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ASSISTANCE TO THE EXPERIMENTAL CENTRE OF APPLIED ENZYMOLOGY AND MICROBIOLOGY IN THE PRODUCTION OF STERILE ENZYME PRODUCTS (CHYMOTRYPSIN, TRYPSIN AND PANCYPSIN)

DP/MON/82/002

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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Vienna

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1 INTRODUCTION

Mongolia is a land-locked developing country making considerable efforts to overcome difficulties resulting from the country's geographic isolation, its small domestic market, the shortage of skilled manpower, dependence on a few agricultural products for export and severe climatic conditions. The live-stock production is the most important part of the agriculture sector, and is largely based on a nomadic way of life herding the farm animals in conditions of natural pasture the whole year without any artificial feed supplement. As a result of natural selection, the farm animals in Mongolia acquired high resistance against various diseases and sharp temperature fluctuations.

The pharmaceutical industry in Mongolia is still in its initial stage of development and is mainly confined to the production of dosage forms. The Government in its Seventh and Eighth Five-Year Plans (1981-1985 and 1986-1990) has given top priority to the establishment of a local pharmaceutical industry based on the abundant animal by-products being available in slaughterhouses. The Experimental Centre of Applied Enzymology and Microbiology (ECAEM) was set up within the premises of the Meat and Canned Meat Works in Ulan Bator, as the first step to establish a local industry for the utilization of these indigenous raw materials with the purpose of manufacturing bioactive substances such as enzymes, hormones, etc. for pharmaceutical use. The ECAEM has developed its own production technology for a few enzyme products such as Pancypsin, chymotrypsin and trypsin, as well as dry bile. Pancypsin is a new product consisting of a mixture of enzymes extracted from sheep and goat pancreas glands, and is patented in Mongolia. Technologies for production of pancreatin, pepsin (from porcine and bovine gastric mucose), peptone, serum gonadotropin and several other bioactive substances are at different stages of development. It should be noted that the above results have been achieved in the modest equipped facilities of the ECAEM.

The Government requested UNDP/UNIDO cooperation and technical assistance in developing of the pharmaceutical industry with particular reference to the utilization of animal by-products in 1980. A feasibility study on the"Establishment of the Pilot Plant for Processing of Biochemical Products" DP/MON/80/004, was carried out in 1981. The study prepared by Polytechna-Spofa, a subcontractor from Czechoslovakia, found that processing and utilization of animal wastes in Mongolia would be technically feasible, however neither economic prefeasibility nor preinvestment study has been carried out yet.

Based on the above technical feasibility study a project was developed to create technological capability, research and development of a suitable technology for the utilization of locally available raw materials of animal sources in order to attain a relative self-sufficiency in enzymes and other bioactive substances. The project entitled "Assistance to the Experimental Centre of Applied Enzymology and Microbiology in the Production of Sterile Enzyme Products", DP/MON/82/002, was implemented from 1985 to 1987. The major outputs of the project were the establishment of the sterile filling line for final enzyme products, and the introduction of quality control procedures both for in-process and final control.

2 OBJECTIVES AND LOGIC OF PROJECT

The objectives of the project are quoted here according to the Project Document.

2.1 Development Objectives

The development objectives of the project are to contribute to the improvement of the country's social health sector to create the infrastructure needed for the establishment of a local pharmaceutical industry in order to reduce drug import to make available essential drugs required in the country and to promote exports. In addition, the project aims at developing the technological capability, research and development of suitable technology and the utilization of locally available raw materials in order to attain self-sufficiency within the country. The project foresees also the development of local skills.

2.2 Immediate Objectives

- Development, adaptation and updating of technologies for the production of sterile enzyme products (Trypsin, Chymotrypsin and Pancypsin).
- Attainment of international standards of quality control for the sterile enzyme products.
- Development of new sterile enzyme products derived from animal wastes through research work and pharmacological and toxicological tests.
- Manpower and technical skills development through in-plant training, fellowships and study tours.
- Preparation of appropriate design for the establishment of industrial scale production.

2.3 Taken from the General Information of the Project Document

The project is the first stage in the programme to enhance the development of a local pharmaceutical industry based on the utilization of locally available raw materials. The production programme which is being proposed for this stage is based on the experience and results already achieved at the Experimental Centre of Applied Enzymology and Microbiology and envisages the manufacture of pharmaceuticals and enzyme products both for local consumption as well as for export. The production programme will be as follows:

Products:	Quantity per Year:
- Trypsin	6 kg
- Chymotrypsin	10 kg
- Pancypsin	80 kg

In view of the great d mand for Serum Gonadotropin, the production of this drug for veterinary use should also be considered. The technology for the production of Serum Gonadotropin is now at the stage of development in Mongolia. After installation of some additional equipment and solvent recovery unit, the Centre will be able to produce up to 5 kg Gonadotropin in bulk and in final dosage form.

3 ACTIVITIES CARRIED OUT AND OUTPUTS PRODUCED

3.1 Activities Carried Out

The project DP/MON/82/002 was approved on 29 March 1984, and the planned starting date was January 1985, with the duration of one year and six months.

The Counterpart Organization was the Experimental Centre of Applied Enzymology and Microbiology, a section of the Meat and Canned Meat Works in Ulan Bator, under the Ministry of Light and Food Industries of the Mongolian People's Republic.

The National Counterparts were:

- Mr. Z. Lhundev, machanical engineer, Chief Engineer of the Meat ans Canned Meat Works in Ulan Bator, and
- Mr. J. Tserendendev, biochemist, Director of the Experimental Centre of Applied Enzymology and Microbiology.

The UNDP contribution as initially approved amounted to US$ 384,000.

By the end of the project, UNDP contribution reached an amount of US$ 464,991, as per the UNIDO computer-run of 31 August 1987.

The total cost of the equipment increased from US$ 252,000 to US$ 311,484, by the end of the project operation. The main reason of this increase was the fall down of US dollar value.

The Mongolian Government inputs were Tugriks 3,220,200 in kind.

As a matter of fact the project started in April 1985, when the first field mission of the Chief Technical Adviser (CTA), Prof. Oleg Ščedrov, began. The project was completed on November 1987, and lasted two years and seven months.

The main reason of the prolongation of the project activities occurred due to late delivery of the main equipment and delayed arrival of the supplier, "Rota" Company[x], installation engineer to Ulan Bator.

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[x] ROTA Apparate- und Maschinenbau Dr. Hennig GmbH and Co KG, Koeln, B.R. Deutschland.

3.1.1 CTA Preparatory Mission

The CTA first mission in Mongolia was carried out from 14 April to 14 June 1985. The Mission Report was submitted to the UNIDO Headquarters on 19 June 1985.

The CTA and the ECAEM Director, as the National Counterpart, agreed on the selection of the equipment for a sterile pharmaceutical production line for enzyme products in vials, and on some apparatus for the quality control improvement of the produced enzymes, as well as for the Research Department of the ECAEM (among others a "Sartorius" analytical balance and two "Buechi" Rotavapor vacuum distilling apparatus). The requisition forms for the purchase of the equipment and apparatus were completed by the CTA and sent to UNIDO on 6 and 10 May 1985. The ECAEM Director and Mr. L. Damdinsuren, the Deputy Minister of the Light and Food Industries of the Mongolian People's Republic, were very interested in having the whole sterile pharmaceutical production line.

The delivery of the main equipment was expected not later than January 1986. However, the pharmaceutical filling line machines of the "Rota" Company, were received only on 7 January 1987, that is one year later. The capacity of the filling line was 3,000 vials per hour. The list of equipment provided by UNIDO/UNDP is annexed as 8.1.

Study-tour and fellowship programmes for the counterpart personnel were prepared in consultation with the CTA and agreed upon by the Mongolian authorities concerned in early 1985.

The study tour was arranged for Mr. J. Tserendendev, Mr. H. Tugs and Mrs. I. Selenge, to the companies "Hoechst" and "Uhde" in West Germany and "Novo" in Denmark, from 22 to 29 October 1985. The relevant report is annexed as 8.2.

Two groups of the ECAEM specialists were trained in the Pharmaceutical and Chemical Works "Galenika", Belgrade, Yugoslavia, in the field of the new production technologies in enzymes processing, and the new international quality control methods of enzymes produced. The first training programme participated by: Dr J.

Alimaa, Mrs. G. Altantsetseg, Mrs. Ts. Ariuntsetseg and Mrs. Ts. Adiasuren, was arranged from 16 October to 16 November 1985, whereas the second one, partcipated by: Mr. K. Kabden, Mrs. L. Urtnasan and Mrs. G. Enkhtsetseg, was carried out from 13 November to 11 December 1986. The relevant reports are attached as annexes 8.3 and 8.4, respectively. Consequently seven specialists of the ECAEM underwent the training programme.
Prior to his departure in June 1985, the CTA prepared the Project Work Plan, which was agreed upon by the ECAEM Director and the Deputy Minister of the Light and Food Industries. The Project Work Plan was accomplished during the project operation.

3.1.2 Field Mission of the Three Experts

The second four-month field mission of the CTA, and the first four-month field mission of the experts' Mr. V. Vávra, Expert Technologist, and Mrs. M. Čobanović, Quality Control Expert, started on 26 January and completed on 26 May 1987. The joint Technical Report, "Production of Sterile Enzyme Products by a Compact Filling Line", was submitted to UNIDO and cleared on 18 August 1987 as DP/ID/SER.A/887 document.

3.1.3 Compact Filling Line

The main task of the mission was to set up a new "Rota" line for sterile enzymes production. Since no technical documentation was sent to the project site by the supplier, adaptation of the premises for installation of the new line could not be completed. The mission members together with the specialists of the ECAEM prepared the final detailed plans and drawings for the future production rooms and accomplished all necessary preparatory works for installation of the whole line, in such a way to meet the requirements and rules of a sterile production. The engineer of the compact line supplier - "Rota" Company - arrived to the project site with almost three months delay. The engineer installed, adjusted and put into operation the new line. Since the installation engineer arrived towards the end of the experts' mission in Ulan Bator, the experts actively participated in the trial production

only one week instead of six, as envisaged by the Project Work Plan, dated 3 June 1985. Observation of the trial production could be continued only after 16 weeks, i.e. during the CTA's return six-week mission, which started in October 1987. The report on setting into operation of the line and on its trial production was prepared jointly by the CTA and the ECAEM Director on 23 October 1987. The report is annexed as 8.5.

According to the data collected from the ECAEM management (Mr. Tserendendev, Dr Alimaa and Mrs. Urtnasan), during the last week of the CTA's stay in the field in November 1987, the capacities of some "Rota" line machines were smaller than quoted in the offer and in the "Rota" line documentation. The capacity of the washing machine Jiffy/I was maximum 2,500 vials per hour, instead of declared 3,600 vials per hour. Using the speeds higher than 2,500 vials per hour, the vials were not washed properly. The crimping machine FLR-50/B highest capacity was declared as 3,000 vials per hour. As a matter of fact the machine cannot close more than 1,500 vials by aluminium caps. Using higher speeds the aluminium caps are popping out in all directions around the machine. All data mentioned were checked and reconfirmed by the CTA during the run of the machines.

A meeting was held with Dr H. Pete, the "Rota" Company representative, in UNIDO Headquarters in Vienna on 27 November 1987 during the CTA's debriefing. The "Rota" Company representative was informed on the difficulties in connection with the machines in question, and asked to make arrangements either to replace the machines or to adjust them to the required standards without delay.

At the same time it was uncovered that the guarantee period of the "Rota" line is one year, according to the original contract between UNIDO and the "Rota" Company, instead of six months as quoted in the Protocol of 11 May 1987 in Ulan Bator (Technical Report DP/ID/SER.A/887, annex 5.14). Thus, the guarantee will expire by 11 May 1988. It was required by UNIDO, as well, that the "Rota" Company engineer visits Ulan Bator during the guarantee period to check the line.

Lack of an air-conditioning system in the sterile rooms is one of the main problems of the "Rota" line. This problem, as recommended by the Technical Report DP/ID/SER.A/887, should have been solved immediately upon starting the trial production. So far, nothing has been done and the air supply in the sterile premises without ventilation is insufficient. Moreover the air contains chlorine smell (used as disinfectant). In such working conditions it is not possible to stay in the premises longer than one hour.

The "Rota" line runs every working day, as during the trial production, using 65 g per day of Pancypsin for approximately 2,200 to 2,300 vials of 25 mg of Pancypsin. The daily working protocols are filled in regularly and orderly.

Until now the "Rota" line, whose capacity is 3,000 vials per hour, was used only about one hour per day or approximately 12% of its capacity, calculating with 8 working hours per day. However, such a line in the pharmaceutical production is generally used in two shifts, that is 16 working hours a day.

3.1.4 Quality Control in the ECAEM

During his first field mission, in spring 1985, the CTA found that the quality control of Pancypsin, chymotrypsin, trypsin and dry bile was done only for the final products, using a bit out-dated methods. The Quality Control Unit of the ECAEM was located in a very small and inadequate premises. Consequently the CTA recommended to introduce up-to-date quality control methods and provided a number of relevant papers, especially on chymotrypsin, trypsin and pancreatin activity determination by FIP (Fédération Internationale Pharmaceutique) methods. Several ECAEM specialists were trained in new quality control procedures during 1985 and 1986 in "Galenika", Yugoslavia. However, the new quality control methods of Pancypsin, chymotrypsin, trypsin, pancreatin, pepsin, and of raw materials, as well as the regular microbiological checking of sterile final enzyme products, were introduced only during the field mission of the Quality Control Expert in spring 1987. The ECAEM specialists were trained to use these new methods

and to run daily quality control protocols. It was found that the quality of the ECAEM products, tested during the mission, meets the requirements of the world market. Moreover, the enzymes activities checked were even higher than it was quoted by the FIP or USP XXI (United States Pharmacopeia Twenty-First Revision) requirements. Following the Quality Control Expert's advice, quality control of raw materials, including glands and chemicals, as well as of all final products of the ECAEM shall be carried out. The quality control methods, that were introduced during the expert's mission, shall be used (according to the Recommendations of the Technical Report DP/ID/SER.A/887).

The working conditions of the Quality Control Unit have considerably improved. The chemical control laboratory is now located in two bigger rooms of 23 m^2. Six staff members (three with university degree) work in this laboratory. (Previously, the rooms were of less than 10 m^2 and the laboratory employed only four staff members.)

The working standard (reference preparation) for chymotrypsin determination was prepared and approved by the Government Authorities in October 1987, whereas the working standard for the trypsin activity determination is being elaborated now. The daily protocols are run well. The quality control is carried out for the final Pancypsin, chymotrypsin, trypsin and dry bile products only, using the out-of-date quality control methods (as according to Kunitz and Anson, and others), because they are not too expensive, as explained in the ECAEM. From time to time the newly introduced FIP and USP XXI methods are used to check the everyday figures obtained by the old methods.

The difference between the old and the new quality control methods are remarkable. The old quality control methods, as according to Kunitz, are only group specific, that means that they measure the activity of a group of enzymes only, e. g. proteases (enzymes hydrolyzing the proteins). Many enzymes belong to the proteases, as pepsin, trypsin, chymotrypsin, etc. The old methods measure the total activity of these enzymes. The new methods, especially the FIP methods, are highly specific measuring the activity of a definite enzyme only, as e. g. trypsin, and not the activity of

chymotrypsin and trypsin together, that happens when the old quality control methods are used. There is no correlation between the old and the new quality control methods. It is not possible to transfer the activity units determined by the old methods (Kunitz and Anson) to the new units (determined by the FIP methods), and vice versa. The old quality control methods are not defined precisely enough.
The quality control of other final products and raw materials, as introduced by the Quality Control Expert, are not being carried out. The ECAEM did not succeed yet to acquire "pro analysi" grade reagents, nor the highest purity substrates, nor apparatus and glassware, as well as manual and pharmacopeias, recommended by the Quality Control Expert. Perhaps it may be possible to procure all these during the project second phase.

3.1.5 ECAEM Products

There are three main slaughterhouses in Mongolia: Meat and Canned Meat Works in Ulan Bator, Meat Works in Darchane and Meat Works in Choybolsane. The CTA asked to visit these slaughterhouses several times. However, only the visit to the Ulan Bator Meat and Canned Meat Works was arranged. The data on the slaughterhouse capacities and the by-products available, were provided by Dr Alimaa, the ECAEM Deputy Director, in November 1987. Ulan Bator and Darchane are well linked with railway. The distance between them is around 200 km. Between Ulan Bator and Choybolsane there is neither railway nor good road connection. Transportation of raw materials from Choybolsane slaughterhouse to Ulan Bator is carried out by truck, with a limited speed of 40 to 50 km/h. The distance between two cities is around 600 km. All by-products from Ulan Bator and Darchane slaughterhouses can be collected and transported, including the blood. The blood transportation from Choybolsane slaughterhouse is hardly possible. All other by-products collection and transportation can be done in Choybolsane. There are also two smaller slaughterhouses with good cooling facilities, located in Zapchane and Dorngobi, which cannot be taken into consideration because of bad transport possibilities. The list of the bigger slaughterhouse capacities in Mongolia and the amounts of the

slaughterhouse by-products available in the country and feasible to collect and transport is annexed as 8.6. Testicles are not collected because only gelt animals are slaughtered. Last year only 300 bulls were slaughtered in Ulan Bator Meat and Canned Meat Works.

During the first field mission in spring 1985, the CTA found that the ECAEM is reasonable equipped for the production of Pancypsin, chymotrypsin and the dry bile. The dry bile was produced at pilot plant scale, and the complete yearly production was exported. Applied research work was performed as well on the production procedure for trypsin, pepsin, hyaluronidase, ribonuclease, uridine diphosphate, serum gonadotropin, and some other substances. The CTA recommended new production procedures and testing methods for the above mentioned products emphasising the production and testing of hyaluronidase and blood hydrolysate. He also provided a number of technical papers on the products mentioned.
During the mission of experts in spring 1987, the ECAEM had the same well established production at pilot plant scale, as well as some new products at laboratory scale as pancreatin, peptone, ribonuclease, deoxyribonuclease, cytochrome C, and others. The existing ECAEM technologies were discussed and advisory services rendered throughout the mission. Selection of new products for the future production was also discussed. As a result, the yield of trypsin was approximately 20% higher in autumn 1987 than in spring 1987.

The serum gonadotropin production for the veterinary use as sterile hormone in vials was envisaged from the very beginning of the project. The production procedure was elaborated in the ECAEM, but the collection of the raw material, the pregnant mare blood, has not been solved yet. The country is huge and has rather bad communication facilities.The transportation with some regional centres (aimaks) can be done only by air. There is also lack of electricity in many parts of the country.
Another serious problem in connection with the serum gonadotropin production is the "Rota" compact line utilization. One of the main reasons for selection of such a pharmaceutical line, during the

CTA's first mission in 1985, was the expected production of 15 kg per year of serum gonadotropin in the ECAEM, mainly in the final dosage form as 5 mg sterile powder in vials (according to the ECAEM Director). From 15 kg of serum gonadotropin approximately 3 million vials can be prepared. This quantity would fulfil six months run of the "Rota" filling line per year, using the full capacity of the line, that is eight hours run per working day.

With the help of Mr. J. I. Litoukhin, Resident Representative UNDP, Ulan Bator, a visit was arranged to the Sangino "Bioplant" 20 km distant from Ulan Bator on 20 November 1987. According to the "Bioplant" Director, Mr. Sodnomdorge, the efforts were done in the "Bioplant" to introduce the serum gonadotropin production. The purification of the hormone is still in question, but it is expected to be solved. However, the biggest problem represents collection of the pregnant mare blood. They expect to solve this problem as well. The most of the Sangino "Bioplant" specialists are veterinarians and as such they have very good connections with the veterinarians in the field. They can initiate such a blood collection. The "Bioplant" intends to produce 10 to 50 kg of purified serum gonadotropin per year.

The CTA sees no reason to have a paralel production of serum gonadotropin in Mongolia. It is much more realistic that that hormone production would be located in the Sangino "Bioplant", than in the ECAEM, due to a better possibility of the raw material collection. An alternative can be a cooperation both in research and production of serum gonadotropin.

3.1.6 Suggestions to the ECAEM for its Future Production at Pilot Plant Scale

During their mission in spring 1987 the experts recommended that: Pancypsin, dry bile, chymotrypsin, trypsin, pancreatin, pepsin (medical and food grade) and maybe peptone be produced in the new pilot plant primarily in bulk. As the next step it was suggested that the blood processing including blood hydrolysate and albumin, as well as dry bile purification to the bile acids be introduced in bulk (Technical Report DP/ID/SER.A/887).

An economic survey of all existing and future products of the ECAEM was never done. Such an economic survey was recommended in the Technical Report, and it is indispensable for sales on the world market, as well as for the local consumtion. The production capacities of all ECAEM products should be set to meet the expected local market, as well as the export possibilities.

3.1.6.1 - Pancypsin, a Mongolian patent, can be considered as the top product of the ECAEM, well run at pilot plant scale and of the excellent quality. Approximately 35 kg of Pancypsin was produced in 1986. According to the yield of 2.5 g of Pancypsin from one kg of sheep and goat pancreas (Technical Report DP/ID/SER.A/887, annex 5.18.1), 14 tons of pancreas was used last year for the Pancypsin production. The experts' advice was to increase that production. The CTA now suggests to use the whole amount (around 72 tons per year) of sheep and goat pancreas being available in the three biggest slaughterhouses in Mongolia (annex 8.6), and produce 180 kg of Pancypsin per year. Pancypsin could be exported in bulk, and may be interesting for the world market as an antiinflammatory drug. In summer 1987 the CTA visited "Galenika" Works in Belgrade, Yugoslavia. "Galenika" was interested in purchasing an antiinflammatory drug, such as Pancypsin in bulk, but not less than one hundred kg of product in one batch. Probably the same condition may be requested by any other buyer. Only a very small amount of Pancypsin can be sold in the final drug form of 25 mg sterile powder in vials, using the "Rota" filling line, since for the finished product only the local market could be taken into consideration. The problem is that neither pharmacological nor clinical examinations have been completed for Pancypsin so far. Any new drug may be used and sold only with a positive pharmacological and then clinical certificate, and without that certificate no drug can be exported. Considering the number of animals in Mongolia, larger quantity of Pancypsin could be used in the veterinary than in the human practice. In spring 1987 the ECAEM sold for veterinary use one million sterile vials of Pancypsin of 25 mg, amounting to 2 million Tugriks. It is expected that 40 kg of Pancypsin in one g packages would be sold for the veterinary usage.

3.1.6.2 - Chymotrypsin and trypsin are produced in the ECAEM from cattle and yak pancreas. The technology is elaborated and introduced, especially after improvement of the trypsin yield in 1987. The production of both enzymes is run on the same equipment as Pancypsin. Chymotrypsin and trypsin are of very high activity. They are produced as freeze-dried substance in bulk and may be interesting for export. Only a very small amount of these two enzymes could be made in the final drug form as sterile powder in vials for a local consumption in human medicine.

3.1.6.3 - Dry bile is the second well introduced product in the ECAEM, manufactured at pilot plant scale. The amount of 4.5 tons of the dry bile produced in 1986 was exported. Approximately 65 tons of bile was used for the last year production (according to the ECAEM Deputy Director). In three biggest slaughterhouses of Mongolia (annex 8.6) 112 tons of bile can be collected per year. The capacity of dry bile production in the ECAEM amounts to 13 tons per year (Technical Report DP/ID/SER.A/887, annex 5.19.1). At present, the dry bile production is run half a year only. With better capacity utilization in the ECAEM, the double amount of dry bile per year, approximately 7.75 tons, could be produced resulting in a significant foreign currency earning. Introduction of a new quality control method is needed as soon as possible. The elaboration of a technology for purification of dry bile to the bile acids would be very useful for the ECAEM in the near future.

3.1.6.4 - Pancreatin was produced in the ECAEM at laboratory scale only. The product is of a very good quality. There is lack of experience at large scale production. According to the CTA, the pig pancreas available in Ulan Bator Meat and Canned Meat Works, 2 tons per year (annex 8.6), could be used for the pancreatin production, as well. The pig pancreas is one of the best sources for the pancreatin production. There is real possibility of selling a certain amount of pancreatin for the local consumption.

3.1.6.5 - Medical grade pepsin is produced from pig stomach mucous membrane only. The ECAEM has the technology developed at laboratory scale. The pepsin is of a very good quality. However experience is required for production at pilot plant scale. It

would be possible to sell a certain amount of pepsin on the local market. There is good possibility of export, as well.

3.1.6.6. - Food grade pepsin is produced from cattle stomach mucous membrane. Experience is required in production, starting with laboratory scale. This pepsin is usually used for cheese processing. In his spring 1987 mission the CTA found an interest in the cheese production by pepsin in the Scientific-Experimental Centre of the Foodstuff Industry in Ulan Bator. For the beginning a relatively small amount (about 50 kg per annum) of pepsin could be used for a local production of cheese. A bigger amount of pepsin might be exported.

3.1.6.7 - Peptone was occasionally produced at laboratory scale, using rennet and paunch of cattle as raw material. There is lack of experience in the ECAEM at large scale production. The quality of such a peptone is mediocre, and according to the Expert Technologist, the world market demand is low.

3.1.6.8 - The slaughterhouse blood processing was suggested by the CTA in the ECAEM, in the Ulan Bator Meat and Canned Meat Works, and in the Scientific-Experimental Centre of the Foodstuff Industry. Meetings and discussions were held with several officials in 1987. Technical papers were provided on the subject, however no experiment was done in this respect so far. The CTA proposed again to the ECAEM Director and to the Deputy Director to start immediately small scale laboratory experiments on the blood separation and preparation of albumin and blood hydrolysate. It is not advisable to hydrolyse the whole blood, separation of the blood to plasma and red blood cells have to be the first step in the blood processing.

3.1.7 Assistance to the ECAEM in Planning of an Experimental Biochemical Plant, and Completion of the Draft Terminal Report of the Project DP/MON/82/002.

A new small scale project UC/MON/87/126, "Assistance to the ECAEM in Planning of an Experimental Biochemical Plant", was implemented in autumn 1987. Three experts were fielded in Ulan Bator for 45 days, that is from 14 October to 28 November 1987.

The CTA's main task during this mission was to prepare the Draft Terminal Report of the project DP/MON/82/002/
The Expert Technologist, Mr. V. Vávra, and the Expert Mechanical and Plant Engineer, Mr. J. Frýda, prepared the technological profiles including specifications of equipment and essential services for the production premises of new multipurpose pilot plant facility for processing of enzymes and other bioactive substances obtained from animal by-products.

3.2 O u t p u t s

3.2.1 - The main output of the project was the procurement of the compact filling line for sterile drug in vials. The line (of "Rota" Company) was set up, put into operation, and the ECAEM specialists and workers were adequately trained for its use. The trial production was completed, and the line is run every working day. Pancypsin in vials, 25 mg of freeze-dried substance in a vial, was the only product. Approximately 2,300 vials per working day was the output, that corresponds to approximately one hour run of the filling machine of the line. The preparatory works, washing of vials, sterilization, filling and transfer the filled vials into the freeze-drying machine, takes four working hours daily. Better utilization of such a very costly equipment could not be achieved up to now.

Another serious problem with regard to the use of the "Rota" line is the lack of air-conditioning in the sterile premises, where consequently the working conditions are inappropriate.

Both problems have to be solved and it is expected to do it soon. In any case, an equipment such as the "Rota" line represents a considerable achievement for the whole pharmaceutical industry of the country.

3.2.2 - A strengthening of the quality control in the ECAEM was the second output of the project. Several new quality control procedures were introduced in the ECAEM. The relevant employees were adequately trained in "Galenika" Works in Belgrade, Yugoslavia, and in the field during the Quality Control Expert's stay in Ulan Bator. As a matter of fact, this is only a beginning and the introduction of new quality control methods for other final products and raw materials in the ECAEM has to be done in the near future. The newly introduced quality control methods have to be carried out for every batch. The old methods have to be disregarded, because there is no correlation between the old and the new quality control methods. It is not possible to transfer the activity units determined by the old methods (according to Kunitz and Anson) to the new units (determined by the FIP methods), and vice versa.

The working conditions in the ECAEM Quality Control Unit were improved recently by providing a bigger and better working space and more employees in the chemical quality control laboratory. The other recommendations of the Technical Report DP/ID/SER.A/887, such as the purchase of "pro analysi" grade reagents, substrates of the highest purity, reference standards for all enzymes produced, apparatus and glassware, manuals and pharmacopeias, remain to be carried out in the near future.

3.2.3 - The ECAEM current production may be considered only as a partial output of the project, as Pancypsin, chymotrypsin and dry bile were already produced in the ECAEM before commencement of the project.

3.2.4 - The new pilot plant production, including the new building, could be considered as a partial output of the project. The 1981 feasibility study, project DP/MON/80/004, initiated planning of the building construction, and the new small scale project UC/MON/87/126 helped substantially in the arrangement of the new building for the expected pilot plant scale production. Two experts prepared in autumn 1987 all the technological profiles needed, including specifications of the equipment and essential services for the production premises of the new pilot plant building.

The current production of the ECAEM will be enlarged and the name of the enterprise will be changed to "Monenzyme", as from January 1988. Within "Monenzyme" a laboratory scale research and development unit will also be included and run as a separate section along with the pilot plant production unit.

3.2.5 - Selection of the products for the new pilot plant was proposed by the experts in spring 1987 (Technical Report DP/ID/SER.A/887, annex 5.33).

It is expected that the example of serum gonadotropin production will not be repeated and that the forthcoming phase of the project shall be based on more realistic and less ambitious programme. The ECAEM has excellent and well introduced products of Pancypsin and dry bile. Chymotrypsin and trypsin could also be considered as well introduced, partcularly after improving of the trypsin

yields, as suggested by the Expert Technologist in spring 1987. Pancreatin and medical grade pepsin production for the local consumption are well selected, especially taking into account the digestion problems of the people in the country, caused by their habits of feeding.

3.2.6 - The slaughterhouse blood processing, and albumin as well as blood hydrolysate production, represents an objective which remaines to be realized as soon as possible. The blood processing is a necessity in all bigger slaughterhouses in the world, because the slaughterhouse blood highly polutes the environment, and on the other hand the blood consists of very valuable substances. These substances can be saved by processing of blood.

3.2.7 - The expected pilot plant production in the new building of the "Monenzyme" enterprise could be increased again in the future by other new products such as gelatin, heparin, blood hydrolysate, albumin, bile acids etc., which may be of interest for the world market.

Production of hyaluronidase could be very interesting and it was solved in the ECAEM at laboratory scale. However there is complete lack of raw material, that is testicles, as only gelt animals are slaughtered at the Meat and Canned Meat Works in Ulan Bator. These data were uncovered by the CTA only by the end of his last field mission.

3.2.8 - Introduction of the newest generation of the bioactive substances production technology, as ultrafiltration techniques, as proposed by Dr Z. Csizér, UNIDO Substantive Officer during his November 1987 visit to the project, could be done for all existing and anticipated ECAEM products. Such a technology transfer could be one of the major objectives of the project second phase.

4 ACHIEVEMENT OF IMMEDIATE OBJECTIVES

Immediate objectives of the project have been achieved.

4.1 - The new compact filling line of the "Rota" Company represents the development, adaptation and updating of the production technology of the finished sterile enzyme products. Pancypsin as antiinflammatory drug has been produced in vials. The problem of use of the "Rota" line at full capacity, i. e. of its viability, remains to be solved.

4.2 - The international level of the quality control for Pancypsin, chymotrypsin, trypsin, pancreatin and pepsin was obtained, as the Quality Control Expert introduced the FIP and USP XXI methods. However, after the completion of the expert's mission, the ECAEM Quality Control Unit continued to use the out-of-date quality control methods. The enzyme activity has been checked by the newly introduced methods (of FIP and USP XXI) only from time to time. The problem is that it is not possible to transfer the activity units determined by the old methods (according to Kunitz and Anson) to the new units (determined by the FIP and USP XXI methods), and vice versa, because there is no correlation between the old and the new quality control methods.

4.3 - The development of new sterile products derived from animal wastes through research work was fully discussed during the field missions of the experts, and many technical papers and patent documents were given to the ECAEM specialists.

4.3.1 - The pharmacological and toxicological examinations are highly specialized, long lasting and very costly. The clinical examinations have to be carried out, as well. All examinations have to be done for every new drug as the condition for obtaining the registration and the allowance for a new drug usage. The pharmacological and the clinical examinations are not yet completed for Pancypsin. That is why Pancypsin cannot be exported in a final drug form.

4.4 - The training was realized through the study tours, fellowships and in-plant training. The latter included training in operation of the new filling line, work in sterile conditions, carrying out of the newly introduced quality control procedures,

as well as improvement of the technologies of the ECAEM products. The one month fellowship of the seven ECAEM specialists in "Galenika" Works in Belgrade, Yugoslavia, was too short. No new quality control method was introduced by the fellowship holders in the ECAEM upon their return home. Introduction of the new quality control methods in the ECAEM was done only by the Quality Control Expert.

The team of experts suggested after that, that the training programme should last at least three months.

4.5 - The appropriate layout for the establishment of the new pilot plant scale production was prepared by the two experts in autumn 1987, arranged through the small scale project UC/MON/87/126.

5 UTILIZATION OF PROJECT RESULTS

5.1 - The project results will be utilized by a more efficient use of the "Rota" aseptic filling line. The efficiency could be increased by using the machines eight hours per day, during 250 working days in a year, that is (250 x 8 =) 2,000 hours per year. Considering the capacity of the filling line of 3,000 vials per hour, it amounts to 6,000,000 vials per year. So far, the Pancypsin production of 25 mg in a vial has been the only product of the "Rota" line.

The production of Pancypsin as a sterile substance in vials cannot be enlarged much more, and especially not to such an extent (of six million vials per annum), because this form of Pancypsin can be used only for the local consumption in Mongolia. The problem is that neither pharmacological nor clinical examinations have been completed for Pancypsin so far. Such examinations are required and any new drug may be used and sold only with a positive pharmacological and then clinical certificate. Without that certificate no drug can be exported. Moreover, the present ECAEM facilities do not meet the requirements of GMP (Good Manufacturing Practice) and therefore the finished products cannot be exported.

It seems that it is easier to sell Pancypsin as substance in vials for the veterinary use at the local market than for the human use because of a large number of animals in Mongolia. However, to achieve this, a close cooperation with the veterinary authorities should be developed.

5.2 - Production of a larger amount of Pancypsin as substance in bulk for export purpose.

During her field mission in spring 1987 the Quality Control Expert found unexpectedly high activity of the ECAEM enzymes. The activities of Pancypsin, trypsin, chymotrypsin, pepsin and pancreatin were higher than it was quoted by the FIP or USP XXI requirements. It seems that the quality of the slaughterhouse animals in Mongolia is higher than in other parts of the world due to natural selection. Severe winters and various diseases usually cause death of the weak animals while only the strongest

ones can survive. That is why the bioacive substances, including enzymes, produced from such animals glands and organs are of higher activity than in many other countries.
That was the reason why the CTA recommended to the ECAEM the manufacture of a highest posible quantity of Pancypsin, using the whole amount of sheep and goat pancreas available in Mongolia, i. e. an annual amount of approximately 72 tons (annex 8.6). In that way 180 kg of Pancypsin can be produced per year.
After all it seems as the most realistic to export as substance in bulk the entire amount of Pancypsin produced.
5.3 - The project which has been accomplished represents a good starting point for the future production of bioactive substances in the ECAEM. The manufacture of new products based on new production technologies, such as ultrafiltration, could further facilitate the export possibilities.
5.4 - The recently introduced quality control methods in the ECAEM have to be practiced everyday. There is no correlation between the old and the newly introduced quality control methods, and it is not possible to transfer the activity units determined by the old methods (according to Kunitz and Anson) to the new units (determined by the FIP and USP XXI methods), and vice versa. Therefore it is not advisable to the ECAEM the use of the out-of-date quality control methods.
The new quality control methods for all products and raw materials need to be introduced in the daily practice. The usage of the new quality control methods represents one of the most significant achievements of the project.
5.5 - Since the present premises of the ECAEM are unsuitable and too small, no new product can be developed there. It is indispensable that to the ECAEM be given a new building.
The transfer of the compact "Rota" filling line to a more suitable premises with the possibility of proper air-conditioning and other requirements is urgently needed so that the requirements of quality assurance and GMP would be met.

5.6 - The new enterprise "Monenzyme" will substitute the ECAEM starting from January 1988. It will be an independent enterprise, no more a section of the Meat and Canned Meat Works in Ulan Bator, as was the case with the ECAEM. It will belong to the same Ministry of the Light and Food Industries, like the ECAEM. It will be financially supported by the Ministry during the first few years of run. The "Monenzyme" will be constituted of a pilot plant manufacturing unit of bioactive substances from animal organs and of a laboratory scale research and development unit.

6 CONCLUSIONS

The project DP/MON/82/002, which may be regarded as continuation of the project DP/MON/80/004, has been completed in the course of two years and seven months.
The UNDP contribution had to be increased from US$ 384,000 to US$ 464,991, due to the fall down of US dollar value.
All of the project outputs have been achieved by the implementation of the project activities.

6.1 - The new compact filling line for the production of sterile drug in vials, purchased from the "Rota" Company, West Germany, represents the main achievement of the project. The line was set up, put into operation in the ECAEM premises, and the trial production was completed. The ECAEM specialists and workers have been adequately trained by the experts how to run the new line. Special emphasis in the course of the training was made on the work in the sterile conditions. The line daily produces approximately 2,200 to 2,300 vials of 25 mg sterile powder of Pancypsin. However this represents only approximately one hour daily run of the filling machine. Better utilization of the line have to be achieved as soon as possible.
6.2 - A study-tour was made for the ECAEM leaders, to the companies "Hoechst" and "Uhde" in West Germany, and "Novo" in Denmark in 1985.
6.3 - A training abroad was carried out for seven ECAEM specialists in "Galenika" Works in Yugoslavia in 1985 and 1986, as well as a training in the field during the experts' stay in the ECAEM in 1987.
6.4 - The new quality control methods were introduced in the ECAEM for the most important products, as Pancypsin, chymotrypsin, trypsin. pepsin and pancreatin. It is expected that the new quality control methods be introduced for other ECAEM products, as the dry bile and for all of the raw materials, as well.
The newly introduced quality control methods are expected to be used in the everyday practice.

6.5 - In addition to rendering technical advisory services the experts provided to the ECAEM numerous technical papers and patent documents for improvement of existing technologies.

6.6 - The experts have suggested a new product-mix for "Monenzyme". The list of these products and their justification are given in the Technical Report DP/ID/SER.A/887, as annex 5.33.

6.6.1 - Pancypsin is an excellent product of the ECAEM of a very high quality and it is patented in Mongolia. It is recommended to produce Pancypsin from all of the raw materials available in the country, and look for the export market of the product in bulk.

6.6.2 - Dry bile is a well introduced product of the ECAEM. The entire production of the dry bile was exported in the last years. It is suggested to use all of the raw materials available in Mongolia and produce more dry bile for export. The purification of the dry bile to the bile acids would enlarge the market possibilities for the ECAEM.

6.6.3 - Production of chymotrypsin and trypsin of a high quality was introduced in the ECAEM.

6.6.4 - Pancreatin and the medical grade pepsin of a high quality was produced in the ECAEM at laboratory scale only. The production trials at large scale are required to be commenced soon.

6.6.5 - The slaughterhouse blood processing in order to produce albumin and blood hydrolysate has to be developed at the ECAEM as soon as possible.The blood processing represents a necessity in all bigger slaughterhouses in the world. Otherwise, the slaughterhouse blood highly polutes the environment. The blood is an organ, consisting of very valuable substances. The processing of blood will prevent losses and save these substances, such as albumin and blood hydrolysate are, and some others.

6.7 - The ECAEM products should be marketed preferably as substances in bulk. Only a very small amount of Pancypsin, and perhaps chymotrypsin and trypsin, could be formulated as sterile drugs in vials (using the "Rota" filling line),but only for the local consumption.

A few ECAEM products, as pancreatin and pepsin, can be formulated in tablets. It is recommended that all tablets in the country be produced in one place, that is in the Tabletting Unit of the

Pharmaceutical Factory in Ulan Bator. The production capacity of any tabletting machine is rather high and can be never fully utilized by using only bioactive substances.

6.8 - An economic survey of all ECAEM products has not yet been done. However, there is an urgent need for economic survey since even an experimental centre cannot be run on a long run without economic viability.

6.9 - The project DP/MON/82/002, which has been just terminated, represents a good start for the future enterprise "Monenzyme", the successor of the ECAEM since January 1988. It will be composed of a pilot plant scale manufacturing unit and of an experimental centre with a laboratory scale research and development unit. "Monenzyme" is going to be located in the new building, which the Mongolian Government decided to construct in the very near future. At the existing ECAEM premises neither new products can be developed and nor the existing production can be enlarged. It is a necessity that the ECAEM be transfered to a new building as soon as possible.

It is urgently needed that the compact "Rota" filling line be placed in properly designed aseptic suit that meets the requirements of GMP.

6.10 - Two experts, recruited in the UNIDO project UC/MON/87/126 in autumn 1987, prepared the technological profiles including specifications of equipment and essential services for the production premises of the new multipurpose pilot plant facility, "Monenzyme", for processing of enzymes and other bioactive substances obtained from animal by-products.

7 RECOMMENDATIONS

7.1 - An air-conditioning system providing filtered air has to be installed in the sterile filling rooms as soon as possible.

7.2 - Better utilization of the "Rota" line, at least in one shift per day, have to be achieved soonest.

7.3 - The "Rota" Company should be immediately requested to revise and improve the maximal speed of the washing machine Jiffy/I and the crimping machine FLR-50/B, to meet the specifications.

7.4 - An economic survey of all products of the ECAEM is recommended to be carried out as soon as possible.

7.5 - It is highly recommended that the production capacities of al ECAEM products should meet the expected local consumption and the export needs.

7.6 - All improvements in the ECAEM Quality Control Unit, in line with the Recommendations of the Technical Report DP/ID/SER.A/887, have to be carried out without further delay. In the case of lack of funds, purchase should be made at the time of the project second phase.

7.7 - The new quality control methods introduced in the ECAEM shall be used in the daily prectice.

7.8 - Introduction and daily application of the new quality control methods for the dry bile and all of the raw materials is one of the priority needs of the ECAEM.

7.9 - It is recommended that the surplus of the slaughterhouse by-products, which cannot be processed by the ECAEM, be exported by the slaughterhouses.

7.10 - Produce Pancypsin using all sheep and goat pancreas available in Mongolia. Pancypsin is the best ECAEM product with an expected good prospect for selling at foreign market. It would be noted that there is considerable demand on the world market for an antiinflammatory drug as Pancypsin.

7.11 - Use all bile available in Mongolia and produce more dry bile for export.

7.12 - The purification of the dry bile to the bile acids is suggested to the ECAEM in the nearest future.

7.13 - Produce pancreatin from pig pancreas available in the Meat and Canned Meat Works in Ulan Bator. Pig pancreas is the best source for pancreatin production.

7.14 - Blood processing in order to produce albumin and blood hydrolysate is a primary economic need of all bigger slaughter-houses in the world. It is strongly recommended to the ECAEM to perform that in the nearest future, by using the whole amount of blood available in Mongolia.

7.15 - According to the existing experience, implementation of new production technology takes a very long period of time in Mongolia. The diversification of the products should be facilitated by the transfer of technology. With regards to the technologies to be transfered to Mongolia, it is strongly recommended that the new generation of technologies, based on ultrafiltration techniques, should be considered.

7.16 - Construction of the new facilities for the pilot plant should start as soon as possible. With regard to the architectural and engineering design of the new building, it should be noted that the drawings of the feasibility study prepared in 1981 are out-of-date and therefore are not recommended for the direct use. The new design should be based on the technological profiles provided by the project UC/MON/87/126. The plan for the new production premises should be flexible enough to house the multipurpose type of pilot plant for processing of bioactive products. This type of flexibility can also ensure introduction of new type of technology to be developed locally or to be obtained by technology transfer.

7.17 - All of the aseptic premises in the planned new building have to be arranged according to the requirements of World Health Organization (WHO). The new facility should preferably be licenced by the National Drug Quality Control Authority.

8 ANNEXES

Annex 8.1

Equipment Provided by UNIDO/UNDP for the Project DP/MON/82/002

Item No.	Description and Specification	No. of Units	Cost in US$	Date of Delivery	Applied in
1	Compact filling line for sterile drugs in vials production, "Rota" Company.		298,131.00	7 Jan.1987	Final form of drug production.
1.1	Washing machine, "Rota" Company, Type Jiffy/1, for vials of 5 ml, 3,600 vials/h, including: - Pump-over aggregate, - Electrical heating for pump-over aggregate, - Set of spare parts.	1 each			Sterile enzymes production; a part of the compact line.
1.2	Sterilizing tunnel, "Rota" Company, Type TU-11/300 ST-1, including: - Set of spare parts.	1 each			Sterile enzymes production; a part of the compact line.
1.3	Vials filling and closing machine, "Rota" Company, Type FLR-50/G, 3,000 vials/h, for vials of 5 ml, including: - Filling pump, - Laminar-flow cleanroom unit, - Set of spare parts.	1 each			Sterile enzymes production; a part of the compact line.
1.4	Crimping machine, "Rota" Company, Type FLR-50/B, 3,000 vials/h, including: - Noise protection hood, - Set of spare parts.	1 each			Sterile enzymes production; a part of the compact line.
1.5	Labelling machine, "Rota" Company, Type RE-50, 3,000 vials/h, including: - Hot stamper, - Set of spare parts, - Printing plates, - Labels selfadhesive.	1 each			Sterile enzymes production; a part of the compact line.

Item No.	Description and Specification	No. of Units	Cost in US$	Date of Delivery	Applied in
2	Analytical balance, electronic, "Sartorius" Company, Model 2004 MP6, 10 µg.	1 each	2,057.80	28 Apr.1986	Quality Control Unit.
3	Vacuum distilling apparatus, "Buchi" Company, Rotavapor-M-Compact, 250 ml.	2 each	1,540.00	27 Feb.1986	Research Department.
4	Syringe filter holder, "Sartorius" Company, SM 165 29, SM 166 85, SM 1325, SM 16514.	1 set	277.20	11 Feb.1986	Research Department and Quality Control Unit.
5	Sigma Pipettes, "Sigma" Company, Micropipettes, Dispenser Pipettes, Tips Polypropylene.	1 set	880.00	13 Mar.1986	Research Department and Quality Control Unit.
6	Manual: Methods of Enzymology, Academic Press, New York, 112 Volumes (1955 to 1985).	1 set	8,598.00	8 Aug.1985	All the Experimental Centre of Applied Enzymology and Microbiology.
		Total:	311,484.00		

Assistance to the Experimental Centre of Applied Enzymology and Microbiology in the Production of Sterile Enzyme Products (Chymotrypsin, Trypsin and Pancypsin).
DP/MON/82/002/32-00 STUDY TOUR

REPORT

JAMGANA TSERENDENDEV, Director, Experimental Centre
of Applied Enzymology and Microbiology

The team of three seniour specialists consisting of Mr. Tserendendev Director, Experimental Centre of Applied Enzymology and Microbiology, Mr. Tugs, Mechanical Engineer of the above Centre and Mrs. Selenge, Engineer, Ministry of Light and Food Industries paid a short visit to HOECHST (BRD), UHDE (BRD) and NOVO (Denmark) from 22 October 1985 to 29 October 1985.

The team was received by Dr.Mixich, Dr. Wiezer, Dr. Summe (HOECHST), Mr. Hundgen, Mrs. Dorsemagen (UHDE), Mr. Biedermann and Mrs. Maiboll (NOVO) whom the writer would like to express his gratitude for fruitful discussions and valuable assistance during the mission.

At HOECHST the team had a possibility to get acquanted with the activities of the Biochemical and Biotechnological Institutes, the Pilot Food Proteines Plant and industrial scale Waste Water Treatment Plant. HOECHST came into being in 1929 and started its activity with a small scale production of insulin.By the present time the company has become multifunctional industrial chemical and pharmaceutical business concern manufacturing pharmaceuticals, fine chemicals, plastics, fertilizers, insecticides, etc. The company pays great attention to the production of insulin from pig pancreas and its modification into human insulin using modern methods of biotechnology and genetic engineering. A new amylasa inhibitor for treatment of diabets has been developed recently by means of microbiological synthesis.

HOECHST is one of the three leading chemical enterprises of the BRD. It employs 350 thousand persons including 170 professors and more than 13,500 scientists working at 10 Researdh Centres belonging to the company. The yearly production of HOECHST reachs 40 billions DM, the daily expenses for research programmes being of 6 millions DM. A network of agents representing of the company's marketing department is backed up by some 3,500 skilled personnel. Most recent innovations in modern biology and chemistry are widely used to develop and investigate new products and to improve the existing technology.

Being the filial of HOECHST, UHDE is engaged in the manufacture of equipment for chemical, biochemical, microbiological and food industries. In addition the company carries out feasibility studies in the above fields and general designing new industrial scale plants. The company delivers its products such as equipment, fertilizers and food all over the world.

Samples of ferment drugs - pancypsin, trypsin and chymotrypsin produced by the Mongolian Centre of Applied Ensymology and Microbiology have been handed over to Dr. G.Summe, Head, Biochemica Department, HOECHST. It has been agreed that the results of investigation of the quality and specific activity of the above drugs will be sent back in a possibly short period of time.

R&D of a new drug requires approximately 8-12 years including : 2-3 years of general investigation and screening, 2-3 years of experimental research before clinical tests, 3-4 years of clinical tests, 2-3 years of post clinical examination, 2-3 years of drug registration procedures and official approval by the Health Authority and finaly distribution of a new drug. The team was particularly interested in the organization of experimental research (pharmacology and toxicology). Apart from general recommendations we have kindly been offered some concrete manuals for determination of toxicity and pyrogen agents and for pharmacokinetic studies of ferment drugs. Other topics of discussions were the production of insulin from pig pancreas and its transformation into human insulin, major means of production of proteolytic ferments of animal origin, utilization of modern methods of genetic engineering for the production of amylasa inhibitor. We consider that recommendation with respect to the most efficient dosage forms of ferment drugs and combination of the above drugs with antibiotics should be implemented at the Experimental Centre of Applied Enzymology and Microbiology in the nearest future.

The team has had an opportunity to visit NOVO (Denmark) for one day. The company produces trypsin and chymotrypsin the drugs of particular interest to the mongolian side. Unfortunately we have

not been shown the plant itself which is situated 100 km from the headquarter. The team has been acquanted with the general activities of the company and its pilot plant. NOVO manufactures various ferment drugs in the amount of 3 billions US $ per year. Each year about 3,000 tons of pig pancreas are processed and thus obtained insulin is modified into the human one. In total approximately 20 insulin based drugs are produced. In comparison with HOECHST which along with traditional means of drug production successfuly develops modern biotechnological methods, NOVO specializes in the production of ferment drugs of animal and microb origin. The excellent quality of collected and properly kept raw materials ensures the production of trypsin possessing very high specific activity. Catalogues describing ferment drugs made by NOVO contain trypsin kinetic data.

All the companies the team had a chance to get acquanted with, apart from industrial scale production are widely engaged in basic and applied research, scaling up the production technologies and designing of modern industrial enterprises. R&D and further introduction of scientific and technological innovations are carried out by the scientists and engineers of various disciplins at the institutes belonging to the companies. Thus HOECHST and NOVO have become at present not only industrial but huge scientific centres as well.

Recommendations.

1. Since the development of new ferment drugs requires carrying out broad experimental research work the creation of modern well equipped pharmacology and toxicology laboratories should be envisaged in the nearest future.
2. Taking into consideration the recent achievements in application of proteolitic ferments and tendency of their use in combination with antibiotics in the form of capsules and dragee it is necessary to establish a new production line for the manufacture of such dosage forms as intestines soluble capsules and dragee (enteric forms).

Annex 8.3

ASSISTANCE TO THE EXPERIMENTAL CENTRE OF APPLIED ENZYMOLOGY AND MICROBIOLOGY IN PRODUCTION OF STERILE ENZYME PRODUCTION (CHYMOTRYPSIN, TRYPSIN AND PANCYPSIN)

PROJECT MON/82/002/11-01

MONGOLIA

F E L L O W S H I P R E P O R T

Prepared by:
Team Leader J.ALIMAA
Candidate of Chemical Sciences

ULAN BATOR

1.General Review

A team of specialists from the Experimental Centre of Applied Enzymology and Microbiology, Meat and Canned Meat Combine in Ulan Bator had a month Fellowships study on pharmaceutical and Chemical industry "Galenika", Jugoslavia, from 16 October to 16 November 1985.

The Jugoslavian Pharmaceutical and Chemical Industry is a more rapidly developing branch and has an export significance.

"Galenika" is one of the largest pharmaceutical organization in the country. Number of employees is more than 6000 and it has 5 factories: 1. Drug Factory; 2. Plastics Factory;3.Chemicals Factory; 4.Agrochemicals Factory; 5. Cosmetics Factory.

Besides that there is a Research and Development Institute "Galenika", where they deal with the scientific and research works, development,engineering,trade,economy and quality control problems. For the Idstitute financing is alloted 2 per cent of the pharmaceutical and chemical industry's yearly income.

Fellows J.Alimaa,G.Altantsetseg and Ts. Ariuntsetseg worked in the "Galenika" institute till 8 November and on 15 November 1985 and from 11 November till 14 November they worked on production. Fellow Ts. Adyasuren worked in Quality Control Department of Galenika" institute during the whole training period.

Fellows has collected papers concerning their scientific and research works.

2.Activities carried out during the training period.

According to the Work Programme,approved by the MPR Deputy Minister of Light and Food Industry and agreed with "Galenika" institute and Pharmaceutical and Chemical Industry (see Annex 1), the Fellows have carried out the following:

2.1. J.Alimaa -Chief Engineer of ECAEM working in the extracting laboratory of the Scietific and Research Sector on Production Technology of Organotherapeutical Preparations has assimilatedà

- determination methods of free and total proteolytic activities in pancreatin powder and tablets and pancrease in "PI P" units;

- determination methods of amylolytic activity in pancreatin powder and tablets and pancrease in "FIP" units;

-determination methods of lipolytic activity in pancreatin powder and tablets and pancrease.

She has also got familiarised with:

- all technologies and equipments for pancreatin and pancreatic preparation "Digestal-forte", including mincing and homogenisation of swine pancrease, extraction,filtration,evaporation and drying of pncreatic powder on ball mill, screening, drage preparation stages and methods of control;

production technology of enzyme preparation "Chymocyclar", Chymoral", "Chymoral-100 forte", pepsin,insulin,bile acids, thyroid hormone;

- organization,structure,fuction of the Technical Control Department of "Galenika" institute.

She also has visited a Factory for production of sterile, tablet and capsule medical preparations,oitments and creams.

2.2. G.Altantsetseg- Head of the Biochemical Experimental Plant of ECAEM has carried out the following:

has got familiarised with:

- technology of washing,drying sterilization of vials and ampules,rubber stoppers,aluminium caps, glassware and other inventories and premises;technology of sterile filtration,automated filling,closing,freese-drying, crimping,labelling and packaging of sterile pharmaceutical preparations.

- Name, type and technical characteristics of equipments used in sterile medical preparations production, especially, complex line of "Strunk" company, West Germany;

- working principles of equipment for sterile preparation production line;

- organization and structure of Capsule Plant;

- pepsin production technology;

- analyses and controls needed on the definite steps of technological process of pancreatin, "Digestal-forte", pepsin, insulin production.

2.3. Ts. Ariuntsetseg - Head of the Technical Control Department of ECAEM has carried out the following.

Has assimilated:

- determination methods of Chymotrypsin and Trypsin specific activities in units;

- determination methods of pepsin proteolytic activity in units;

- determination methods of amylolytic activity in units;

- determination methods of lipolytic activity in units.

Got familiarized with:

-structure, organization, funstion of Quality Control Department of "Galenika" institute including chemical and biological and pharmaceutical, bacteriological laboratories and vivarium of animals under tests;

- methods of pre-clinical tests of enzyme medical preparations;

- methods of chemical, biochemical, bacteriological and biological controls of pancreatin and pepsin.

2.4. Ts.Adyasuren -Bacteriologist of ECAEM Technical Control department has carried out the d following.

Has assimilated:

- methods of preparation of nutient medium;

-methods of sterilization of mediums;

- methods of the biological control on sterility of mediums;

- determination methods of the medium pH;

- methods of bacteria identification by their biochemical activities;

- methods of direct sowing of the medical preparations;

- methods of sowing on membrane filters;

- determination methods of the microbial cells amount including pathogenous, conditioned pathogenous, saprophylitic bacteria, fungi and mould;

- determination methods of the test dosage of enzyme preparations;

- determination methods of hystamine and hystamine like substances.

Got familiarised with:

- structure, organization, function of the bacteriological, biological and pharmacological laboratories.

3. According to the Work Programme approved by the MPR Deputy Minister of Light and Food Industry will introduce the following:

3.1. J. Alimaa and Ts.Ariuntsetseg will train four specialists to the methods of:

- determination of proteolytic activity of pancypsin, chymotrypsin, trypsin

- in FIP units

- in USP units

- determination of amylolytic activity in FIP units;

- determination of lipolytic activity in FIP units.

3.2. Ts.Adyasuren will train a bacteriologist of the Bacteriological laboratory methods of:

- preparation, sterility control of the selective nutrient medium;

- test of the pharmaceutical preparation by the direct sowing and membrane filter sowing methods;

- determination of microbial cells saprofit bacteria, fungi amount;

- identification of microbes by their biochemical activity groups Salmonella, E.Coli,Shigella.

3.3. On receipt of the sterile ensyme preparation production line equipments G.Altantsetseg will train the workers in the following technological operations;

- washing,drying and sterilisation of vials;
- dosing and filling of ensyme solution;
- closing and crimping;
- labelling.

All collected papers are presented to the ECEAM scientific workers.

4. A list of gathered literature.

4.1. Pharmacopeias

- Panreatin, from US,British and Jugoslavian pharmacopoeias
  in English - 5 pages
  on SerboCroatian - 6 pages
- Chymotrypsin, from US,Br tish,French,European pharmacopoeias
  in English - 14 pp
  in French - 4 pp
- Trypsin,from USP and National Formulary, French,British pharmacopoeias
  in English - 5 pp
  in French - 2 pp
- Heparin,from US,British,Jugoslavian,French pharmacopoeias
  in English - 10 pp
  in French - 4 pp
  on Serbo-Croatian - 4pp

- Insulin,from British,Jugoslavian pharmacopoeias
  in Snglish - 15 pp
  on Serbo-Croatian - 13 pp
- DNA,from French pharmacopoeias - 1 page
- Pepsin,from British,Jugoslavian pharmacopoeias
  in English - 2pp
  on Serbo-Croatian -1page
- Hyaluronidase, from US,British Pharmaceutical Codex
  in English - 5 pp

4.2. From articles issued by the Federation of International Pharmacopoeias, Part "Pharmaceutical enzymes"- 80 pages

4.3. Papers on conducting the bacteriological controls and pre-clinical tests of Pharmaceutical preparations - 426 pages.

4.4. Scientific articles dealing with the subjects carried out in ECAEM - 55 pages. Total 650 pages.

4.5. Catalogues of equipments and apparatus for production and quality control of enzyme preparations - 38 pieces.

Approved by: L.DAMDINSUREN
Deputy Minister of Light and Food Industry,MPR

WORK PROGRAMME

OF THE SPECIALISTS TEAM FROM EXPERIMENTAL CENTRE OF APPLIED ENZYMOLOGY AND MICROBIOLOGY SENT FOR TRAINING ON PHARMACEUTICAL FACTORY "GALENIKA",JUGOSLAVIA ACCORDING TO PROJECT MON/82/002 "ASSISTANCE IN STERILE ENZYME PRODUCTION"

5 persons
Duration: 1 month

1. Familiarisation and study the experience in activities on the sterile pharmaceutical ensyme preapartion production including:

- technology, methods on washing,drying and sterilisation of vials, rubber stoppers and aluminium caps and other equipments;
- technology of sterile filtration, automate dosage closing, frees-drying and crimping of ensyme preparations in vials;
- lab elling and packaging of sterile ensyme preparations.

2. Study the experience in organisation of production and keeping the rules for sanitary and hygiene requirements at sterile pharmaceutical ensyme preparations production.

3. Familiarisation and study the production technology of medical pepsin production and methods of preparations proteolytic activity determination.

4. Familiarisation and study the pancreatin production technology and methods of preparations lipase and amylase activities determination.

5. Familiarisation and assimilation of the methods in determination of activity quality of proteolytic ensyme by international pharmacopoeia units, including trypsin,pepsin,chymotrypsin, pancreatin.

6. Familiarisation and study the experience on activities of quality control laboratory of sterile ensyme and other biological active preparations.

7. Familiarisation with structure and organisation of bacteriological laberatory for sterile enzyme preparations prèduction.

- Familiarisation and study the modern methods in preparation and sterilisation of nutrient medium, conducting of biological control on medium sterility and pH;
- Familiarisation and assimilation of methods on preparation of enzyme preparation samples and sowing on nutrient medium;
- Conducting tests on sterility of enzyme preparation final froms;
- Familiarisation with methods in study of saprophytic bacterias amount, fungi and mould and presence of the following bacteria: E.Coli, Shigella, Salomonella.

8. Prepare reports on works carried out during the training.

HAED OF FOOD INDUSTRY DEPARTMENT B.ALZAHGHE.

Annex 8.4

ASSISSTANCE TO THE EXPERIMENTAL CENTRE OF APPLIED ENZYMOLOGY AND MICROBIOLOGY IN THE PRODUCTION OF STERILE ENZYME PRODUCTS (CHYMOTRYPSIN, TRYPSIN, PANCYPSIN)

DP/MON/82/002/31-00

Mongolia

F E L L O W S H I P R E P O R T

Prepared : Mr. Kabden Kunanbain
Chief of the team
Head of the Laboratory

ULAN BATOR, MONGOLIA

1. INTRODUCTION.

A team of specialists from Experimental Centre of Applied Enzymology and Microbiology of Ulan-Bator Meat and canned meat combine had one month training at Pharmaceutical and Chemical industry "Galenika", Yugoslavia, from 13 November to 11 December 1986.

On the arrival the Fellows were met by the representative of Serbian Administration for International Scientific,educational, Cultural and Technical Cooperation. They were also received by Mr. Misho Katich, head of the Department of UNDP Office in Beograd and Mr. Dragan Dmitrich,head of Department of the Administration for Intrenational Scientific,Educational,Cultural and Technical Cooperation.

On November 17th, Monday, the Fellows have been taken to the Pharmaceutical and Chemical Industry "Galenika" by Mr. Abramovich, representative of the Administration.

On the meeting at the institute they were received by Mr. O. Botich, director of "Galenika" institute, Mr.O.Shedrov,Project Manager,Mrs.M.Chobanovich, haed of the laboratory for control of the raw materials, Mr. Kovachevich, head of the laboratory for the chemical control of final pharmaceuticals, Mr. Jivkovich, head of the biotechnical laboratory,Mr.Stoyanovich,head of pharmacological laboratory. Three were discussions on Fellows' training programme and elaboration of the work plan for the training period.

The pharmaceutical and chemical industry of Yugoslavia is rapidly developing and has an export significance. "Galenika" is one of the largest factories in the country.

There are 6 factories at this industry where work more than 6000 persons:

- factory of medical preparations
- factory of pharmaceutical and raw materials and antibiotics
- factory of agrochemical products
- factory of inorganic preparations
- factory of plastic masses
- factory of pharmaceutics.

Besides that, there is an institute "Galenika", dealing with scientific research, engineering, trade, economical and quality control problems.

2. ACTIVITIES CARRIED OUT DURING THE TRAINING.

Due to the working programme, approved by the Deputy minister of Light and Food Industry, MPR and agreed with the "Galenika" Administration (EnclosureI) the Fellows have carried out the following.

2.1. K.Kabden - head the department for technical controlof Experimental Centre of Applied Enzymology and microbiology of Ulan Bator Meat and canned meat combine has mastered:

- study of the acute local toxicity;
- toxicity on izolated organs;
- determination of LD-50 on mice;
- general methods and techniques of hystological preparations
- clinical methods in izolated assays, Litsfild and Wilkonson methods;
- general principles of chronical toxicity (30,90,180,360 days

- methods in determination of DLM (minimal dose of Letalis)
- application of statistical methods of Karierh, Pershin;
- determination of analgezic effects;
- acetylcholinic effects of pancypsin;
- study of allergic properties;
- test-dose on toxicity;
- test-dose on pyrogenity;
- determination of hypotensive effects;
- determination of tensive effects;
- general principles;
- determination of DNC (Irvin's test);
- study of locally irritated effects on rabbit's eyes;
- study of anti-inflamantory effects.

During the training Mr. Kabden had an oppotunity to get acquainted with:

- study of concerogenic properties;
- therotogenic and embiotoxic activities of the preparation;
- study of the preparation's consistance;
- organiztion of production and keeping the rules of sanitary and hygienic requirements for the laboratory animals;
- keeping, feeding and breeding the laboratory animals;
- structure of the organization, function of the quality control department of "Galenika" institute, including the biological and pharmaceutical and vivarium of the experimental animals.

2.2. L.Urtnasan - scientific collaborator of the Experimental Centre in Ulan Bator worked from 17th to 24d November 1986 in the laboratory for control of raw materials, from 24d November to 7th December - in the laboratory for extraction of the research

sector on production technology of organotherapeutic preparations on 8-9th December - in the microbiological laboratory. During the training she has mastered:

- methods in determination of free and common proteases' proteolitic activity in pancreatic raw materials in FIP units;
- methods in determination of amylasa activity of pancreatic materials in FIP units;
- methods in determination of pepsin activity in pepsin-raw materials in NF and FIP units;
- methods in determination of pepsin pH, humidity, fatness and activity in mucous membrane of pig's stomach;
- technology of obtaining and purification of pepsin in the laboratory conditions;
- methods in determination of pepsin activities and yield on the definite steps of its obtaining.

Besides that she has got acquainted with:

- technology and equipment for pepsin production, including steps of grinding, homogenization, automatization, filtration, purification, centrifugiration and drying etc.;
- process of pepsin filtration on ultrafiltration apparatus;
- physical and chemical indexes and various capsules for pills;
- organization, function and activities of microbiological requirements for pepsin and pancreatine.

2.3. G.Enkhtsetseg - chemist of the Experimental Centre of Applied Enzymology and Microbiology of Meat and canned meat combine in Ulan Bator, from 19 to 24d November worked in the laboratory for raw materials quality control, form 24d November to 10th December - in the laboratory for quality control of products

and has mastered:

- methods in chemical control of enzyme preparation in a drug form such as: chymociclar capsule, chymolar and digestal drage on the foolwoing tests:

a.oragnoleptical fpms of capsules and drages;

b. decomposition;

c. cruelty;

d. depreciation;

e. an average mass and its deffection;

f. identification;

g. checking of the packed drugs;

- tests of tetracyclin chemical composition and properties, including:

a. activity;

b.solubilization;

c. acidity;

d. weight losses on drying;

- determination of the pancreatic proteolytic, amylase and lipase activities in pactreatin-raw materials by FIP units;

- determination of pepsin activity in raw pepsin on NF and FIP units;

- analysis of the empty capsules and its composition, application of the papar chromatography;

- qauli ty and quantity determination of ions in the mdneral salts of the enzyme solution and dried preparations.

She has also got acquainted with;

- technology of the production of oitments and its - quality tests;

- equipment for production of capsules, tablets and oitments;

- technology and equipment for chymocyclar production in capsules;

- operation of the technological line and equipment for drage production.

During their training the Fellows had an oppotunity to visit and be acquainted with the factory for production of the medical preparations: sterile, tablets, drage and capsules and oitments.

On termination of the training the Administration of "Galenika" institute and deputy director of Serbian Administration for International scientific,eductional,cultural and technical cooperation have received the Fellows and discussed their opimion on results of the Fellowship programme realization.

The Fellows were awarded by the CERTIFICATE of the Administration for International scientific,eductional,cultural and technical cooperation,Serbia.

The Fellows have collected some literature on the scientific research works.

3. ACTIVITIES,PLANNED FOR INTRODUCTION OF THE GAINED EXPERIANCES AND SUGGESTIONS;.

3.1. For the purpose of the pre-clinical tests of the pharmaceutical enzyme preparations, a new laboratory for pharmaceutical and toxicological tests with the sufficient equipment should be established. Besides that two more specialists should be trained and an order of the necessary apparatus and chemical reagents should be placed.

At the moment a part of possible pre-clinical tests should be started such as:

- determination of test-dose on pyrogenity
- determination of test-dose on acute toxicity
- determination of test-dose on chronical toxicity
- determination of allergic actions
- determination of anti-inflammatory actions.

3.2. Carry out the experiments on obtaining of pepsin in the laboratory conditions and complete a preparatory work for the introduction in production at a new biochemical plant.

Check the possibilities of obtaining a serum pepsin from cattle's stomach.

Determine pepsin activities in NF units.

It is necessary to purchase needed equipment and standard samples for the application of methods in determination of activities of the enzyme preparations for medical purpose on FIP units.

An experimantal work on obtaining of the technical pancreatin will be carried out through the scientific and technical cooperation

Enzyme activities should be determined by FIP units.

4. A LIST OF COLLECTED LITERATURE.

4.1. Pharmacopeia articles:

- Sterility tests
- BIOLOGICAL TESTS
- Modern embriotoxic methods
- Pyrogenity tests
- Pharmacodynamic toxicity
- Measurements of the differencialmeter
- Analogymeter
- Manometer registration
- Determination of the hystamine similar actions.
- Modern toxicological and pharmadynamical tests and antibiotic control

- Hystaminological methods in the pharmaceutical preparations tested on rabbit's eyes

- Experimental and clinical tests on effect of the sterigal different concentrations (on rabbit's eyes conjuctives)

- Toxicological, pre-clinical tests of the pharmaceuticals

-Logical tolarency of the streptomycin

- Controling of the depressive materials of the parental preparation

- Pharmacodynamy of the semisintetic penicillin

- Pharmacodynamic methods under the intestine rectum

- USP-XXI- Biological methods in tests

- USP-XX- Biological methods in tests

- USP -XXI- Insulin tests

- USP XXI- Depressor methods

- Modern experimental methods in determination of the toxicological property of the pharmaceuticals

- FIP- Methods in biological tests

- Recommendations for practical physicians

- Litchfild and Wilkonson methods

- Tetracyclin hydrochlorid in capsule

- Tetracyclin hydrochlorid for injections

4.2. Scientific research acticles dealing with the research work carried out at Experimental Centre of Applied Enzymology and Microbiology,

- On growing factors

-About Gonadotropin

- Methods in Immunology

- Methods in pre-clinical tests

- Copies of scientific articles and patents
- About pancreatin
- About lypase
- About pancreatic amylase
- Other scientific articles

4.3. Catalogues of equipment,apparatus,blanks and samples.

- Copies of Catalogue of equipment for ultra and sterile filtration
- Technical documentation on capsules
- Catalogue of Ermak apparatus for determination of tablets and drage hardness
- Catalogue of Ermak apparatus for determination of tablets and drage decay
- Catalogue of Ermak apparatus for determination of tablets and drage stability
- Technical requirements for tablets, covered by capsule "Degistal"
- Correlation of tablets FIP and NF
- Constant for viscosymeter

4.4. Assay methods

- Pancreatic BP-801 analysis
- Determination of decay
- Analysis of Degistal drage

a. proteolytic activity - methods FIP/E

b. amylolytic activity - methods FIP/E

c. Gelycellulose activity

d. contents of bile extraction

- Methods in chymoral drage analysis

- Methods in chymocyclar capsule

-a. General enzymatic activity AE

b.Tetracyclin determination

- Methods in capsule No. 0,No.7,No.2 analysis

- Tetracyclin hydrochlorid BP-801

APPROVED BY

L.DAMDINSUREN
Deputy minister of Light and
Food Industry, MPR

F E L L O W S H I P P R O G R A M M E
of Mr.KABDEN, pharmacologist, sent to pharmaceutical and chemical cooperation "Galenika", Yugoslavia

Project MON/82/002 "Assisstance in Enzyme production Ulan Bator, Mongolia

Duration - 1 month

1. Acquaintance with the enzyme preparations specific, pharmacological actions, including:

- determination of the preparations LD_{50} on mice and other types of animal;
- consistance of the preparation
- strong and chronic toxicity
- Locally irritating actions
- Allergic property of the new enzyme preparation (test on guinea-pig, rabbit)
- Cancerogenic property
- teratogenic and embriotoxic activity of the enzyme preparations
- antiinflammatory actions.

2. Experience on organization and production and sanitarian hygienic requirements for vivarium of the laboratory animals, experimental and biological clinic.

3. Acquaintance with methods of toxicity, pyrogenity tests of the enzyme by international pharmacopeia methods including:

- determination of toxicity by test-dose
- determination of pyrogenity
- determination of hypotensive actions

4. Acquaintance with literature: obtaining of gonadotropin, growing factors from cow's embrion, technological process of preparation "Activin T", timosin, fetuin, protain (liquid) from cow's embrion.

5. Aoquaintance with organiztion of keeping, feeding and breeding of laboratory animals.

6. Preparation of the report on the Fellowship Programme realization.

HEAD OF DEPARTMENT FOR FOOD
INDUSTRY, MINISTRY OF LIGHT
AND FOOD INDUSTRY, MPR — B.ALZAKHGUI

APPROVED BY L.DAMDINSUREN
DEPUTY MINISTER OF LIGHT AND
FOOD INDUSTRY, MPR

F E L L O W S H I P P R O G R A M M E

Mrs.Urtnasan, scientific collaborator, sent to pharmaceutical and chemical cooperation "Galenika" , Yugoslavia

Duration - 1 month

1. Acquaintance with the main activities of the work organization and technical and economical indexes of the pharmaceutical industry.

2. Study of the technology of final form of pharmaceuticals in a capsule form and acquaintance with equipment operation (type)

3. Study of the operation of technological line of the drage production and equipment (capacity, type, model).

4. Experience in production of medical oitment, acquaintance with equipment (capacity,type, model).

5. Study of the requirements for the quality of basic and suplementary materials for production of the above pharmaceuticals

6. Acquaintance with production technology of pepsin in pharmaceutical forms and obtaining the methods of the control and quality of the preparation.

HEAD OF DEPARTMENT FOR FOOD
INDUSTRY,MINISTRY OF LIGHT
AND FOOD INDUSTRY,MPR B.ALZAKHGUI

APPROVED BY

L.DAMDINSUREN
DEPUTY MINISTER OF LIGHT AND
FOOD INDUSTRY, MPR

F E L L O W S H I P P R O G R A M M E

Mrs.Enkhtsetseg,chemist,sent to pharmaceutical and chemical cooperation "Galenika",Yugoslavia

Project MON/82/002 "Assisstance in Enzyme production, Ulan Bator, Mongolia

1. Mastering of methods in chemical control of pharmaceuticals quality such as: chymocyclar, chymoral, degistal.

- solubility
- transparency
- colour
- pH
- optical density
- weight losses on drying
- sulfate ash
- identification

2. Mastering of the methods in chemic-al assay of the tetracyclin composition and property:

- quantity determination
- activity
- solubility
- original
- specific rotation
- optical density
- acidity
- weight losses on drying
- toxicity

3. Mastering of methods in determination of the pancreatin proteolytic, amylase and lypase activities.

4. Mastering of methods in capsule analysis and study of their property.

5. Study of methods in gastroresistant capsule, its composition.

6. Acquaintance with the technology of production of the medical iotments and its quality analysis.

7. Study of methods in quality and quantity determination of the mineral salts in the enzyme solutions and dried preparation

8. Acquaintance with equipment for capsule, tablet and oitment productions (administration, technical charactristics, type, price, producer).

HEAD OF DEPARTMENT FOR FOOD
INDUSTRY, MINISTRY OF LIGHT
AND FOOD INDUSTRY, MPR — B.ALZAKHGUI

Annex 8.5

Report on Findings upon Setting into Operation and on the Trial PRODUCTION OF THE "Rota" Line, Project No. DP/MON/82/002.

Prepared by the Chief Technical Adviser of the Project, and the Director of the Experimental Centre of Applied Enzymology and Microbiology in Ulan Bator, as the National Counterpart, on 23 October 1987.

This Report represents an addition to the Technical Report DP/ID/SER.A/887 of 18 August 1987.

The setting into operation of the "Rota" line was reported (3.4.5, p.16 of the Technical Report refers), and the first part of the trial production performed from 11 May to 19 May 1987 was reported as well (3.4.6, pp.17 to 19).

The relevant data are being currently collected from Dr.J.Alimaa, the ECAEM Deputy Director, Mrs. L.Urtnasan, the ECAEM Chief Engineer, Mrs.Ts.Adjasuren, the ECAEM Microbiologist, Mr.K. Kabden, the ECAEM Pharmacologist, and Mrs. Enkhjargal, the ECAEM chemist in the Quality Control Unit.

61 batches of Pancypsin were done on the "Rota" line until now, usually one and sometimes two batches every working day. The same amount of Pancypsin was used for each batch, 65g, with 25 mg of Pancypsin in a vial. Approximately 2 500 vials resulted in each batch. No other products (as trypsin or chymotrypsin) were processed on the "Rota" line.

The "Rota" line did not work from 18 June to 5 August, as the dosage device broke. A request for replacement was sent immediately to "Rota". It was received after 40 days. As from 5 August the "Rota" line works every working day.

The quantity of Pancypsin in a vial was checked every working day for every batch by the ECAEM Quality Control Unit. At the beginning of the trial production the quantity of Pancypsin was several times 23 or 24 mg in a vial. This was improved and

the batch was repeated the following day. In all other batches the weight of Pancypsin in vials was correct, 25 mg per a vial.

The microbiological control was done by the ECAEM Microbiologist. Every batch was controlled according to the ECAEM Microbiologist Work Programme (Annex 5.15, pp 84 to 86 of the cited Technical Report). Only eight batches were not sterile. This also includes the batches done during the period from 11 to 19 May, when two batches, first one on 11 May and third one on 13 May were not sterile due to the lack of experience in the sterile work at the beginning of the trial production. (This was already reported in the Technical Report.) After that it happened twice, on 8 and 17 June, batches No. 19 and 31, that the premises were not sterile. (Usually the premises were sterilzed by a chloramine solution and ultraviolet lamps). Following day the condition improved. On 10 and 11 August, batches No. 33 and 34, the autoclave did not work correctly, and so the rubber caps and the flasks for Pancypsin solution were not sterilized properly. On 3 and 30 September, batches No. 39 and 48, the sterile filtration of Pancypsin solution was not achieved, because of the troubles with the pump needed for the filtration, and the Pancypsin solution remained unsterile. The quoted reasons of the unsterile final product of freeze-dried Pancypsin in vials in all cases were known, and the location of the sterility break was known as well. It was improved in all cases the following day.

The ECAEM existing autoclave was repaired and it works well. The capacity of the autoclave is too small for the needs of production. Procurement of the second autoclave is indispensable.

The ECAEM Pharmacologist performed the control everyday for every batch of Pancypsin according to his Work Programme (Annex 5.17, p 89 of the cited Technical Report). Only once on 24 September, batch No. 46, the final product was pyrogen due to the pyrogenity of the distilled water. All other batches were apyrogen. All batches were atoxic as well.

A new compressor of the miximal pressure of 10 kg/cm^2, with receiver, made in USSR, was purchased by the Mongolian side in

July 1987. It is being used completely for the needs of the "Rota" line. The capacity of this compressor is big enough to supply at once all the "Rota" line machines with compressed air. It is placed in the basement, i.e. below the ECAEM production premises.

According to the Protocol on the Installation of Rota Automatic Filling Line for Production of Sterile Products in Vials, of 11 May 1987 (Annex 5.14,p.83 of the Technical Report), the "Rota" firm was obliged to send, among others, all necessary operating instructions for workers and for necessary repair operations, within one month period, as promised by the "Rota" installation engineer. Nothing arrived so far. All other things that the "Rota" firm had to send to the ECAEM according to the Protocol, arrived only at the beginning of October, and were mounted in the "Rota" line machines immediately. The printing plates for labels were repaired by the "Rota" firm, and sent back to the ECAEM, as well. The printing plates were tested immediately on the "Rota" labelling machine, and it was found that they work satisfactory.

According to the Mongolian side the electrical schemes of the "Rota" machines are another problem, because they do not correspond completely to the type of the ,machines provided by the firm. It seems that the schemes were done for other types of the machines. The same was quoted in the Technical Report as a serious problem.

J. Tserendendev,
ECAEM Director

Prof.Oleg Scedrov,
CTA of the Project

Annex 8.6

Slaughter in the Three Biggest Mongolian Slaughterhouses, Ulan Bator, Darchane and Choybolsane

Animals Slaughtered	Heads per Year			
	Meat and Canned Meat Works in Ulan Bator	Meat Works in Darchane	Meat Works in Choybolsane	Total
Cattle and yaks	120,000	50% of Ulan Bator	50% of Ulan Bator	240,000
Sheep and goats	1,200,000	50% of Ulan Bator	50% of Ulan Bator	2,400,000
Pigs	30,000	Nil	Nil	30,000

Slaughterhouse Animals By-Products in Ulan Bator, Darchane and Choybolsane

By-Product	Cattle and [illegible]s			Sheep and Goats			Pigs		Grand Total
	kg per Head	Tons per Year		kg per Head	Tons per Year		kg per Head	Tons per Year	
		Ulan Bator	Total		Ulan Bator	Total		Ulan Bator	
Blood*	7.000	840	1260	0.850	1020	1530	3.000	90	1620
Pancreas	0.150	18	36	0.030	36	72	0.070	2.1	110.1
Adrenal glands***	0.015	1.8	3.6	0.003	3.6	7.2			10.8
Pituitary glands****	0.0025	0.3	0.6	0.0005	0.6	1.2			1.8
Testicles**									
Bile	0.170	20.4	40.8	0.030	36	72			112.8
Spinac chord	0.100	12	24						24
Stomach mucous membrane	0.600	72	[illegible]				0.225	6.75	150.75
Rennet	4.250	510	1020	0.665	798	1596			2616
Pounch	0.950	114	228	0.133	159.6	319.2			547.2
Rennet and Pounch	5.200	624	1248	0.798	957.6	1915.2			3163.2

*Choybolsane is not included.

**Only gelt animals are slaughtered.

***Collected and exported to Hungary.

****Never collected.