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DEMONSTRATION OF MODERN TECHNOLOGY FOR DRUG PACKING

DP/MON/84/001

MONGOLIA

Terminal Report*

Prepared for the Government of the Mongolian People's Republic
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

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Abstract

Demonstration of modern technology for drug packing.

Project Number : DP/MON/84/001

The main purpose of the project is the improvement of quality of locally produced tablets. In the course of the project implementation the following has been achieved :

- The Tablet Department has been reconstructed so as to meet the requirements of Good Manufacturing Practice.
- The model tablet production line with the capacity of 110,000 tablet per hour and consisting of up-to-date equipment has been installed and put into regular production.
- The quality of presently produced tablets has been improved by introduction of tablet blister packing system as well as revision of technology and quality standards.
- The Quality Control Laboratory and R&D Unit have been modernized and strengthened by provision with modern equipment, instruments and labware enabling to carry out activities related to adaptation and development of tablet manufacturing technology and to ensure the proper in-process control and quality assurance of final products.
- 13 specialists have been trained through fellowship and in-service training in the field of modern technology and equipment for tablet manufacturing, in-process control and modern methods, means and procedures for quality control of dosage forms, maintenance of equipment.

CONTENTS

INTRODUCTION

The Government of Mongolia gives high priority to the development of various National Health Programmes, an important element of which being the supply of the population with essential drugs. Certain measures have already been undertaken to establish a local pharmaceutical industry although at present the major amount of drugs consumed in the country (about 70%) are imported. The Government's main trust has been in the direction of industrial utilization of locally available raw materials for the production of pharmaceuticals. Therefore the support has been given to the development of local manufacture of blood derivatives, drugs obtained from slaughterhouse waste products and drugs of medicinal plants origin both by the Government and through a number of UN sponsorred projects (DP/MON/82/004 Programme "BIOMED", DP/MON/82/002 Assistance to the Experimental Centre of Applied Enzymology and Microbiology in the production of sterile enzyme products). Besides, the very important component of the Mongolian pharmaceutical industry is formulation of pharmaceuticals mainly from raw materials imported in bulk. The pharmaceutical formulation factory in Ulan Bator was built in 1959 and started operations with the manufacture of tablets and injectables. In 1981 within the framework of UNIDO project SI/MON/79/801 a team of experts visited Ulan Bator with the aim to observe the operation of the formulation factory and to advice on the plan of action for making it suitable to meet the increase of drug demands. Their terminal report "Survey of the Pharmaceutical Industry in Mongolia" gave the detailed describtion of the existing situation and proposed several solutions for revamping the formulation factory in Ulan Bator. According to the Mongolian side one of the first priority was the reconstruction of the Tablet Department and introduction of modern means for tablet packing. Before the beginning of the present project the produced

tablets were packed manually in packages of 6 in paper strips. That obsolete method of packing does not prove to ensure the quality of locally produced tablets and often results in shortened shelf live and even disintegration of products espessially taking into consideration specific climatic conditions of the country and long ways of transportation to deliver the products to remote districts (Aimaks). Besides, the manual packing does not prevent the microbiological contamination of tablets and has a harmful effect on workers whose work brings them into direct contact with active ingredients of tablets in the process of drug packing. Bearing in mind that introduction of a modern drug packing system would lead not only to the improvement of quality of locally produced drugs but would contribute to further development of the production capacity and to increasing effectiveness through the improvement of labor productivity, i.e. the objectives set up by the National Development Plan, the Government Authorities concerned have requested an international assistance and jointly with UNDP have approved the present project. The project can be considered as the very initial step in the total reconstruction of the pharmaceutical factory in Ulan Bator which aims at increasing the manufacture of pharmaceuticals from the present level of 16 million Tughriks to 40 million Tughriks in the year 1995 and further to 70 million Tughriks within forthcoming 20 years.

Development problem and immediate problems attacked

The development objectives of the project are as follows :

- An increase of qualitative and quantitative outputs of the local pharmaceutical industry
- Achieving self-sufficiency in local formulation of essential drugs from imported pharmaceuticals in bulk and indigenous raw materials

Although the project is directly related to the output in industry and to the quality of locally produced pharmaceuticals in dosage forms its development objectives envisage the assistance to the Government of Mongolia in supporting the successful implementation of National Health Programmes. The knowledge and practical experience gained by the Mongolian specialists in the course of project implementation as well as establishment and running of a modern tablet production line including a tablet packing unit and modernization of Quality Control Laboratory and R&D Unit should create a techical basis for further development of a pharmaceutical formulation industry. Nevertheless realization of the Government's Plan and achievement of development objectives will require further efforts and additional capital investment. First of all it should be emphasized that construction of a new building to accomodate the production of tablets and injectables is inevitable. The new building is to be erected within the area of existing factory. It should meet all modern standards relating to the formulation of pharmaceutical dosage forms. The UNIDO document "Technical profiles for production of pharmaceutical dosage forms" (ID/WG.393/14/Rev 1, 1985) as well as preliminary layout of the new factory proposed by the "Survey of the Pharmaceutical Industry in Mongolia" (UNIDO project SI/MON/79/801) can serve as a guidance for the design and construction of the new factory. However, taking into consideration the lack of experience in this particular field it seems to be reasonable to establish the new plant on the basis of international or bilateral assistance. It is quite understood that even if the decision concernig a new pharmaceutical formulation factory is finaly adopted without delay and necessary funds are made available the new factory would be operational only within several years. Therefore as an immediate goal there should be installation of the second independent tablet production line within the area of the existing Tablet Department. By reaching the targeted capacity it will be feasible to increase almost three times the output of already reconstructed Tablet Department and to decrease spendings on import of drugs

in finished forms.

The other problem to be solved without delay is identification and definition of health and drug policies. It is feasible for the Ministry of Health in collaboration with WHO Office to examine the overall health situation in the country and to consider and approve the Country's List of Essential Drugs. The priority for local production should be given to the drugs of the "first level". Therefore the range of tablets to be manufactured by the pharmaceutical factory should be the major means to cure the most commonly spread diseases that are as follows :

- Respiratory diseases
- Diseases of digestive system
- Diseases of nervous system and sensory organs
- Infectious and parasitic diseases

As far as concrete drugs are concerned their choice and priorities for local production should be based on the List of Essential Drugs and determined by the Ministry of Health. Besides, the most expensive pharmaceuticals in dosage forms even if their consumption is moderate should be manufactured locally.

The three immediate objectives of the project were planned as follows :

- Increase quality of packing and other quality aspects of locally produced pharmaceutical preparations (tablets) ;
- Advice to pharmaceutical industry on adaptation and development of modern technology of drug production and packing ;
- Creation of a basis for further development of the national pharmaceutical formulation industry.

The pharmaceutical industry is rather delicate and difficult. Its development requires a broad range of specialists with wide practical experience and knowledge, well outfited R&D and quality control facilities with a range of highly specialized equipment and instruments as well as production facilities meeting the requirements of Good Manufacturing Practice (GMP). All these factors are closely interlinked and only by their

proper arrangement it is feasible to attain the project's goal. Therefore, although the very first priority was introduction of a modern drug packing system instead of manual packing of tablets the project dealt with strengthening all steps of tablet manufacturing. In this connection besides the creation of an automatic tablet packing unit in the course of project implementation it was proposed to establish a modern tablet production line as well as to modernize R&D Unit and Quality Control Laboratory.

Outputs produced and problem encountered

A. Technical appraisal of project requirements and settlement of project implementation.

In December 1985 Mr. Luvsannamjil Director, Pharmaceutical factory was appointed as the National Project Coordinator directly responsible for project implementation. After his retiring in December 1987 Mr. Tsensuren, who had been nominated for fellowship programme at SPOFA, Czechoslovakia held the post. In addition counterpart personnel of 10 specialists including industrial pharmacists, mechanical enginners and analytical chemists were assigned to carry out the project activities. The project became operational in December 1985 when CTA was fielded to Ulan Bator.

In the course of the first investigation on the spot it was found out that almost all items of tablet production equipment had to be replaced without delay. As a rule the tablets manufactured did not have sufficient hardness. The granulate happened to be uneven and contained too high percent of pieces with dimension of more than 0.5 mm along with the high content of fines (less than 0.2 mm). As a result of lorg transportation and consequent storing the imported raw materials sometimes were not free-flowing. If in principle milling was possible by using the existing wet granulator of vertical type the mechanical sifter to obtain a uniform particle size was not available. The drying

process had never been controlled and the old and obsolete tray dryer used did not have any temperature regulating and recording system. Radical improvement of R&D Unit and Quality Control Laboratory was also mandatory due to the lack of basic suitable equipment and instruments. Upon discussion the situation with the project counterpart personnel and with the Government Authorities concerned it was proposed therefore to explore all possibilities to establish besides a tablet blister packing system a modern tablet production line with all necessary items of equipment as well as to modernize and strengthen the existing R&D Unit and Quality Control Laboratory. As a result the project budget was increased several times. Considerable support to the project was also given by the Ministry of Health that had provided it with some items of equipment and spares, like mechanical sifter, wet granulator, tablet toolings etc., as well as made available through WHO project MOG/DSE/001 analytical and in-process control equipment and instruments, packing materials and some machinery for the manufacture of tablets.

B. Reconstruction of the Tablet Department.

The design and working drawings for the reconstruction of the Tablet Department have been prepared based on the recommendation of the "Survey of the Pharmaceutical Industry in Mongolia" (UNIDO project SI/MON/79/801). In the course of actual civil work the main attention has been given to those physical aspects of the premises that could affect the quality and safety of final products, to convenience of maintaining the manufacturing premises according to strict sanitary standards and to adequacy of the working space and storage areas. The working and storage premises have been constructed so as to prevent the entry of animals and insects. The new floor has been made of polished concrete allowing easy wet and dry cleaning. It has been made flat and level as well as suitable for insallation of rather heavy machinery.

All edges forming the joints of floor, walls and ceiling have been made rounded so as to prevent them from getting easily dirty. To reduce the possibility of contamination all open raceways for cables and pipes have been eliminated. The interior surfaces (walls, ceilings, floors) are presently smooth and free from cracks. The walls and ceilings are covered with a washable paint permitting easy cleaning and disinfection. The reconstructed Tablet Department has been furnishes with new doors safely separating working premises. In the course of project implementation the workers are motivated to keep the doors constantly shut in order to avoid interlinkage of outside air. The new windows also reliably separate the working premises. The working areas where considerable quantity of dust can be developed have their own connections to the newly installed exhaust ventilation system. The exhaust air outlets of tray dryers have been connected to exhaust air line. Unfortunately due to financial difficulties the whole ventilation system designed to supply the Tablet Department with filtrated air (5 changes per hour) has not been completed in time. At present two separate air exhaust systems in granulation and tablet compressing areas are operational while air compressor to feed the department with filtrated air has not been installed yet. The completion of the whole ventilation system is planned for the first quarter 1988.

In the reconstructed Tablet Department the working space is sufficient to assemble two independent tablet production lines in accordance with the requirements of GMP, i.e. equipment forming these lines can be placed orderly and logically allowing to minimize the risk of omission of any manufacturing or control steps and to minimize the risk of confusion between the different drugs or their components. Adequate storage areas to allow proper placement of raw materials, semiproducts and finished tablets have been also provided in the reconstructed Tablet Department.

C. Creation and running an automatic drug packing unit and a modern pilot tablet production line.

The choice of equipment for the creation of a model tablet production line has been based on the order of priorities and availability of funds. On the other hand such parameters as high reliability of equipment, convenience of cleaning when changing the types of products and requirements for maintaining the equipment have been taken into account. Where possible highly sophisticated equipment controlled by electronics that requires special knowledge and experience for its maintaining has been avoided. All items of equipment ordered for the project have been designed and made in accordance with strict criteria of the pharmaceutical industry.

The tablet production line has been assembled from the machinery made by Manesty Machines Ltd. (Great Britain). The items included into the line are as follows :

- Steam heated Tray Dryer 20 S to hold 20 trays with maximum capacity of 5 kg wet granulate per tray. The dryer ensures constant temperature conditions in drying chamber and even air movement around each tray thereby producing uniform granulate drying at prescribed temperature. (The second 20 S Tray Dryer has been provided through WHO project MOG/DSE/001).
- Oscillating Granulator Rotorgran Mark IV with set of screens for wet and dry granulation. Since the old but quite reliable wet granulator of vertical type continued to be used in the new line the granulator MK IV was used almost entirely for dry granulation. In this mode of operation it is capable to process more than 500 kg dry materials per hour reducing them to a pre-determined size and thus ensuring obtaining the very even and free flowing particles.
- Fitzmall model S44D6 Comminuting Machine with set of screens At present the machine provided through WHO project MOG/DSE/001 is used for size reduction of raw materials, rejected tablets and dried granulate. But the flexibility

and high throughput of the machine as well as large choice of screens will allow to widen the areas of application when the second production line is assembled.

- Model B 4, 25 station single sided rotary tabletting press with set of tablet tooling for round flat bevelled edge tablets with breakline dia of 9 and 12 mm. The output of 75,000 tablet per hour as claimed by the manufacturer has been reached in practice. Another B 4 tabletting machine provided by WHO will be the part of the second production line.

Besides the above mentioned machinery the model production line includes Russian made mechanical sifter of rotary-vibratory type, capacity 80-400 kg per hour with set of sieves steam heated kettle for the preparation of granulation liquid (mostly starch paste), the ploughshare mixer capacity of 50 kg, the vertical wet granulator and 15 station tabletting machine RLE 15 PH Kilian (West Germany) with maximum capacity of 35,000 tablet per hour.

The new tablet presses as well as the old one have been provided with dust control equipment. This system introduced for the first time at the Tablet Department enables to minimize the hazard created by airborn dust, to protect the compressing machines and to efficiently remove the surface dust thus resulting in better appearence of tablets. At the same time the installed Manesty tablet de-dusters and dust extration units considerably reduce the possibility of dust damage to sophisticated packaging equipment.

Another very useful and important practice first introduced at the Tablet Department during the life of the project is regular polishing of punches that has become the obligatory part of the whole maintenance system. Installation and putting into operation Manesty Punch Polishing Unit along with Manesty Punch Polishing Kit helps to keep or even to restore high finish punch faces thus reducing tooling costs, perhaps the most expensive spares, and ensuring consistent production of high quality tablets.

The manuals for each item of equipment supplied by the manufacturer have been translated and working instructions for machine operators and maintenance personnel have been prepared in Mongolian, the documents being in writing and approved by the Chief Mechanical Engineer. Special attention has been paid to proper lubrication of the machinery bearing in mind the lubrication is cheaper than spare parts. Lubrication scheme has been established for each machine and department's mechanic responsible for maintenance constantly watches for the established time between cleaning and lubrication to be never exceeded for any reason.
The new tablet production line is totally operational at present. Assuming an efficiency of 80% as far as the machinery is concerned the tablet compressing section can make as many as 700,000 tablets daily in one shift of 8 working hours. Since the average weight of tablets varies between 0,2 and 0.56 g the maximum quantity of granulate to be produced in one shift should be approximately 400 kg. At the rate of one batch per hour 8 mixing batches of 50 kg is necessary that is quite realistic (the capacity of the existing mixer is 50 kg). The capacity of wet and dry granulators and mill is also sufficient to produce the required quantity of granulate ready for consequient compressing. Some difficulties still exist in drying of wet granulate. As a matter of fact the drying cycle fluctuates between two and five hours depending on the type of the product. Therefore, even taking into account that actual quantity of granulate required is less than 400 kg the overall drying capacity at present does not match the capacity of compressing section. In order to increase the output of the Tablet Department it has been decided to work in two or sometimes in three shifts at granulation section and correspondingly in one or two shifts at compressing section. The output of the Tablet Department has been increased from the previous figure of 33,000 million 6 pieces confections per year to 47 million packs of 6 tablets. Further increase of produc-

tivity can be reached by proper production planning. It is recommended to carry out not more than three production campaigns for the same product each year. At present it cannot be achieved because of unregular supply of the Tablet Department with raw materials. In fact the production planning is based on actual availability of active ingredients and even lubricants such as stearic acid and its salts the stockpile of which is not sufficient. Therefore, the proper coordination with the organization responsible for import of raw materials is essential particularly in view of the plans for the development of the local pharmaceutical formulation industry. If we consider technical means and availability of experienced specialists and labour further increase of the output of the Tablet Department is quite achievable in the nearest future. Actually the core of the second independent tablet production line already exists. Besides the second B 4 tabletting press the trial runs of which have been completed putting into operation recently bought Kilian tabletting machine RLS 15 PH with the output of 40,000 tablet per hour the overall capacity of the compressing section will increase to 225,000 tablet per hour or, 410 million tablets yearly assuming the work in one shift only. The main attention when considering the installation of the second line should be given to mixing and drying. It is feasible to include into the second line the large capacity tray dryer like Manesty 80 S (similar to the existing 20 S tray dryer) or fluid bed dryer (Glatt, Stokes or Aeromatic). As far as wet and dry mixing is concerned Manesty "F" mixer or Collette mixer like Gral 50 combining the operations of mixing and wet granulation are quite suitable.

The blister packing of tablets started in 1986 when previously bought table-top-version blister machine ECONOM 740 (E.TH.Noack, West Germany) was put into operation. Within the framework of the project the machine has been

brought up to the full strength by the purchase of coding types and cliché rollers with rubber mats according to the ordered artwork, but in manual version only. The machine is operated by three workers who manually place tablets in blisters on band running along feeding table. By this mode of operation the output of 14,000 packs of 6 has been reached. Furter step also envisaged by the project was introduction of automatic packing system. It is understood that for this purpose blister packing has been chosen. Taking into consideration the relative simplicity of ECONOM 740 blister packer and its low price (it was almost twice cheaper in comparison with other machines submitted for bidding) this machine but completed with feeding devices for tablets dia 9 and 12 mm has been bought for the project. The main and the only difficulty in reaching the above output was considerable delay in delivery of the machinery. The first set of machines was received in March 1987. As far as the blister packing machine is concerned it was ordered as early as in January 1986 but delivered in June 1987 only. Besides, the contract includes services of manufacturer's engineer for installation and trial runs. Although his arrival was expected in September 1987 his mission is still pending. Therefore, the blister packing machine received in June 1987 has left unpacked up to the present.*

Lengthly delivery and further assistance to be provided by manufacturer for installation turned out to be the common problem for other projects implementing in Mongolia. This factor should be taken into account when planning and implementing the project with rather heavy equipment component.

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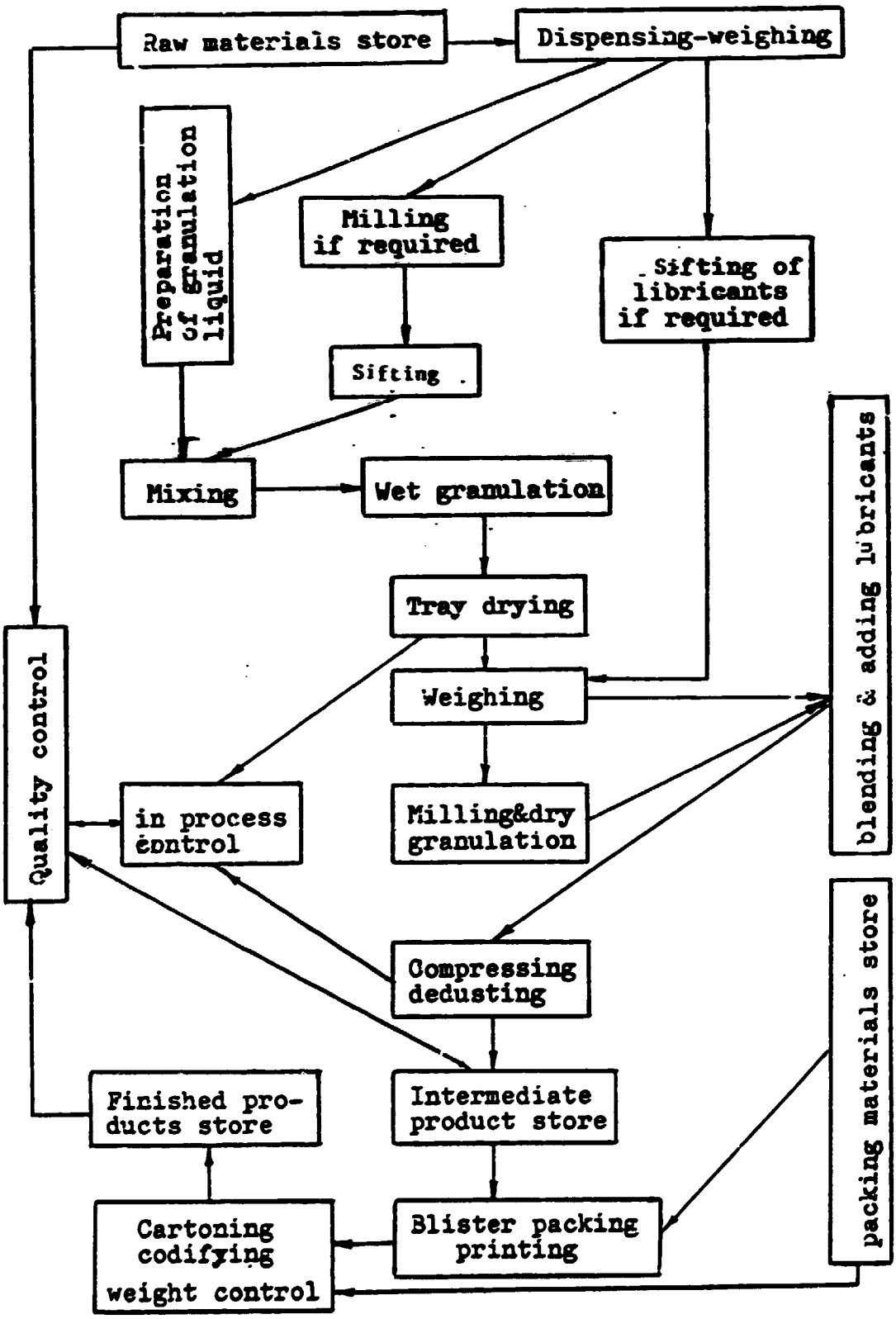
* In February 1988, the mission of engineer was cancelled and the blister packing machine has been put into operation.

D. Manufacturing technology and packing of tablets.

The production of tablets is arranged according to the diagram shown on page 16. The ingredients are weighed in batches of 50 kg after grinding and sifting. At present the careful weighing is done by industrial precision electronic bench scale 46 kg capacity with automatic taring and accuracy 5 g. The granulation liquid is prepared in steam heated kettle for each batch just before mixing. As binding medium 5 - 10% arch paste is used sometimes with addition of gelatine and sugar syrup. Other binders are not available. The only available lubricants are talc., stearic acid and its calcium and magnium salts. The lack of choice of auxiliary materials to certain extent limits the technological capabilities. By using presently installed equipment it becomes possible to obtain even free flowing dry granulate. Therefore, the revision of technological documents was concentrated on determination of optimum composition of binding medium, loosenning substances, sliding and lubricating additives for each type of tablets and on specificating the limits of water content in a ganulate. The latter parameter is essential to obtaining the granulate possessing good compressing properties. For its determination and for subsequient working out regime of drying the desiccator method has been introduced into practice, the moisture content being determined by new express method (IR balance). In spite of the fact that revision of technology for all types of products being manufactured has started and for 18 products the revision has actually been completed this work cannot be considered as finished. Some more precise definitions and specified parameters are still needed. The completion of this research is expected upon the receipt of such ordered in-process control devices as Granulate Flow Tester, Tablet Tester of rolling and impact durability, Tablet Breaking Point Tester and Tablet Dissolution Tester, but still during the life of the project.* Upon defining and

* All above contract equipment arrived in February 1988



Flow diagram for formulation of tablets

and specifying the permissible limits of the above parameters they should be included to the technological documents as obligatory control points. Further improvement of the technology should be combined with commencing the research of drug aging.

The quality of blister packing with ECONOM DPN 740 is good, i.e. the main goal of the project has been achieved. Besides even in manual mode of operation this machine considerably increases the labour productivity. Operated by three persons it is capable to yield as many packs of 6 tablet as 22 - 24 workers who manually pack tablets in paper strips.

Particular attention has been paid to proper training of local personnel in fulfilling the requirements of GMP. The followings have been done in the course of project implementation :

- Sanitation programme indicating areas to be cleaned and cleaning intervals, cleaning procedures for equipment and containers has been introduced and thoroughly kept up.
- Equipment and containers are identified by labels bearing the name of processed materials and necessary batch data.
- All manufacturing steps are carried out in accordance with written and approved instructions.
- Implementation of manufacturing record system designed to provide the manufacturing history of each batch of a drug has been commenced. However, as discussed with the project counterpart personnel this system needs to be further improved and strengthened. For instance, the limits of actually obtained yield as compared with the theoretical one should be specified at different stages of manufacture. Observations made throughout the manufacture of the drug have to be properly recorded. Special attention should be paid to regular checking the strict adherence to all manufacturing procedures and prescribed controls. To this effect it is highly desirable to establish a self-inspection system by designating the experts responsible for regular conducting inspections of overall manufacturing and control operations.

E. Modernization of R&D Unit.

Well outfitted R&D facilities are perhaps one of the main characteristic features of a modern pharmaceutical enterprise. Bearing in mind that it is unfortunately far from reality at the Pharmaceutical Factory it has been suggested to modernize the existing R&D Unit and to create within the framework of the project the core for commencing research aiming at adaptation, development and improvement of the technology for tablet manufacturing. With this in view R&D Unit has been provided with such laboratory scale equipment as Collette Mixer/Granulator Gral 10 with two bowls effective capacity up to 7 l, capable to combine the operations of dry and wet mixing and granulation as well as Manesty Hand Tablet Press with set of tooling for round flat bevelled edge tablets dia 9 and 12 mm with breakline. Both machines are suitable also for experimental production of small batches of drugs. For instance, the output of approximately 6,000 tablet per hour can be achieved by the hand tablet press. It is also important that this machine produces tablets equal in every respect to those produced on industrial tableting machines. Other instruments and deviees such as constant temperature vacuum oven used to speed up the process of wet granulate drying and devices described in the previous chapter will be in common use with the Tablet Department and Quality Control Laboratory.

The unit's staff consists of pharmacist and technieian which is obviously insufficient to carry out their numerous duties properly. The staff has been tought to handle all items of equipment, to carry out research aiming at selecting the optimum composition of granulate depending on the physical properties of a drug and defining the optimum limits of a water content in a granulate. They took part in revision of techological documents relating to manufacturing operations in accordance with the existing production programme for tablets. The development of new technology for the produc-

tion of tablets with main active ingredients derived from medicinal plants (extracts, oils, parts of herbs grinded to a powder) has been commenced too. Small batches of three such drugs have been prepared for trials. Assimilation of the technology for manufacture of coated tablets should be the next stage of development.

F. Drug Quality Control at the State level.

The central Drug Quality Control Laboratory is responsible for quality assurance of drugs both imported and produced in the country. The laboratory consists of two sections for chemical and biochemical analysis. It carries out pharmaceutical, chemical and biochemical control of imported in bulk and in dosage forms drugs according to the Pharmacopoea of the USSR, Compendium Medicomentorum and other analytical quality certificates. Besides, some typical control functions of one laboratory include :

- Drug registration
- Examination and approval of quality standards for locally produced drugs
- Inspection of drugstores, the Pharmaceutical Factory and other units engaged in preparation of drugs
- Supervision of aimak (district) drug quality control laboratories.

The laboratory staff consists of 5 pharmacists, 3 biochemists and a number of technicians. In this report only those activities of the laboratory directly relating to the project are touched upon. It is common practice as a drug manufacturer provides information concerning all active ingredients when conducting negotiations on delivery of drugs. All batches of imported drugs should be accompanied by analytical certificate indicating actual results of all tests performed as well as adopted quality standards and the source of specification used. Unfortunately this practice is far from reality. There is a lack of coordination between the organization responsible

for import of drugs and the one responsible for quality assurance. As a result the drugs delivered from abroad often do not have even registered batch number. This situation is inacceptable and should be overcome as soon as possible. Before concluding the contract arrangement on drug import the trade organization should require from the supplier complete analytical documentation for every imported drug and consult on the above with the Central Board of Medical Production and Supplies and with the Central Drug Quality Control Laboratory. As far as the laboratory itself is concerned it should be capable to test each batch of imported drugs in bulk or in dosage form immediately after delivery. Only by doing this in due time it would be possible to guarantee the unimpaired drug characteristics in spite of transportation and would enable the Government Authorities concerned to submit any claim to the supplier in case obtained analytical data do not correspond to the specification. On the other hand it would ensure the quality of drugs directly distributed on the local market or passed to the Pharmaceutical Factory for further processing.

In terms of equipment available the laboratory is in a position to carry out most analytical tests so as to ensure identification, purity and assay (except IR spectrophotometry and gas chromatography). Some instruments however ought to be replaced (for instance, UV spectrophotometer). But the number of qualified laboratory staff is inadequate. As a result only approximately 70% of imported pharmaceuticals in bulk and 40% of imported finished dosage forms are tested in accordance with the pharmacopoea of producing country. Therefore, there is an urgent need to increase the laboratory staff at least by two specialists in order to enable the laboratory to fulfil its major task of timely controlling every batch of all imported drugs. It is especially important taking into account that the major quantity of drugs consumed in the country is imported. As far as the project itself is concerned only those bulk pharmaceuticals and auxiliary substances necessary for the preparation of

pharmaceutical dosage forms that prove to conform the approved analytical standards could be transfered from the Central Store to the Pharmaceutical Factory. It means that additional quality control of each batch of bulk parmaceuticals is required if after the receipt the shipment has been kept for long periods.

G. Quality assurance at the Pharmaceutical Factory.

A drug quality control service is an essential element of any pharmaceutical production. It should not be limited to constant testing and verifying the quality of products being manufactured, but to monitor the quality aspects of manufacturing operations, to carry out the in-process control tests and to study the stability of finished products. All these functions could not be fulfilled successfully by the Quality Control Laboratory mainly due to the lack of equipment, instruments and even volumetric flasks and pipettes. Therefore, funding allocated by WHO to strengthen the drug quality control in the country has been used for the purchase of equipment and instruments needed for this laboratory.

First of all taking into account specific conditions of Mongolia as remote and landlocked country it has been decided to supply the laboratory with unbreakable polypropylene, polymethylpentene and tetrafluoroethylen labware. This choice has been based on excellent chemical and solvent resistancy of these materials and possibility to have used this labware for very long period of time thus making the laboratory independent from necessity of regular supply with chemical glassware. The labware ordered and supplied includes volumetric flasks, burettes with self-zeroing adapter, complete Buchner funnels and filtering flasks, Erlenmeyer flasks, Teflon TFE and Nylon filters, separatory funnels, graduated cylinders and other labware of common use in analytical practice. The other problem of routine laboratory practice that has been solved is reliable weighing. The range of analytical balances bought has the capacity and sensitivity for weighing the quantities

corresonding to "accurately weighed" as well as ones of lower sensitivity for tests in which a measurement of mass is involved. The laboratory has been supplied with macro and micro pipettors with disposable tips allowing accurate measurement of volums within the range 5 µl - 10 ml. Among other equipment and instruments that have been put into operation there is Air Cadet vacuum/pressure pump used for vacuum filtration and vacuum evaporation. Both these methods were not available in the laboratory practice since even water steam jet pump could not be used due to low pressure in water supply line. Installation of rotary evaporator with Soxhlet extraction system made it possible to increase the laboratory productivity when analysing the content of active ingredients in medicinal plants or carrying out the tests requiring the prior separation and subsequient removal of solvents. Other items of equipment that have been made available to the project include vacuum oven with temperature regulating system and vacuum pupm, Vortex mixer, laboratory sift mill with set of sieves, melting point apparatus with set of precision thermometers, digital PH/ion meter with set of electrodes. It is very essential that such new analytical methods as spectrophotometry in visible and ultraviolet regions and thin-layer chromatography have been introduced into laboratory practice.

Together with the laboratory staff the complete revision of quality control standards and procedures for tablets and most other products being manufactured has been commenced during the life of the project. The new quality control standards for 16 preparations including tablets, ampouls and solutions have been submitted to the Government Authorities concerned for consideration and approval. The preparation of the final version for other analytical standards according to the present production programme is under way.

Thus, at present the Quality Control Laboratory is capable to ensure the quality and safety of almost all products being manufactured except galenic preparations. Due to complicated nature of materials to be processed and variability of chemical components in medicinal plants careful analytical work

is a prerequisite of industrial utilization. At the very first stage the analysis of raw materials, the quality assessment of extracts, standartization of final products and monitoring all steps of extraction should be placed on acceptable scientific basis. It can be achieved by introducing High Performance Liquid Chromatography technique. The corresponding draft project document requesting an international assistance was submitted to UNIDO in 1986. Its approval and implementation would be of utmost importance to the country. Another task of the laboratory is to start the evaluation of the stability of finished drugs with the aim to establish expiry date and shelf-life specifications on the basis of stability tests under various storage conditions (including so called "accelerated method"). It is achieved by investigating and evaluating the chemical degradation and secondary substances present in the drug after storing as well as the change of the drug's physical properties. This study can be commenced without delay by using already available equipment, but involved analysts should be further trained abroad in this particular field. It should be emphasized however that the present staff consisting of 3 experts and 1 technician is inadequite to properly fulfil the present duties without saying of the future demands.

H. Training of local specialists.

A systematic industrial training policy including training specially adapted to the requirements of the Pharmaceutical Factory is the key element in successful implementation of the project and in realization of the future plans for the development of the pharmaceutical formulation industry in the country. A broad range of specialists is required for transfer, adaptation and development of drug formulation technology. Various training programmes having been carried out in the course of project implementation cover such areas as technology for tablet production, adaptation of the technology for local conditions, in-process control, quality

assurance of finished products and methods and procedures ralating to their testing, maintenance of equipment.

Four specialists three of whom from the Pharmaceutical Factory - two mechanical engineers and industrial pharmasist and Head of Manpower Department, State Board of Medical Production and Supplies, who later on as planned has been appointed as Director, Pharmaceutical Factory, have been nominated for two months training at pharmaceutical company SPOFA, Czechoslovakia. The training abroad took place in February - March 1987. The team of Mongolian specialists have visited a number of industrial enterprises engaged in manufacturing the pharmaceutical dosage forms as well as research institutions. They have got acquanted with organization of activities relating to the industrial scale production of tablets including knowledge of equipment and in-plant's maintenance scheme, requirements to the elaboration of technical and technological documentation, R&D relating to improvement and adaptation of technology, requirements to in-process control, industrial hygiene conditions at manufacturing areas, safety aspects of pharmaceutical manufacturing, etc. Based on the experience gained they have proposed the plan of action to improve the effectiveness of the Tablet Department. The activities to be carried out included measures for introduction of GMP requirements, procedures to carry out every technological step in accordance with the approved documents and instructions, re-arrangement of in-plant maintenance network. The implementation of the proposed plan is under way, most of the activities being completed. The fifth fellow - Chief Engineer, Pharmaceutical Factory nominated by the Government is expected to leave for training at SPOFA, Czechoslovakia (one month training programme) in April 1988.

An important element of in-service training has been practical training with the new equipment acquired for the project both through UNIDO and WHO. The manufacturer's manuals have been translated and after thoroughly having studied them by Mongolian specialists the detailed working instructions

have been prepared for technicians and workers. Special attention has been paid to maintenance network. The emphasis has been laid on stronger links between maintenance and production and on promotion of maintenance spirit to all levels of personnel. Mongolian specialists have started training of those directly engaged in manufacturing operations and maintenance This practice, however should be placed on more regular basis that has not been achieved yet. As far as maintenance network is concerned one should always remember preventive maintenance is much more cheaper than repair. Therefore, strong discipline is mandatory to proper use the equipment and to keep the maintenance benefits to working conditions and safety of the equipment. In fact considerable progress has been achieved in this field and all items of equipment acquired for the project are kept in good shape and working conditions. But further efforts are needed for keeping the personnel up-to-date with changes in technology and technological equipment.

Theoretical and practical in-service training have been carried out in such fields as general requirements of GMP and Good Laboratory Practice relating to the manufacture of dosage forms, technology of granulate preparation, working out the composition of granulate depending on type of products, determination of optimum water content in granulate ready for compressing, appropriate drying of granulate.

Separate training programme has been devoted to the requirements and means of in-process control and quality control standards, methods and procedures for finished dosage forms. In total 13 specialists have been trained in the course of project implementation. Their knowledge and practical experience are adequite to ensure independent work in the field of tablet manufacturing.

Achievement of Immediate Objectives.

Immediate objectives related to the project has been achieved in total. As a result of project implementation the technological capability and skill have been increased thus creating conditions for further development of the local pharmaceutical formulation industry. The manufacturing premises of the Tablet Department have been copmletely reconstructed so as to meet the major requirements of GMP. The model tablet production line consisting of up-to-date equipment has been assembled and put into operation. Regular production of tablets has been commenced and full capacity of the production line has been reached. The output of the Tablet Department has been increased by 40%. At the same time the necessary prerequisites for further increase of the output by installation of the second production line at the same working areas has been created as well. The quality of tablets produced has been improved by adaptation of modern technology and by introduction of the tablet blister packing system. Modernization and strengthening of R&D Unit and Quality Control Laboratory has made it possible to revise the technology of tablet manufacturing, to introduce the modern means and procedures for in-process control and for quality assurance of finished dosage forms. Besides the revision of quality standards of tablets produced the renewed Quality Control Laboratory became in a position to develop the new quality control standards for other products such as ampoules and solutions that had been commenced in the course of project implementation too. Sufficient number of local specialists have been trained to independently carry out the activities relating the manufacture of tablets. The fellowship and in-service training programmes covered such areas as proper handling and maintenance of equipment, modern technology of tablet manufacturing, quality assurance including in-process control. Thus, the project will facilitate the realization of the Government's plan for drastic increase of the output of national pharmaceutical formulation industry.

Recommendations.

A. Further direct utilization of the project achievements.

In order to further improve the effectiveness of the Tablet Department and other factory's sectors engaged in manufacturing and quality control of tablets the following should be accopmlished :

- To complete the ventilation system by installation and putting into operation of an air compressor to feed the working areas of the Tablet Department with filtrated air.
- To strengthen the in-service training network for technicians and workers especially for those who directly carry out the manufacturing and in-process control operations. The training should be placed on a regular basis with emphasis on understanding to the practical problems encountered.
- To complete the revision of technological documents for each type of products according to the existing production programme by introducing the prescribed in-process control procedures.
- In order to ensure strict adherence to all manufacturing procedures and prescribed control to establish a self-inspection system by designating the experts responsible for regularly conducting inspections of overall manufacturing, control and maintenance operations.
- To strengthen the R&D Unit and Quality Control Laboratory by increasing their staff.
- To start assimilation of technology for production of tablets with acid resistant film and other coated tablets.
- To begin investigation of drug aging first after storing at general conditions and then by introducing the "accelerated methcd".

B. Development of the national pharmaceutical formulation industry.

An immediate action that can at least twice increase the output of the Tablet Department is the creation of the second independent production line. This approach does not require the construction of a new building thus permitting to start installation of the second line in the working areas of the already reconstructed Tablet Department without delay. As a matter of fact the core of the second line, i.e. the most expensive part (compression section) has already been assembled during the life of the project. The trial runs of the second Manesty B 4 rotary tabletting machine has been completed and the tabletting press Kilian RLS15PH can be put into operation as soon as tablet tooling is received.

There are two alternatives for revamping the manufacture of injectables. Since the presently available premises do not meet the requirements of GMP the Ampoule Department can be reconstructed as proposed by the "Survey of the Pharmaceutical Industry in Mongolia (project SI/MON/79/801). However, it can be considered as only a temporary decision realization of which will meet certain difficulties. By all means erection of a new building for the manufacture of tablets and injectables should be envisaged in the nearest future. Nevertheless if necessary funds to be alloted for designing and construction of a new building are not available at the moment reconstruction of the existing facilities should be commenced as soon as feasible. As far as production equipment is concerned it is advisable to assemble an united production line consisting of machinery well matching each other to avoid as much as possible manual operations. Since glass tubes are traditionly imported from the USSR the recently offered Russian made ampoule manufacturing line appears to be most suitable. In any case international or bilateral assistance is required for modernisation of ampoule manufacturing and

intensive training abroad of local professional staff is essential.

The future production programme of the Pharmaceutical Factory should be revised by the Ministry of Health based on the country's List of Essential Drugs for elaboration of which the collaboration with WHO Office is highly recommended.

Besides the Pharmaceutical Factory where a number of galenic preparations from collected and cultivated medicinal plants is produced several scientific institutions are engaged in research of the country's medicinal flora (the list of medicinal plants in Mongolia consists of more than three hundred species). The technological capabilities of all these organizations are far from up-to-date level. As the very first stage it was proposed to put the analytical work on a modern scientific basis. To this effect the draft project document "Strengthening of the Laboratory for analytical monitoring of extraction processes and standartization of plant derived pharmaceuticals" aiming at introduction and application of High Performance Liquid Chromatography technique was submitted to UNIDO. The requested assistance is totally in line with UNIDO's mandate and similar on-going programmes. The approval and implementation of this project will promote the industrial utilization of the country's medicinal plants as recommended by the Third Consultation on Pharmaceuticals.