available from the A.O.A.C., P. O. Box 540, Benjamin Franklin Station, Washington, D. C. 20204.
10. Obtain a copy of parts 200 to 299 of the Code of Federal Regulations from the Superintendent of Documents, U. S. Printing Office, Washington, D. C. 20402. This book of regulations not only contains the requirements of Good Manufacturing Practice at 210 and 211 but also contains labeling requirements at 201 which can be used as a guide.

SEPTEMBER 1989

PHARMACARE  
LIST OF LABORATORY EQUIPMENT

	DESCRIPTION	MANUFACTURER	MODEL/TYPE
1. AUTOCLAVE	FOR STERILIZAITON	-	-
2. SPECTROPHOTOMETER	RANGES: 601UV-VIS	SPECTRONICS	-
3. SPECTROPHOTOMETER	DIGITAL	PERKIN ELMER	MODEL 35
4. DISINTEGRATOR	TESTER FOR TABLETS, COATED TABLETS & CAPSULES	ERWEKA	TYPE ZT2
5. DISSOLUTION TESTER	TESTER FOR TABLETS, COATED TABLETS & CAPSULES	ERWEKA	TYPE DT
6. FRIABILITY TESTER	FOR ROLLING, ABRASION & IMPACT DURABILITY	ERWEKA	MODEL TA
7. LAMINAR FLOW	VERTICAL	-	-
8. MILIPORE FILTER	WITH PUMP	MILIPORE	-
9. BALANCE	ELECTRONIC	OHAUS - GALAXY	SERIES 4000
10. BALANCE	ELECTRONIC	METTLER	AE120
11. MOISTURE DETERMIN- ATION BALANCE	ELECTRONIC	OHAUS	MODEL MB300
12. WATER SOFTENER	-	LINDSAY	-
13. INCUBATOR	56X47X60 CM.	ARIJ-LEVY	-
14. DRYING OVEN	56X47X60 CM.	ARIJ-LEVY	-
15. HOT PLATE	-	-	-
16. MAGNETIC STIRRER	-	-	-
17. SHAKER	-	-	-