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PROGRAMME "BIOMED"

DP/MON/82/004

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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Abstract

Programme "Biomed": Strengthening of Facilities for Production and Quality Control of Gamma-Globulin and Albumin at the Institute of Biological Products and Blood Transfusion

Project Number MON/82/004/A/01/37

The purpose of the project was the direct support of UNIDO to assist the Government of Mongolia in its efforts to develop the pharmaceutical industry in the field of biological products and so obtain self-reliance.

The main objectives of the Project were to modernize and strengthen the Blood Fractionation Unit at the Institute of Biological Products and Blood Transfusion through installation of new up-to-date equipment, introduction of suitable technologies of Albumin and Immunoglobulin (gamma-globulin) production and modern quality control procedures so as to ensure meeting of WHO requirements and standards.

The duration of the Project originally stated in the Project Document was one year and six months.

All purposes and objectives were achieved and the duration of the Project was one year and ten months.

As a result of the observations and experience gained during the implementation of the Project it may be concluded that for countries like Mongolia, remote from Europe and with limited transport connections, one year and six months is a rather short term for the fulfilment of activities of even modest projects like this one.

For the consolidation, further development and utilization of the project results the major recommendation to the Government authority is to take care constantly to enlarge the supplies with raw materials (plasma, serum, placentae) for the production, to ensure proper maintenance of the equipment and undertake practical steps for the further qualifica-

tion of professional personnel.

In order to ensure the efficient assimilation of technology and the efficient utilization of equipment supplied through the Project it is suggested also that a long term support programme be implemented through UNIDO and/or by bilateral way between the technology holder and the recipient.

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INTRODUCTION

Blood products such as albumin and gamma-globulin are among the WHO list of essential drugs. Gamma-globulin (Immunoglobulinum humanum Normale) is a solution of the immunologically active protein fraction, isolated from human donor or placental blood, which contains the serum antibodies of adults in concentrated form. Normal immunoglobulin is effective in humoral immunodefficiencies and particularly for prophylaxis against measles and hepatitis A. Current normal immunoglobulin preparations may be effective also for hepatitis B prophylaxis. Several studies have demonstrated that normal immunoglobulin is not effective for prophylaxis of rubella or mumps at the doses administered. Specific immunoglobulins from donor plasma could be produced for the purpose.

Albumin is a water solution of the purified albumin fraction of human donor or placental blood. It is applied intravenously. The preparation is free from antibodies and disease causing agents, including the hepatitis B virus. It does not contain isoagglutinins and is injected without prior determination of the blood group of the recipient. The albumin molecule performs two main functions: a) maintaining effective oncotic pressure and b) transporting nutrients, drugs (sulphonamides, penicillin, digitalis glucosides, etc.) hormones, enzymes, toxins, etc. The function of oncotically active molecules is to retain water in the blood and albumin is one of the major factors that contribute to intravascular fluidity. Diluted solutions (5%) of albumin are used as plasma substitute when it is necessary to fill the blood system after great loss of blood or body fluids resulting from burns, nutrition disorders, cholera-like syndrome, traumatic or operative shock. Concentrated solutions (20%) of albumin are used when it is necessary to remove excessive fluids from organs and tissues (brain oedema, increased intracranial pressure, chronic hypoproteinemia and hypoalbuminemia with oedema due to liver cirrhosis, nephrotic syndrome, shock). It removes quickly the

oedematous fluids from the organism and intensifies diuresis.

Self-sufficiency in the production of blood derivatives, therefore, constitutes an important element in the supply of these essential drugs to meet the needs of health care programmes. The prevalence of hepatitis in the country is high (it has been found that there were 4,6% positive of hepatitis A antigen blood donors in Mongolia. Normally the immunoglobulin content in serum reflects the epidemiological situation and it is assumed that gamma-globulin produced from local raw materials has high antibody titre to hepatitis and is undoubtedly essential to communicable diseases control programme. Therefore, in spite of the fact that the Government has to import gamma-globulin preparations, imported gamma-globulin cannot be considered equivalent to the locally produced with regard to antibody distribution and quality and the Ministry of Health cannot afford to rely only on imported gamma-globulin.

With this in view the Government with own sources established in 1971 a laboratory for the production of gamma-globulin from retroplacental serum. This laboratory operates as a department of the National Institute for Biological Products and Blood Transfusion, the only Institute in the country which is authorized by the Government to produce biological and haematological preparations for human use. Production of gammaglobulin started by using retroplacental serum as raw material collected in maternity homes in Ulan Bator. Later the collection of retroplacental serum has been arranged also from departments of obstetrics in several of the regions (aimaks) which are directly connected with the capital by air service. Together with donor plasma collected from donations in Ulan Bator about 1500 litres of raw materials were utilized in the production of blood derivatives.

The adopted technology for the production of gamma-globulin was modified Cohn's cold ethanol fractionation method 6+9. Since, however, this method did not permit to obtain hempigments free albumin in 1975, the CTA acting as WHO expert strongly recommended a new manufacturing scheme to produce

albumin meeting international standards. The proposed technology was introduced into practice and the laboratory could produce 5% and 10% solutions of albumin.

The quantities of gamma-globulin and albumin,which were produced in this laboratory were far less than the real needs of the country to carry out its health programme. The possibilities of raw material collection were limited because of the underdeveloped voluntary blood donation and the lack of suitable equipment for storage and transportation of placental materials. Also the production equipment was of low capacity and quite old so it needed to be exchanged by up-to-date technique to expand the production. Besides, the blood derivatives produced by the old technology and equipment did not meet completely the requirements of WHO in stability,sterility,pyrogenicity.All this has brought the Government to the need to ask for assistance from the corresponding organizations of UN.

The assistance has been requested on 29 March 1984 and approved on 10 August 1984 by UNDP RR on the basis of UNIDO's letter of 24 April 1984.

The project became operational in June 1985 and it lasted one year and ten months.

The associated agency was WHO but it has not participated in the project so far.

The total contribution of UNDP originally stated in the Project was US $ 321,000 with subsequent adjustment to US $ 355,850 .

The host Government's contribution in kind stated in the Project Document was Tughriks 3,220,000.

The original development and immediate objectives stated in the Project Document were logical. They were not revised and were attained.

Formal training arrangements were done in the form of a study tour for the National Project Coordinator for 40 days in several countries. The fellowships of two candidates were

organized.

A 5-days course for training of specialists from regional (aimaks) centres of blood transfusion on the methods of collection, storage and transportation of raw materials (retroplacental serum and placentae) for the production was organized.

On-the-job training was carried out continuously both theoretically and practically according to comprehensive programmes prepared by foreign specialists.

The results of the training experiences were positive. This was confirmed by the round table discussions and by the fact that most of the trainees have gained self-confidence and are capable of leading the work themselves.

I. OBJECTIVES AND LOGIC OF PROJECT

A. Development objectives

The original development objective of the Project was to assist the Government of Mongolia in supporting its successful implementation of the Health Programme which forms part of Government's development strategy. The programme is expected to result in the provision of modern and improved facilities, development of national technological capabilities and skills necessary for the local production to attain self-reliance in supply of population with blood derivatives.

B. Immediate objectives

The immediate objectives stated in the Project Document were:

- to modernize and strengthen the Blood Fractionation Unit, through the introduction of suitable technology of albumin and immunoglobulin (gamma-globulin) production;

- improvement of the quality of blood products and introduction of quality control procedures so as to ensure meeting WHO standards;

- development of national technological capability and skill through courses and in-service training;

- achievement of an acceptable level of research programme and a team of trained research workers.

II. ACTIVITIES CARRIED OUT AND OUTPUTS PRODUCED

A. Activities

The Government authority appointed in January 1985 Dr.D.Dandii as National Project Coordinator who had to be responsible directly for the implementation of the Project. Counterpart professional staff of 14 persons, administrative and support services, office premises and facilities, vehicles, etc. were provided. The National Project Coordinator had a 40 days study tour in May-July 1986 in Bulgaria, Hungary, Czechoslovakia and USSR where he got acquainted with the specific problems of large scale fractionation of retroplacental serum and placenta proteins, its organization, material security, management, methodology, performance, etc. In the different countries he studied the technologies in the production of blood derivatives. He got acquainted with the qualification of the personnel and the training programmes there. The equipment and its situation in the production premises was also studied. Special attention was paid to the organization of the collection of the raw materials, the schedule of supplies with fractionation reagents, the coordination of work of the different groups (on fractionation, lyophilization, sterile departments and quality control) in these large units. This study tour was very useful to his further work as Project Coordinator and head of the new enlarged, modernized and strengthened Blood Proteins Unit at the Institute of Biological Products and Blood Transfusion.

In May-June 1985 UNIDO as executing agency sent the Chief Technical Adviser for one-month mission to Mongolia and so it was assumed that in June 1985 the project became operational. At that time the work plan with schedule for the implementation of the project was prepared. The Project Document had

stated the duration period to be one year and six months. That was why all activities in the Work Plan were scheduled in short terms. The practical implementation of the project showed that for countries like Mongolia (far-away from Europe the major source for the delivery of equipment and recruitment of specialists) 18 months were a rather short period of time for a relatively modest project as this one. The above could explain the delay in all activities compared to the work plan schedule.

In order to ensure the achievement of the Development and Immediate Objectives and fulfil the outputs defined in the Project Document it was necessary to enlarge the area of the existing laboratory by 8-10 additional rooms situated on the second floor of the building and property of another Institute before (Annex 2 and Annex 3). The Government authority ensured the vacation of these premises in due time but their reconstruction and reconditioning (Annex 4) took a longer period than expected because of the lack of materials and workers. In fact the reconstruction was carried out practically after the arrival of the foreign experts (October-November 1986) who themselves directed and took part in it. A rather long delay and difficulties were caused by the repair of the old electric net which did not ensure safety for the new equipment and for the workers. The difficulties were due to the lack or delayed supply of suitable electric materials (cables,sockets,plugs,etc.).

Two tripartite meetings unscheduled neither in the Project Document or in the work plan were provoked and held on 3 November 1986 and 1 December 1986 in order to find the solution of the problems caused by the above difficulties and to fulfil the activities. An additional plan with schedule to accelerate the implementation of programme "Biomed" was worked out after the first tripartite meeting. It was highly appreciated that the Government authority took active part in the realization of the additional plan and significantly facilitated the implementation of the Project.

Final selection of equipment according to priority needs was done in June 1985 when the Project Requisition Document was prepared. The nomination of suppliers was coordinated between Purchase and Contract Service (PAC) of UNIDO HQ and CTA from his home country by letters, cables and telephone conversations (since October 1985 till April 1986).

Procurement and shipment of the greater part of the equipment took place according to schedule but the delivery of some machines sent by railway was delayed 5-6 months because of the remoteness of Mongolia and the limited transport facilities to this country.

The equipment was installed by the foreign specialists with the assistance of local personnel. The installation took place 3-4 months behind schedule because the reconstruction of the premises was not finished on time and the equipment was delivered with long delay (Annex 12). Trial runs of the machines were performed immediately after their installation. The installation and trial runs were performed in a short period due to the intensive work of experts and local personnel.

International experts were recruited and assigned with 3-4 months delay compared to the work plan (Annex 5). Their qualifications and ability to work hard were more than adequate.

The selection of additional local technical personnel was realized with considerable delay compared to the terms of the work plan. It appeared difficult to find suitable candidates (see Annex 6) and still there are vacant positions.

The organization of training in the technology holder's premises through fellowships of two local technical persons two months each was rescheduled to start in February 1987 (see Annex 7). This reschedule would not influence the implementation of the project and the achievement of its targets because the training of local personnel was performed on the spot following comprehensive training programmes prepared by the foreign specialists. Both theoretical and prac-

tical training with the new equipment was carried out. Even, one could say, that the delay in the fellowships would be useful to the fellows who would understand better the problems at local conditions and seek their solution in the practice of the laboratories they would visit.

The processing of blood plasma/serum started on 10 December 1986 and continued in the presence and with the participation of the foreign specialists till the 20th of February 1987.

B. Outputs

The existing facilities for the production of blood derivatives at the Institute of Biological Products and Blood Transfusion were reconstructed, modernized and strengthened. All equipment supplied by UNIDO was installed and put into action (see Annex 12). A number of apparatuses (supercentrifuges, autoclaves, distillators, thermostates, dry heat sterilizers, etc.) bought with local currency by the Government authority were installed also. The CEPA Technicum centrifuge TZ3 was initially intended to be applied for the removal of the placental tissue from the placental extract. This centrifuge was named by the firm "decanting" but it appeared to be the filtering type. At the Blood Fractionation Unit it was used for clarifying of the placental extract but not for the removal of the tissue. The removal of the tissue was fulfilled with a lot of manual labour. That is why the need of a real decanting centrifuge is urgent. This problem would be solved in the follow-up project. The TZ3 centrifuge would be applied for clarification purposes.

All these facilities are capable of processing more than 4000 litres of blood plasma/serum per year. It is not likely that the above quantity of raw materials (4000 l) could be collected per year. One of the reasons is that voluntary blood donation in Mongolia is underdeveloped and only 200-300 l plasma for the needs of the fractionation could be expected per year. The other reason is that the collection of retroplacental serum is hindered because of

the country's geographic peculiarities - huge teritory and no other transport connections with the regional (aimaks) centres except by air.That is why before the implementation of the project it was not possible to collect more than 1500 l per year. Now,after the supply of 25 chest freezers, most of which were distributed to the main maternity homes of the country,possibilities were created for the collection, storage and transportation of the raw materials in a frozen state (Annex 1). So the collection of serum is expected to reach nearly 3000 litres per year. Besides,in order to achieve the targets (quantities of gammaglobulin and albumin produced per year) established by the project document and the work plan, capacities were created to process 10,000 kg frozen placentae - raw material which was not used in the production before and was discarded. The enlarged,modernized and strengthened laboratory with the presently installed equipment has now the capacity to process additional (not stated in the project document)raw materials.

Therefore,production facilities for the fractionation of 4000 l plasma/serum and for the processing of 10,000 kg frozen placentae were created.

From the above raw materials,if available,the size of production of Normal Human Immunoglobulin (gammaglobulin) and albumin in final sterile forms could be as follows:

a) Gammaglobulin ampoules 1,5 ml each, 10% solution

from 4000 l plasma/serum (x 30 amp./l)	=	120,000 ampoules
from 10,000 kg placentae (x 2,5 amp./kg/	=	25,000 ampoules
total		145,000 ampoules

b) Albumin bottles 100 ml each 20% solution

from 4000 l plasma/serum (x 0,5 bottles)	=	2,000 bottles
from 10,000 kg placentae (x 0,125 bottles)	=	1250 bottles
total		3,250 bottles

The above 3250 bottles are equivalent to 6500 bottles 100 ml each 10% solution or 13,000 bottles 100 ml each 5% solution. Since the former equipment did not give the possibility to produce 20% albumin the first quantities of the albumin precipitate were used for the preparation of 5% and 10% solutions which are already known in local hospitals and some time will pass before the recognition of the 20% albumin despite its numerous advantages.

Compared these facilities against the targets established in the latest version of the project document prepared at the tripartite meeting of 1 December 1986 and reflected in the Internal Evaluation Report dated 30 November 1986, page 5, it is evident that they are 50% more capacity for both gammablobulin and albumin.

In former years, before the implementation of the project, with the old equipment and by the old technologies about 45,000 ampoules 1,5 ml each 10% solution of gammaglobulin and about 2000 bottles 100 ml each 5% albumin solutions were produced per year.

The comparison of the above data clearly demonstrates that after the implementation of the project the production capabilities of the Blood Fractionation Unit at the Institute of Biological Products and Blood Transfusion were increased three times for gamma-globulin and more than six times for albumin.

During the mission of the foreign experts, with their personal participation and under their supervision till the 20-th of February 1987, 600 l of retroplacental serum and 300 kg of placentae were processed. Also the fractionation of another batch of 300 kg placentae was started and would be finished after the 20-th of February.

Out of the 600 l of serum 18,100 ampoules 1,5 ml each 10% gammaglobulin solution and 305 bottles 100 ml 20% albumin solution were produced. The processing of the first batch of 300 kg placentae resulted in the preparation of 35 bottles 100 ml 20% albumin and 2,5 l immunoglobulin so-

lution which was decided to be used for experiments and research aiming at the preparation of immunoglobulin for intravenous use.

The processing of placentae was somewhat hindered because of the irregular supply with ethanol and the high tax on this reagent (hence its price) in the country. Placental extract is poor in proteins and relatively large volumes of ethanol are needed. At this stage the fractionation of placental extract was considered experimental. The problem with the regular supply with ethanol and its price is expected to be solved soon.

The fractionation of serum and placentae was performed according to the schemes in annexes 8,9,10 and 11.

Improved quality control facilities were created. New up-to-date equipment for the control in the production stages and the control of the final preparations (autocal pH meters, set of tools for automatic gel chromatography performance, laminar flow hood,electrical pyrogen tester,etc.) was installed and put into action. The quality control methods applied in the Blood Fractionation Unit were thoroughly looked over. New methods,so as to study all parameters according to the requirements of WHO,were introduced.

It was found that the preparations produced by the new technologies with the modern equipment from retroplacental serum and placental extract meet the WHO quality requirements.

The local personnel was trained theoretically and practically according to comprehensive training programmes prepared by the foreign experts in the fields of a) blood plasma/serum processing; b) production of blood derivatives at sterile conditions by means of up-to date techniques; c) lyophilization procedures; d) quality control and e) maintenance of equipment.

Research programme for further complete utilization of blood plasma/serum and placentae was prepared (annex 13).

This programme is aiming at a better characterization of the blood derivatives produced and development and introduction of methods for the preparation of immunoglobulin for intravenous use. This preparation is still produced in limited number of countries.

The work on this programme was started. The new quality control methods were applied for the further characterization of the immunoglobulin and albumin preparations. 2,5 l immunoglobulin solution from placental extract would be used in experiments to prepare immunoglobulin for intravenous use. The fellows in the course of their fellowships starting 13 February 1987 would also work on this programme.

III. ACHIEVEMENT OF IMMEDIATE OBJECTIVES

The Immediate Objectives, stated in the Project Document were totally achieved with 5-6 months delay, due to the reasons described in the 6-months Project Progress Report submitted and in the present Terminal Report.

The Blood Fractionation Unit at the Institute of Biological Products and Blood Transfusion was modernized and strengthened through the enlargement of the basis for production and research, the installation of equipment including a freeze-dryer, ultrafiltration apparatus, laminar flow hood, automatic ampoule filling and sealing machine, etc.

New, suitable technologies were introduced in the gammaglobulin and albumin production. The technologies for the utilization of placentae for the production of these essential preparations were not known in Mongolia before. Despite the fact that the amounts of immunoglobulin and albumin in the placental extract are not as great as they are in the retroplacental serum, the isolation of these important fractions is necessary because of their great clinical value. The analysis of immunoglobulin and albumin isolated from placental extract showed that they meet the quality standards of WHO. That is why all efforts are made to solve the problems with the supply of the needed reagents for the fractionation of

placental extract as soon as possible.

The method of ultrafiltration was applied in the production of albumin solutions and thus the native form of the molecules was preserved and the high quality standards of WHO were met.

Lyophilization procedure was introduced in the gamma-globulin production and thus the preparation of a product meeting the requirement of WHO on stability (one of the important qualities) was achieved.

The qualities of the produced blood derivatives in relation to stability, sterility and pyrogenicity compared to international standards were improved by means of ensuring sterile conditions of work under the protection of laminar flow hoods, automatic ampoule filling and sealing of ampoules, etc.

New quality control procedures and methods were introduced. These were: the determination of the molecular composition of the immunoglobulin and albumin preparations by gel filtration, radial immunodiffusion to determine the quantities of immunoglobulin classes in the gamma globulin preparations, the method of inhibition of the agglutination by blood group substances present in the preparations, the method of inhibition of hemagglutination in the detection of HBsAg, the method for the determination of the anticomplemantary activity of the immunoglobulin preparations, the method for the determination of pyrogens was revised and improved, etc. The above new methods and the improved ones for the quality control of the preparations give the possibility to characterize in more detail the blood derivatives with reference to WHO requirements and standards.

National technical capabilities and skills were developed through on-the-spot courses, theoretical lectures and practical in-service training. Lectures were given according to a schedule approved by the Director of the Institute. During their term of service each of the experts had a one-

hour lecture once a week on a definite day and at a definite time. The professional staff of the Blood Fractionation Unit was divided into three groups. Every expert was responsible for the training of one of the groups. Also in the course of the work practical training was carried out on the spot with professional and assisting personnel. Two persons of the professional personnel took part in the training programmes for 3-4 weeks only and then they were on a long time sick leave. Except the two technicians occupied with the raw material collection, the laboratory workers and the secretary-interpreter all personnel of the Blood Fractionation Unit took part in the training programmes of the groups according to place of work in the Unit.

The fact that capabilities and skills were developed through the training programmes was confirmed by the round table discussions and interlocutions carried out by the foreign experts by the end of their terms and also local personnel proved capable to perform all production and control procedures by themselves without the need to be supervised. These capabilities and skills would be developed further by the fellowships of the two local specialists rescheduled to start 13 February 1987 for two months each (Annex 15). Their programmes are directed to the study of problems connected with the future developments and research on the technologies and the quality control of the preparations.

An acceptable level of research programme (Annex 13) was prepared and a team of relatively well trained research workers was formed.

All these results correspond to that which was expected to be achieved by the project.

IV. UTILIZATION OF PROJECT RESULTS

The utilization of the project results has already started. The enlarged, modernized and strengthened Blood Fractionation Unit at the Institute of Biological Products and Blood Transfusion was put into action. Now the Unit produces Immunoglobulin (Gammaglobulin) and Albumin by means of up-to-date

technique and technologies. The production capacities were increased by more than 50% compared to the targets of the Project Document. Compared to the production capacities before the implementation of the Project the production capacities were increased more than 3 times for gamma-globulin and more than 6 times for albumin.

New methods and new equipment were introduced in the control of the production stages and quality control of the final preparations which guarantee the achievement of WHO standards and highest international requirements.

The national technical staff was trained well and their capabilities and skills ensure their independent work for the local production to attain self-reliance in supply of the population with blood derivatives. Thus prerequisites were created for the fulfilment of the Health Programme of the Ministry of Health, which forms part of the Government's development strategy.

The main factor which might influence adversely the further effective utilization of the project results would be the lack or shortage of raw materials - plasma, serum and placentae to fill the capacity of the enlarged and equipped Blood Fractionation Unit. The availability of raw materials would be ensured by measures of the Government authority to keep the created organization of collection in a good state.

Another factor which might impede the application of the project results would be the irregular or insufficient supply of the Unit with reagents and expendable materials which are imported in Mongolia.

The last but not the least important factor to this end could be the lack of qualified maintenance of the new modern equipment. That is why the Blood Fractionation Unit should appoint as soon as possible a good mechanic, who could work on the maintenance in collaboration with the engineer of fractionation. Spare parts should be timely ordered and supplied.

V.CONCLUSIONS

All activities, inputs and outputs were implemented. The immediate objectives were achieved and conditions for the fulfilment of the development objectives were created. All this was achieved in short terms because of the intensive work both of Executing and Implementation Agencies in the course of one year and ten months instead of one year and six months as originally stated in the Project Document.

The new technologies ensured the production of immunoglobulin and albumin from all available placental sources. The processing capacity of the equipment is used at maximum because when 96% ethanol is applied as precipitating agent the volumes of the fractions at the different stages are kept at minimum. A strict control of the main parameters as temperature, ionic strength, protein concentration, ethanol concentration was achieved. This ensured the production of preparations of good quality. The lyophilization of immunoglobulin gave the possibility to produce stable immunoglobulin solutions. The ultrafiltration method was applied for the removal of ethanol from albumin solutions and 20% albumin was prepared which was not possible before. The method of membrane filtration under the protection of laminar flow hood ensured the sterility of the preparations.

As a result of the observations and experience gained during the implementation of the Project one could conclude that for countries situated far away from Europe with limited internal and international transport connections 13 months were a very short time for the implementation of even a modest project like this one.

To explain this conclusion one could point out to the fact that the supplies of heavier equipment by railway took 10-12 months from placing the order to the date of delivery at the spot (for example double jacketed stainless steel vessel ordered on 30 October 1985 was delivered on 23 October 1986, freeze-dryer ordered on 12 November 1985 was delivered on 13 August 1986, etc.).

Besides,it is advisable for projects which need in advance building or reconstruction works to make the necessary arrangements and plans with detailed schemes and specifications which could be handed over to the Implementation Agency with a clear warning that before the end of these works the foreign experts would not arrive. This would be the way to avoid the occupation of the foreign experts in reconstruction and reconditioning works and they could pay more attention to the timely installation of the equipment and devote more of their time to training of local personnel on the specific production problems. The work plan had scheduled a one month mission of the CTA in March 1986 to make the necessary arrangements to this end but his mission was cancelled.

VI.RECOMMENDATIONS

To consolidate,develop further and totally utilize the Project results Government should:

1.Constantly take care and make the necessary arrangements to ensure the needed quantities of raw materials for processing by the Blood Fractionation Unit through the development of voluntary blood donation and ad maximum collection (not less than 3000 l retroplacental serum and 10,000 kg placentae), storage and transportation of the materials from all maternity homes of the country.

2.Allocate every year the necessary funds for the import of reagents,expendable materials for the production and spare parts for the equipment.

3.Periodically (at least every two years) send members of professional staff abroad to get acquaintance with the new developments in the production of the blood derivatives.

4.Make provision for 2-3 months mission to Mongolia of an expert with wide knowledge and qualification in the production and up-to-date quality control of blood derivatives,who would supervise the progress of the work after the implementation of the project (Programme "Biomed") and

give assistance, if necessary, for the further development of this programme.

5. Apply for the support of a follow-up project (Annex 14) to ensure the efficient assimilation of the technology transferred through the project.

Annex 1

SCHEDULE OF COLLECTION OF RETROPLACENTAL SERUM FROM MATERNITY HOMES IN MONGOLIA IN THE NEAREST MONTHS (1987)

A. From maternity homes with deep freezers - serum is sent by air once a month in the first week of the month

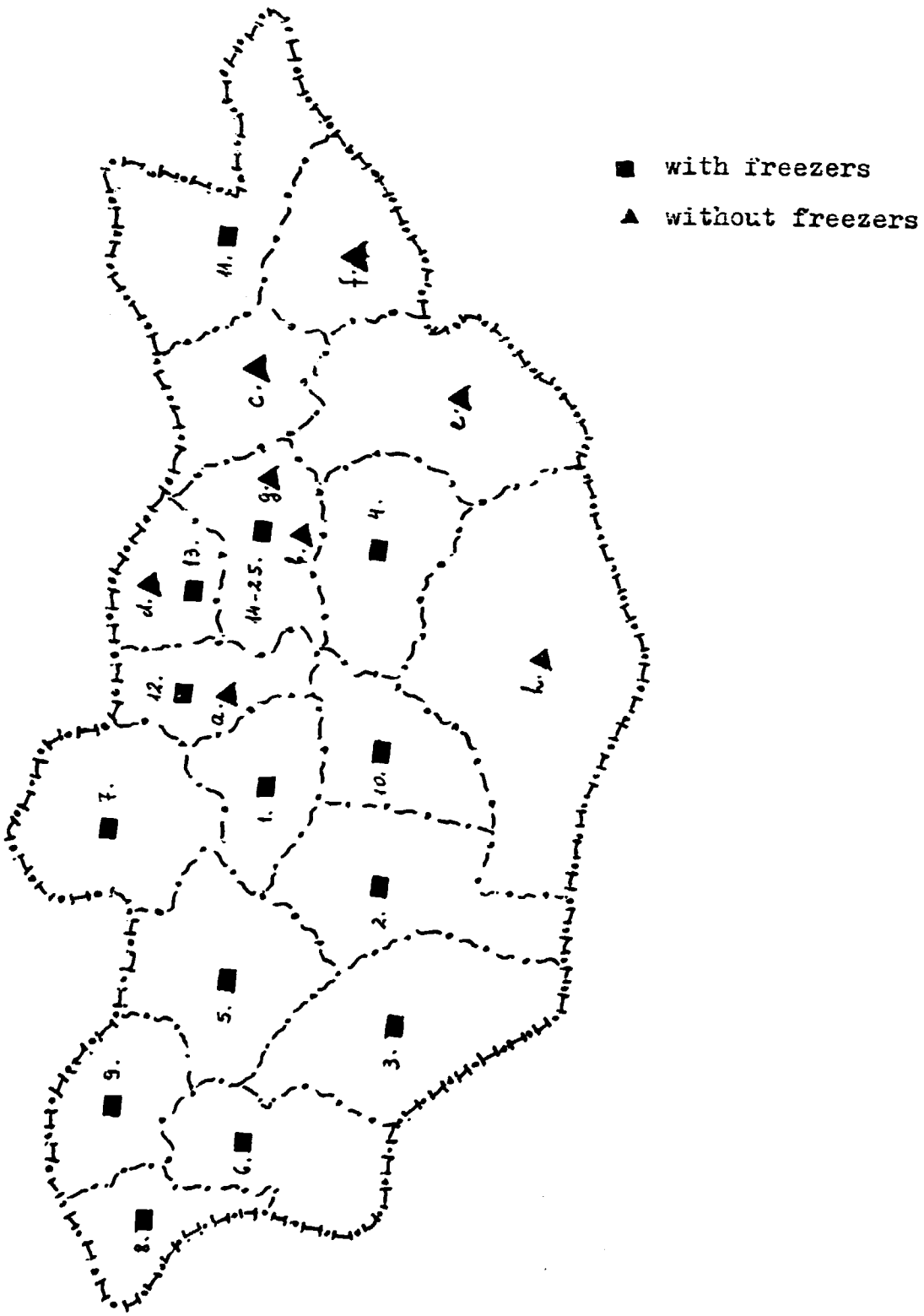
Expected quantity of serum (l) from aimak:		in March	in April	in May	in June
Freezer No					
1	Arkhangai	5	7	7	6
2	Bajankhongor	5	7	7	6
3	Gov-altai	5	3,5	3,5	3
4	Dundgov	3	4,5	4,5	5
5	Zavkhan	5	5	5	5
6	Khovd	3,5	4,5	4,5	6
7	Khovsgol	5,5	6	7	2
8	Bajan-Olgil	5,5	4	7	4
9	Uvsnuur	6	4	3	3
10	Uvurkhangai	3,5	4	6	5
	Dornod	5,5	5	5	5
12	Erdenet	4	5	5	5
13	Darkhan	5	7	7	6

Freezers No 14-17 were placed in maternity homes in Ulan Bator mainly for the collection of placentae. Also 30 l serum per week (120 l per month) are collected in the capital city. Freezers No 18-25 were placed at the Blood Fractionation Unit for storage of raw materials.

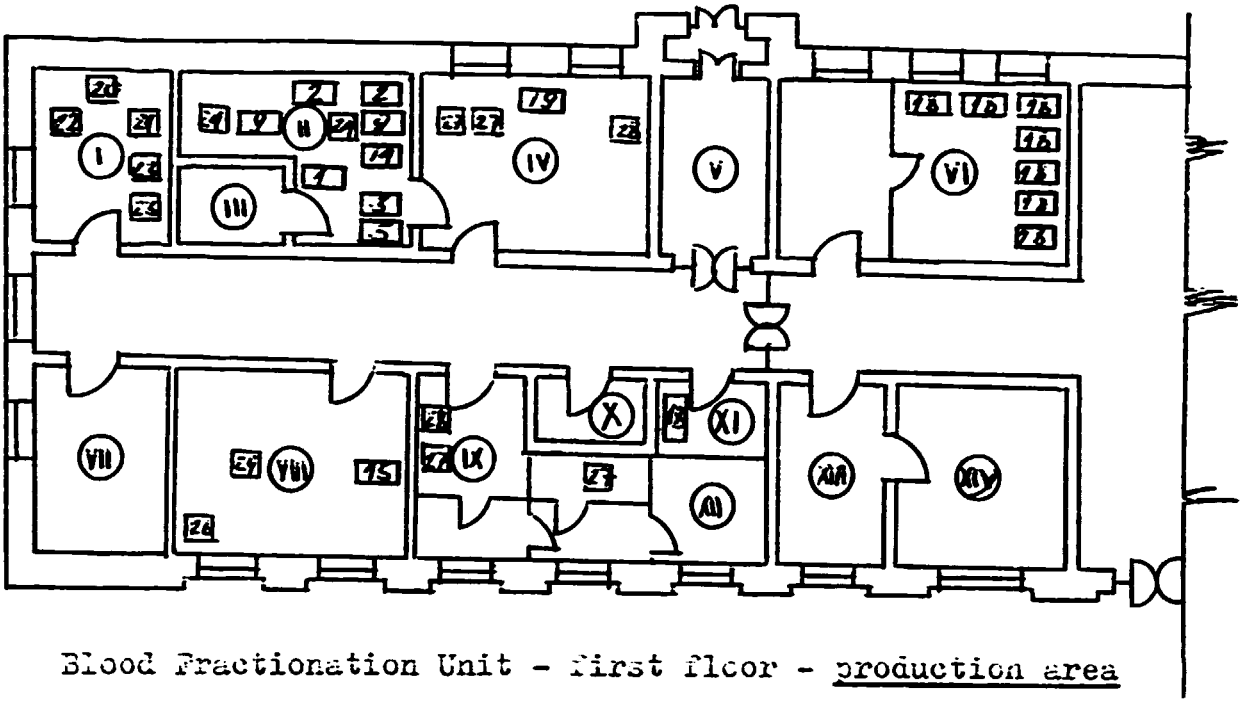
B. From maternity homes without deep freezers - serum is sent to the Blood Fractionation Unit every week

Expected quantity of serum (l) from:	in March	In April	in May	in June
a. Selenge	3	3,5	3,5	3
b. Central aimak	5	3,5	3,5	3
c. Khentej	3	4	3	3
d. Bulgan	3,5	3	3	4
e. Dornogov	3,5	2,5	2,5	2,5
f. Suchbaatar	4	2	2	1
g. Nalaich	3,5	3	3,5	3,5
h. Umnu-gov	3	2	1,5	1,5

Map of Mongolia showing collection points



Annex 2



Blood Fractionation Unit - First floor - production area

Premises

I. Machinery

II. Processing room at -3°C-5°C

III. Cold store

IV. Preparatory room

V. Staircase (between I-st and 2-nd floor)

VI. Storage room (raw materials)

VII. Central heating installation

VIII. Laboratory

IX. Hydrolysis room

X. Store

XI and XII. Stores

XIII and XIV. Director's office

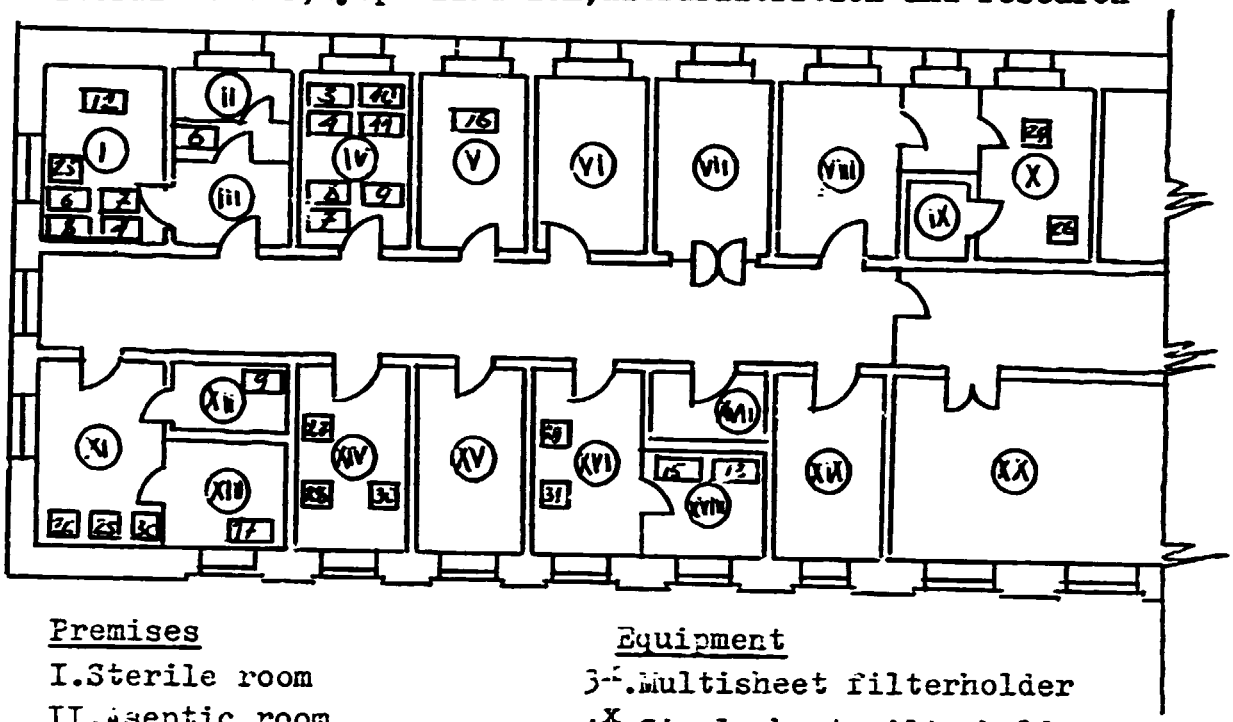
Equipment

1X. Pressure vessel
2X. Transport container
3X. Multisheet filterholder
5X. Pump Rubicon C
9X. Peristaltic pump
14X. Colloid mill
15X. Autocal pH metre
18X. Deep freezer
19X. Centrifuge CEPA TZ-3
20 . Cooling medium
21 . Centrifugal pump
22 . Compressor
23 . Cooling machine
24 . Supercentrifuge
27 . Autoclave
28 . Distillator
29 . Laboratory furniture
26 . Refrigerator

XEquipment supplied by UNIDO

Annex 3

Blood fractionation Unit - second floor - aseptic and sterile rooms, lyophilization, ultrafiltration and research



Premises

I. Sterile room
II. Aseptic room
III. Preparatory room
IV. Ultrafiltration room
V. Lyophilization
VI. Toilet
VII. Staircase
VIII. Recreation
IX. Store
X. Office of head technician
XI. Preparatory room
XII. Store
XIII. Ampoule filling and sealing
xIV. Washing room
XV. Office of research workers
XVI. Research laboratory
XVII. Store
XVIII. Research laboratory
XIX. Office of the head of the department

Equipment

3[x]. Multisheet filterholder
4[x]. Singlesheet filterholder
6[x]. Pressure filterholder
7[x]. Pressure pump
8[x]. Pressure tank
9[x]. Peristaltic pump
10[x]. Ultrafiltration apparatus
12[x]. Laminar flow hood
13[x]. Set of tools for automatic gel chromatography
15[x]. Autocal pH metre 83
16[x]. Ampoule filling and sealing machine
25. Incubator
26. Refrigerator
27. Autoclave
28. Distillator
29. Laboratory furniture
30. Dry heat sterilizer
31. Laboratory centrifuge

[x] Equipment supplied by UNIDO

Annex 4

RECONSTRUCTION AND RECONDITIONING WORKS IN THE ENLARGED BLOOD FRACTIONATION UNIT - TOTAL AREA 750 m^2

1. Reconstruction works

a) Partitioning walls in room VI (1-st floor), between rooms II and III (cold room, 1-st floor) and in room II (2-nd floor) were built.

b) Enlarging of the cold room for the fractionation (the old cold room was 8 m^2, the new one - 25 m^2). This included works on the demolition of walls and isolation, building of new walls and isolation, putting of new doors.

c) Reconstruction of the door of the lyophilization equipment

d) Constructing of shelves in two new store rooms

e) Reconstruction of the sewerage system of the whole department

f) Putting into shape of two washing rooms

g) Reconstruction of the cooling installation (repair of compressors and cooling system, connection of the centrifuges and reactors to the cooling system)

h) Painting of premises

2. Electrotechnical works

a) Installation of one main control panel

b) Installation of 4 switchboards

c) Outfitting of 300 m electric cables

d) Installation of 50 monophase and 10 threephase sockets

e) Installation of electric lines and lighting in the cold room

3. Mounting of laboratory furniture, thermostates, dry-heat sterilizers, etc.

4. Ensuring of safety with ignition gases at ampoule filling and sealing machine

INTERNATIONAL STAFF

Name	Nationality	Expertise	Service dates beginning	Service dates ending
1.Velu Kirov VELEV	Bulgarian	Chief Technical Adviser	14 May 1985 and 11 August 1986	15 June 1985 and 10 January 1987
2.Ludmil Georgiev BOZADJIEV	Bulgarian	Industrial Pharmacist (Expert in blood fractionation)	25 September 1986	24 January 1987
3.Ivan Iliev KJURKCHIEV	Bulgarian	Maintenance engineer	25 September 1986	24 January 1987
4.Ilina Lubenova BINEVA	Bulgarian	Expert in quality control and lyophilization	31 October 1986	28 February 1987

Annex 6

COUNTERPART STAFF

Name	Specialization	Service dates beginning	ending
A.Staff available at the beginning of the Project			
1.D.Dandii	Head of department National Project Coordinator	15.05.1985	Permanent position
2.U.Ganbat	Engineer of Fractionation	-"-	-"-
3.B.Saimchimeg	Technologist-Biochemist	-"-	-"-
4.E.Erdenetuia[X]	Research fellow	-"-	-"-
5.B.Narantuia	Assistant Research Fellow	-"-	-"-
6.C.Tungalag	Head technician	-"-	-"-
7.G.Baiarsaikhan	Mechanic	-"-	-"-
8.G.Ganbold	Mechanic	-"-	-"-
9.G.Nagsar	Technician	-"-	-"-
10.D.Darkhunchuluun	-"-	-"-	-"-
11.T.Javsan	-"-	-"-	-"-
12.H.Sarantsetseg	-"-	-"-	-"-
13.S.Bagnyam	Laboratory worker	-"-	-"-
14.S.Duguitsagan	Secretary interpreter	-"-	till the end of the project
B.Additionally recruited staff			
1.D.Dar[X]	Phisician-Biochemist	16.10.1986	Permanent position
2.N.Jamsranjav	Technologist-Biochemist	25.11.1986	-"-
3.J.Boldbaatar	Technician	21.11.1986	-"-
4.G.Ojunchimeg	Technician	15.10.1986	-"-
5.J.Ulambatar	Laboratory worker	16.10.1986	-"-
6.D.Ojunsaikhan	Laboratory worker	05.02.1987	-"-
7. vacant	Mechanic		
8.vacant	Laboratory worker		

[X]Long time sick leave

Annex 7

STUDY TOUR AND FELLOWSHIPS AWARDED

Name	Field	Place	Duration
1.Dr.D.Dandii	Organization of large scale blood protein fractionation	Bulgaria Hungary Czechoslovakia USSR	43 days
2.U.Ganbat	Technology and research	Bulgaria	2 months
3. Densma	Control and research	Bulgaria	2 months

Annex 8

FRACTIONATION SCHEME IN THE PRODUCTION OF ALBUMIN FROM BLOOD SERUM/PLASMA

retroplacental serum/donor plasma

protein 5-6 %
ethanol 8%
μ =0,14
pH=6,8
t^o = -3°C

---

supernatant

protein 4%
ethanol 25%
pH=6,9
μ =0,09
t^o = -8°C

precipitate
(discard)

---

supernatant

protein 2%
ethanol40%
pH=4,8
μ =0,09
t^o = -8°C

precipitate
(for immunoglobulin)

---

supernatant
(discard)

precipitate
protein 3%
ethanol 10%
pH=4,7
μ=0,01
T^o=-3°C

---

supernatant

protein 2%
ethanol 35%
pH=6,0
μ =0,05
t^o=-8 °C

precipitate
(discard)

---

supernatant

protein 1,5%
ethanol 35%
pH=4,8
μ =0,09
t^o=-8°C

precipitate
(discard)

---

supernatant
(discard)

precipitate
ALBUMIN

Annex 9

FRACTIONATION SCHEME IN THE PRODUCTION OF IMMUNOGLOBULIN FROM BLOOD SERUM/PLASMA

retroplacental serum or donor plasma

protein 5-6%
ethanol 8%
μ=0,014
pH=6,8
t^o= - 3°C

---

supernatant

protein 4%
ethanol 25%
pH=7,0
μ=0,09
t^o=-8°C

precipitate (discard)

---

supernatant (for albumin)

precipitate

protein 2%
ethanol 25%
pH=7,0
μ=0,09
t^o=-8°C

---

supernatant (discard)

precipitate

protein 1,5%
ethanol 13%
pH=4,8 ÷ 5,0
μ=0,024
t^o=-4°C

---

supernatant

protein 0,5%
ethanol 25%
pH=7,0
μ=0,05
t^o= - 8°C

precipitate (discard)

---

supernatant (discard)

precipitate

IMMUNOGLOBULIN

Annex 10

FRACTIONATION SCHEME IN THE PRODUCTION OF ALBUMIN FROM PLACENTAL EXTRACT

placental extract
protein 3%
ethanol 20%
μ=0,12
pH=6,9
t^o= -8°C

---

supernatant
protein 1%
ethanol 40%
μ=0,12
pH=4,8
t^o=-6°C

precipitate
(for immunoglobulin)

---

supernatant
(discard)

precipitate

protein 3%
1. pH=2,1
T^o=5-10°C

pH=6,5
2.[x] ethanol 9%
t^o=68°C (30min)

t^o=35°C
3. pH=4,4
t^o=10°C

---

supernatant
protein 0,5%
pH=4,85
ethanol 40%
t^o=-8°C

precipitate
(discard)

---

supernatant
(discard)

precipitate
ALBUMIN

x=in the presence of sodium octanoate

Annex 11

FRACTIONATION SCHEME IN THE PRODUCTION OF IMMUNOGLOBULIN FROM PLACENTAL EXTRACT

placental extract

protein 3%
ethanol 20%
μ =0,12
pH=6,9
t^o=-8°C

---

supernatant
(for albumin)

precipitate
protein 1%
ethanol 6%
pH=4,9
μ =0,08
t^o=-2°C

---

supernatant

protein 0,5%
ethanol 25%
pH=6,85
μ =0,08
t^o=-8°C

precipitate
(discard)

---

supernatant
(discard)

precipitate
protein 1%
ethanol 17%
pH=4,8 - 5,1
μ =0,01
t^o=-6°C

---

supernatant

protein 0,5%
ethanol 25%
pH=7,0
μ =0,015
t^o=-8°C

precipitate
(discard)

---

supernatant
(discard)

precipitate
protein 8-9%
pH=7,0
μ =0,06
DEAE-sephadex

IMMUNOGLOBULIN

EQUIPMENT PROVIDED BY UNIDO/UNDP

Name	Nos	Cost in US $	date of delivery	applied in
1.Double jacketed stainless steel vessel (pressure vessel) GB 320	1	11,684	10.86	fractionation
2.Transport container MB 200	2	2,133	-"-	-"-
3.Multisheet filterholder Pilot A 20Z	2	8,626	-"-	-"-
4.Single sheet filterholder DGF30A	2	3,427	-"-	-"-
5.Pump rotary type Rubicon 0	1	1,033	-"-	-"-
6.Pressure filter holder,dia 293mm with accessories	2	3,778	03.86	sterile filtration
7.Pressure pump,portable,membrane type with accessories	2	1,764	-"-	-"-
8.Pressure tank,20 l,stainless steel with accessories	2	842	-"-	-"-
9.Peristaltic pump with silicon tubing, 6x2 mm,Nos 20	4	3,229	-"-	fractionation
10.Modular design ultrafiltration apparatus with tie rods for 5 modules and 1 module and cleaning solution	1	5,455	-"-	ultrafiltration
11.Mohno pump Netzsch NL 15A	1	1,226	11.86	ultrafiltration
12.Laminar flow with two working places ASW-up 1200 with 12 Nos activated carbon cartridges	1	7,214	02.86	sterile work
13.Set of tools for automatic gel chromatography consisting of 13 items	1	5,776	12.85	quality control

Name	Nos	Cost in US $	date of delivery	applied in
14.Homogenizer (colloid mill)	1	3,584	02.86	fractionation
15.Autocal pH meter for solutions with two spare combined electrodes	2	2,540	05.86	analysis
16.Freeze-dryer USIFROID Type S.M.H. 50 with one major kit of spares	1	51,568	08.86	lyophilization
17.Automatic ampoule filling and sealing machine Rota R 910/Pa with change part set for 2 ml and 5 ml amp.,LF clean room unit 610/915, spare parts and Nos 40 sterilization trays	1	22,078	07.86	filling of final containers
18.Chest freezers-200 l	25	6,371	04.86	storage of raw materials
19.Centrifuge CEPA TZ-3	1	12,624	01.87	clarification of placental extract

Annex 13

PROGRAMME FOR RESEARCH IN THE FIELD OF PREPARATIONS OF HUMAN BLOOD PROTEINS

1. Improvement of laboratory quality control and further characterization of immunoglobulin and albumin preparations 1987-1990
   a) Study of the molecular composition of immunoglobulin and albumin by means of gel-filtration
   b) Determination of residual proteolytic activity in immunoglobulins isolated from different raw materials
   c) Methods for the stabilization of the physical properties, fragmentation processes and the specific activity of immunoglobulin preparations
   d) Study of the quantities of immunoglobulin classes IgG, IgA and IgM in the preparations
   e) Study on the presence of blood group substances in immunoglobulin and albumin preparations from placental sources
   f) Determination of antibodies in immunoglobulin preparations.
   g) Determination of the anticomplementary activity in immunoglobulin preparations

2. Development of methods for the production of specific immunoglobulins 1987-1989

3. Development of a method for the production of immunoglobulin for intravenous use 1987-1990

4. Research on a technology for the production of albumin from placental raw materials by means of thermal denaturation of ballast proteins 1987-1988

5. Experiments on the application of the ultrafiltration method for the removal of ethanol and concentration of immunoglobulin solutions 1987-1988

Annex 14

Draft

PROPOSAL FOR A FOLLOW-UP PROJECT TO CONSOLIDATE THE RESULTS ACHIEVED AFTER THE IMPLEMENTATION OF PROGRAMME "BIOMED"

I. OBJECTIVE

The objective of the follow-up project is to assist the Government of Mongolia to consolidate further the Blood Fractionation Unit at the Institute of Biological Products and Blood Transfusion, assimilate completely the technologies for the production of albumin and immunoglobulin from all available placental sources (retroplacental serum and placentae) and develop new technology for the preparation of immunoglobulin for intravenous use. These preparations are essential for Mongolia.

II. BACKGROUND

The Blood Fractionation Unit was established in 1971 and started with the production of gamma-globulin from retroplacental serum; later the production of albumin was introduced. Before the implementation of the Project "Biomed" 1500 l retroplacental serum could be processed to produce immunogloblin and albumin. The programme "Biomed" resulted in the enlargement and modernization of the Blood Fractionation Unit. The equipment supplied by UNIDO for the implementation of the Project and the equipment bought with local currency were installed. The production capacity was increased. Deep freezers were distributed in the main maternity homes of the country and better possibilities for the collection and storage of raw materials were created. It is expected that the quantity of serum would reach 3000 l per year and about 10,000 kg frozen placentae would be collected per year. Production facilities for the processing of these materials were created. Only the preparation of the placental extract is still connected with a lot of manual labour because suitable (decanting) centrifuge

is needed. In order to keep the available equipment in good shape some spare parts are needed. To develop the research work on specific immunoglobulins and to improve further the quality control some reagents,laboratory glassware and accessories are necessary.

The future development of the list of essential preparations produced by the Blood Fractionation Unit includes an immunoglobulin for intravenous use. This could be achieved after additional apparatuses for large scale chromatography are supplied.

III.OUTPUTS

- Albumin and immunoglobulin prepared by processing of placental extracts.
- Research programme introduced in the field of blood protein derivatives.
- Technology transferred for the preparation of immunoglobulin for intravenous use.

IV.ACTIVITIES

-Selection of equipment,reagents,spare parts according to priority needs, procurement and shipment of these

-Installation of equipment and performance of experimental and production work

-Recruitment and assignement of short-time experts to assist in the fulfilment of activities

V.INPUTS

a) Experts with wide knowledge in blood fractionation, quality control procedures and maintenance of equipment.
b) Training of local personnel
c) Equipment, spare parts, reagents.

Annex 15

FELLOWSHIPS' TRAINING PROGRAMMES

A. Programme of Mr. Ganbat on fractionation methods and organization of work at the department for the fractionation of proteins, Institute of Infectious and Parasitic Diseases, Sofia

13 February -14 April 1987

1. Study of the organization of work, safety regulations	16-20.02.'87
2. Study of the system of supplies with raw materials and reagents for the fractionation	23-27.02.'87
3. Study of the equipment used at the department a) cooling installation b) centrifuges; functions of the decanting centrifuge c) chromatographic equipment d) ultrafiltration system e) ampoule filling machine f) ampoule labeling machine g) lyophilization h) equipment for sterile work	2-13.03.'87
4. Study of the technologies applied for the production of blood derivatives; special attention to be paid to the production of specific immunoglobulins	2-13.03.'87
5. Experimental work on a method of isolation of albumin from retroplacental serum by thermal denaturation of ballast proteins	16-20.03.'87
6. Study of the final chromatographic stages of purification of the immunoglobulin for intravenous use ("immunovenin") produced at the department	23.03 - 3.04
7. Lyophilization technologies	1-3.04.1987
8. Visit at the laboratory for the production of animal sera	6-7.04.'87

9. Visit at the Institute of Blood Transfusion, Sofia to get acquainted with the organization of collection of specific plasma and production of specific immunoglobulins there — 8-10.04.

B. Programme of Mrs. Densma on quality control of blood preparations at the Institute of Infectious and Parasitic Diseases, Sofia

1. Acquaintance with the system of control of biopreparations in Bulgaria and regulations in this respect in the country (Visit at the Institute of State Control of Drugs) — 16-18.02.'87

2. Visit at the central control laboratory at the Institute of Infectious and Parasitic Diseases and study of the standardization documents and standards — 19-20.02.'87

3. Visit at the laboratory for the production of nutrition media. Control of nutrition media — 23-27.02.'87

4. Study of the control methods with experimental animals — 2-6.03.'87

   a) pyrogenicity

   b) toxicity

   c) hypersensitivity

5. Experimental work on the application of the methods: — 9-13.03.'87

   a) determination of molecular composition

   b) determination of plasminogen and plasmin

   c) determination of anticomplementary activity

   d) determination of immunoglobulin classes

6. Experimental work on the determination of antibodies (visits at microbiological and virological laboratories). Special attention to be paid to the determination of anti-staphylococcus and anti-influenza antibodies — 16.03 - 10.04

7. Study of the methods of determination of HBsAg and the antibodies against it — -"-

8. Study of the methods of determination of placental hormones — -"-