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20214

DP/ID/SER.A/1645
5 May 1993
ORIGINAL: ENGLISH

ASSISTANCE IN ADAPTATION OF MODERN TECHNOLOGIES FOR THE PRODUCTION OF ORAL PHARMACEUTICALS

SI/ROM/90/801/11-51

ROMANIA

Technical report: First mission of the consultant in November 1990*

Prepared for the Government of Romania
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of H.N. Bhargava, UNIDO consultant

Backstopping Officer: M. Quintero de Herglotz
Chemical Industries Branch

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Vienna

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* This document has not been edited.

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ACKNOWLEDGEMENT

I am grateful to Ms Emilia Cheles, Margreta Juvca and Ms Yvonne Cretil of Drug Producing Enterprise, Bucharest (IMB)* for their efforts, cooperation and patience throughout my consultancy such extensive work could not have been completed in a short time without their cooperation and guidance. I am also grateful to all the people at various institutions, who spared time for me from their extremely busy schedules. Everyone I spoke with, was extremely warm, hospitable, cooperative, honest, and open and generously provided all the information requested.

I am especially appreciative of Mr. O. Jannone of UNDP who invited me for this consultancy and guided me during my stay at Bucharest. If I have missed someone by name, it is not because of lack of gratitude but an oversight on my part. (Appendix I)

* IMB has been followed by SICOMED S.A. Trading Company in 1991.

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ABBREVIATIONS

BP	British Pharmacopoeia
CGMP	Current Good Manufacturing Practices
CTC	Chimica Trade Company ETA
ETA	European Free Trade Association
GC	Gas Chromatograph
HPLC	High Pressure Liquid Chromatograph
ICCF	Chemical & Pharmaceutical Research Institute
ICSMCF	Institute for Drug State Control and Pharmaceutical Research
* IMB (SICOMED S.A)	Drug Producing Enterprise, Bucharest (SICOMED S.A.Trading Company)
MOI	Ministry of Chemical Industries : Petrochemical & Chemical Products
MOH	Ministry of Health : Chemical Industries
PIC	Pharmaceutical Inspection Convention
RP	Romanian Pharmacopoeia
SOP	Standard Operating Procedure
SS	Stainless Steel
SSL	Stainless Steel with Low Carbon
UNDP	United Nations Development Program
UNIDO	United Nations Industrial Development Organization
USFDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
WHO	World Health Organization

* As from 1991 SICOMED S.A.

ABSTRACT

The purpose of my consultancy was to evaluate the existing facilities of IMB, the largest pharmaceutical plant in Romania and recommend additional equipment for film coating and microencapsulation. I evaluated the current development, production, and testing system of IMB.

I carried out my assignment by interviewing executives, research, production, quality assurance regulatory, safety testing and administrative personnel and on site visits to three institutions.

IMB was evaluated for its production capacity, sales, earnings, research, production, and testing equipment, training and education of personnel and compliance with Good Manufacturing Practices.

The plant was built in 1962. IMB has well trained, motivated, administrative and research staff capable of adopting new technologies and translating them into production. The IMB has production equipment to manufacture 5 billion tablets and test them. However, most of the equipment though adequate in 1962, is old and not well maintained. The physical plant shows signs of long neglect, IMB has not kept pace with technology to either procure new equipment or modify the facilities. The poor conditions of the plant, old equipment, poor quality and access to limited raw materials, and limited testing equipment have resulted in pharmaceuticals not of acceptable quality in the international market.

Of the 153 tablet and capsule products 53 are sugar coated, some of them are coated unnecessarily to overcome deficiencies of the tablet and others could easily be switched to a more efficient and cost effective film coating resulting in improved economies of production.

Personnel at IMB need education, training and exposure to modern technologies of film coating, microencapsulation, and sustain release dosage forms to improve efficacy, stability and quality of their products.

UNIDO should send research personnel from IMB for training in film coating in Western Europe, procure laboratory equipment for development and testing of film coated products and initiate compliance with CGMP by assiting in the writing of Standard Operating Procedures (SOP'S) for maintenance of all equipment, the manufacturing processes and validate all processes through consultant as soon as possible.

Only with UNIDO's financial and technical assistance could IMB adapt to modern technologies and produce quality pharmaceuticals at a reasonable price.

OBJECTIVE

The purpose of the consultancy was to assist UNIDO in providing technical assistance to the Romanian pharmaceutical industry to adapt modern technologies in production of film coated tablets, microencapsulation of drugs for either delayed or sustain release of the therapeutic agents.

(ii) Evaluate existing pharmaceutical production unit with physical and manpower resources to embark on production of film coated tablets and microencapsulated sustain release dosage forms.
(iii) Recommend additional development, production, and testing equipment for the technologies involving film coating, microgranulation and microencapsulation.
(iv) Provide data on quality parameters and specific consumption of raw materials and auxiliary materials for such purposes and select them for locally available ones.
(v) Recommend candidates for training in production and testing of film coated tablets.
(vi) Advise to resolve instability of Ascorbic Acid tablets.
(vii) Advice on stability testing of pharmaceuticals for validation of expiration date.
(viii) Prepare interim report with recommendations.

METHODOLOGY

The principle methods utilized in carrying out this consultancy were interviewing administrative, research, product development, and quality assurance staff from three institutions involved with development, testing, production and quality assurance of pharmaceuticals in Romania and for export purposes.

Site visits included visits to administrative offices, production area, physical, chemical, microbiological safety or clinical testing laboratories, quality control laboratories and warehouses with a keen eye on compliance with Current Good Manufacturing Practices (CGMP). The institutions were evaluated for:

1. Experience
    (a) How long in business
    (b) Type and variety of products produced or tested
    (c) Experience with pharmaceutical dosage form development
    (d) Experience with sustained action dosage form design and their development
2. Technical Knowledge
    (a) Education and experience of personnel
    (b) Familiarity with pharmaceutical processes
    (c) Familiarity of pharmaceutical dosage form testing In-Vitro and In-Vivo
3. Good Manufacturing Practices Compliance
    (a) Building
        (i) Physical layout
        (ii) Air filtration
        (iii) Climate control
        (iv) Ventilation

(v) Sanitation

(vi) Maintenance

(b) Equipment

(i) Location, design and size of equipment

(ii) Materials of construction, of production and transfer and storage equipment

(iii) Equipment cleaning and maintenance

(c) Control of Components and Drug Products

(i) Testing of raw materials and packaging components

(ii) Production process control

(iii) Testing of finished products

(d) Documentation

(i) Master batch record

(ii) Equipment identification

(iii) In process sampling and testing

(iv) Written procedure deviation

(v) Material control

(vi) Packaging control

(vii) Finished product testing

(viii) Finished product sampling plan

(ix) Methods of analysis

(x) Holding and warehouse

(xi) Stability testing and expiration date validation

(xii) Recalls

(xiii) Inspection by regulatory agency

4. Sales and Distribution

5. Management

(a) Management of research

(b) Commitment to quality, performance, and safety

During the course of my assignment, I visited IMB, Chemical and Pharmaceutical Research Institute, Institute for Drug State Control and Pharmaceutical Research and Chimica Trade Company (Appendix II).

INTRODUCTION

The government of Romania has demonstrated strong commitment to the delivery of social services and has made great strides in developing necessary infrastructure, manpower and national programs for health services, especially through expansion of primary and preventive health care. However serious problems need to be overcome in the quality and efficiency of the services.

Availability and accessibility of pharmaceuticals are key components of any health system. Drugs serve multiple social, psychological and political functions; they are not simply to treat or prevent diseases. Romania has recognized, that appropriate drugs are a necessary element of a health system. It is difficult to provide good quality care without appropriate drugs. On the other hand availability of appropriate drugs represents an insufficient element of a health system. Merely having drugs is not enough to ensure, the processes of regulation, distribution, storage, prescription and pricing and use should work well.

To implement the policies of health care for all, the government of Romania initiated a policy of national drug independence. The policy required minimum importation of chemicals, intermediates, bulk drugs, formula excipients and finished dosage forms. The other aim of the policy was to reduce allocations of foreign exchange for drugs and encourage local production of pharmaceuticals.

Romania has developed its own pharmaceutical industry capable of not only fulfilling 90% of the pharmaceutical needs of the country, but also producing some pharmaceuticals for export as well.

The production of pharmaceuticals is under the Ministry of Chemical Industries coordinated through SINTOFARM, S.A. (previously Industrial Corporation of Drugs and

Cosmetics) which is an association of 24 state chemical factories producing a wide range of products. There are at present six pharmaceutical production units namely: Drug Producing Enterprise at Bucharest (IMB), producing bulk drugs and finished dosage forms, Antibiotice at Iasi, producing bulk antibiotics, Armedica at Tirgu Mures, producing bulk drugs and finished dosage forms, Biofarm at Bucharest, producing bulk chemicals from plant and animal extract, Sintofarm at Bucharest, producing bulk chemicals and Terapiat at Cluj, producing bulk chemicals and finished dosage forms. These factories collectively produce 30 therapeutic agents from plant extracts, animal extracts or synthesize them. Romania also produces starch and sugar locally. Remainder of the therapeutic agents and excipients in the finished dosage forms are imported.

In the area of drug procurement, and supply management the government procures imported pharmaceuticals through Chimica Trade Company and locally produced pharmaceuticals through the Ministry of Health (MOH). The MOH is responsible for distribution and quality of the pharmaceuticals with 20 regional stores and well developed network pharmacies throughout the country.

Romania has established a physical and manpower infrastructure to ensure the quality of pharmaceuticals. The MOH through the Institute of Drug State Control and Pharmaceutical Research (ICSMCF) regulates the quality of drugs in Romania.

ICSMCF monitors registration of a drug prior to its national distribution of imported or locally produced drug. For registration in Romania the drug must go through a New Drug Approval process and should be under clinical efficacy and safety testing at three institutions in Romania and must be registered as a drug in the country of its origin. ICSMCF also monitors the quality and integrity of already registered drug products whether produced locally or imported.

ICSMCF has developed Romanian Pharmacopoeia and is in the process of preparing its 10th edition describing specifications and test methods for raw materials and finished dosage forms. It is also a member of Pharmaceutical Inspection Convention (PIC), a group of European

Free Trade Association which permits mutual recognition of inspection of pharmaceutical manufacturing units.

ICSMCF inspects local manufacturing units frequently and tests their products for quality and integrity. All imported raw materials used in the production of pharmaceuticals are tested and every production batch of high risk drugs like cardiovascular drugs, hormones, antibiotics, etc. is tested and certified before its distribution.

ICSMCF is also responsible for "recall" or "withdrawal"of a drug product found to be unsafe for use. ICSMCF has removed some products from the market in the last two years and has well established infrastructure to do so.

In spite of the notable achievements there are some serious problems. The infrastructure of drug production, supply and management system is heavily strained. Manufacturing facilities, production and testing equipment and technologies at the various institutions are old, outdated and have not kept pace with significant advances in pharmaceutical technology to maintain quality of finished dosage forms. The quality of locally produced pharamaceuticals in regards to their stability and efficacy are below international standards and should be improved to compete in the international market which is only possible by adopting modern technologies.

Additionally the unexpected changes in the government policies to preserve foreign exchange, the manufacturing units would not be allocated foreign exchange to import raw materials, bulk drugs, equipment, etc. used in the manufacture of pharmaceuticals. Each manufacturing unit should earn its own foreign exchange to import the necessary items, through export of its products, making it necessary to improve the quality and efficacy of locally produced pharmaceuticals.

FINDINGS

7.1 Background:

I visited IMB Bucharest and its sister institutions responsible for development, production, testing and regulations of pharmaceuticals in Romania.

The IMB the largest pharmaceutical manufacturing unit in Romania was established in 1962. IMB synthesizes three bulk drugs namely: Ascorbic Acid, Sulfa drugs, and Propranolol. Its major activity is production of various finished dosage forms. It produces 300 products in semi-solid (emulsion,suspension) form for oral, injectable and topical use; injectable drugs, large volume parenterals, tablets and capsule with a variety of pharmacological activities like analgesics, antimicrobials, metabolic preparations, antimycotic preparations, antihistamines, corticosteriods, tranquilizers, etc. (Appendix III), for the treatment or prevention of a variety of diseases. Most of the finished dosage forms are generic formulations of already marketed drugs in the international markets, but the IMB has developed some new drugs with new therapeutic claims. Most popular of such products are Gerovital and Aslavital.

The IMB produces 153 tablet and capsule formulations and has production capacity to produce 5 billion tablets per year. Fifty-three of its tablet and capsule formulations are sugar coated.

The IMB under an agreement with two multinationals namely Pfizer and Ciba-Geigy, produces two film coated products for local distribution only. The 90% production of the IMB is distributed locally and 10% of its production is exported earning precious foreign exchange.

The IMB has consistently shown increases in its sales and the

net income for the past three years. (Appendix IV)

7.2 Personnel:

IMB has a work force of 4005 employees of which about 800 are college graduates in a variety of disciplines. The management is well structured to produce pharmaceuticals at competitive prices. The workers are healthy, hard-working and intelligent with appropriate training or education, and are familiar with pharmaceutical processes to produce quality pharmaceuticals. The average worker has several years of experience in one of the manufacturing processes of solid pharmaceuticals like mixing, granulation, drying, compression, or sugar coating etc. The workers are not exposed to modern technologies like microencapsulation, film coating, enteric coating or spray drying. The use of old equipment, poor quality of raw materials, old physical plant, and very low wages have an adverse affect on the morale of the workers resulting in a lack of motivation and pride. The problem has further compounded because of uncertainties about the future of IMB. In the near future, IMB may become an independent private enterprise with workers having 50% equity in the new enterprise.

7.3 Buildings:

The IMB occupies several large buildings spreading over 72 square km. The buildings are large with adequate square foot area to house various departments like warehouse for storage of raw materials and finished goods, production of solids (tablets and capsules) and their packaging, and production of semisolids and liquids, and production of injectables. Additionally, there are separate facilities for quality assurance laboratories, research and administrative offices.

Separate facilities exist for the synthesis of bulk chemicals namely Ascorbic acid, Sulfa drugs and Propranolol which are prepared at the same location.

Most of the buildings are over 25 years old and neither proper

plumbing, sanitation, water, air or waste treatment facilities expected in a modern pharmaceutical manufacturing unit exist.

Production and packaging facilities for all the solid dosage forms are housed in one building. The mixing granulation, sieving, drying, and compressing for all the tablet and capsule formulations takes place in one large hall with a very high ceiling, no segregation of production areas for each product, probably resulting in of cross contamination of the products. Additionally, IMB manufactures the finished dosage form of various antibiotics like penicillin, ampicillin, amoxicillin, tetracycline, etc. in the same room, a practice forbidden in modern pharmaceutical facilities. None of the facilities for storage or production at IMB have climate control, necessary for storage and production of moisture and heat sensitive raw materials or finished products.

The lighting in the rooms are adequate but neither the sanitation or ventilation are adequate. The windows are kept open allowing the unfiltered air in the entire area and there is an open drain running through the production hall making the environment unsanitary.

The coating of all the products (sugar coating) is performed in one large room with a similar environment as the tablet compression room.

The packaging facilities for tablets and capsules are separate and the area although not climate controlled has separate lines, well segregated packaging lines. Each capsule filling machine is well segregated.

The products made for the multinationals (two film coated products) for local distribution are prepared and coated in the segregated areas in separate rooms reducing the chances of cross contamination. However, even these rooms lack proper ventilation,

air and water treatment and climate control.

The buildings were well designed for 1962 but have not been well maintained or updated with time to comply with Current Good Manufacturing Practices (CGMP). The present facilities are in need of major rehabilitation with proper ventilation, climate control, water, air and, waste treatment units and separate, segregated areas to produce each product.

7.4 Production:

IMB has the production capacity to produce 5 billion tablets annually and has equipment for mixing, drying, sieving, compressing, coating and capsule filling (Appendix V). Some of the equipment purchased in the past few years like a Kilian RF, Manesty tablet press, Uhlmann and King packaging machine, H & K capsule filling machine are very good, high speed machines with appropriate design and made of proper alloy (stainless steel) to comply with CGMP. However, the other equipment like the mixer, tray dryer, fluid bed dryer, tablet press, and coating pans are not only old but also neither properly designed nor made of appropriate alloy. For example some mixers are not well designed, and coating pans are made of improper alloy, copper, instead of stainless steel.

Since most of the tablets and capsules are prepared utilising poor quality of raw materials, improper storage conditons, and outdated, old, inefficient equipment, tablets have high moisture content, prepared with insuffiecient or inappropriate binder and thus are not hard enough to withstand the rigors of transportation, film coating or consumer abuse.

In the past decade there have been significant advances in phamaceutical technology. New polymers allow simplification of coating processes, development of sustained release drugs, produce a coating with wide range of physiochemical properties. In

addition, improved equipment has emerged that is specifically designed for film coating applications. The techniques for evaluating film properties (moisture/vapor transfer rates, elasticity, tensile strength, etc.) allow one to design a coating to meet specific requirements of a core tablet.

Numerous advantages can be cited for film coating in place of sugar coating. Some of the most obvious are:

1. Reduction in coating time and material cost resulting in significant savings. Coating costs are reduced by 50% or more if the tablet is film coated instead of sugar coated.
2. No significant increase in tablet weight.
3. No undercoat or waterproof coat required.
4. Durability and resistance to chipping and cracking.
5. Allows for monogram indentification of the product.
6. Provides effective protection to light, air, and moisture thus improving efficacy and stability.
7. No adverse effects on disintegration time thus making drug readily bioavailable.
8. Standardization of process and material.
9. Film coating can be automated.
10. Film coated tablets are pharmaceutically elegant.

To overcome the inadequacies in the tablet IMB sugar coats them resulting in an expensive end product. Of the 153 tablet and

capsule products 53 are sugar coated and most of them are sugar coated unnecessarily. Some of the products which do not need coating at all are:

1. Aspirin
2. Paracetamol
3. Griseofulvin
4. Propanolol
5. Clotrimazole
6. Nicotinic Acid
7. Meprobamate
8. Hydromorphone
9. Nitroglycerin
10. Calcium Carbonate, etc.

Products that should be switched to film coating:

1. Vitamin C
2. Folic Acid
3. Vitamin A
4. Vitamin A & D
5. Vitamin E
6. Thyroid
7. Tebemycin
8. Guanethedine
9. Sulfacetamide
10. Sulfathiazole
11. Rifampicin
12. Tricomycin, etc.

Film coating significantly improves the stability and therapeutic efficacy of the drugs which degrade via hydrolysis, oxidation or photolysis which encompasses the majority of drugs.

Some examples of drugs that degrade via hydrolysis : Procaine, benzocaine, aspirin, dexamethasone, penicillin, ampicillin, peptides, alkaloids, atropine, nitroglycerine, spirolactone, glutethimide, barbiturates, chloramphenicol, steroid oxines, lidocaine and many more. Examples of drugs which degrade via oxidation are: ascorbic acid, morphine, paraldehyde, amylnitrite, phenothiazine, fatty acids, vitamins, methyl-dopa, catecholamines, isoproterenol, sulfonamides (sulfa drugs), propanolol and many more.

7.5 Quality Assurance:

Drug Enterprise has quality assurance laboratories housed in a large building. The laboratory is responsible for testing of incoming raw materials, in process tests and finished products. The laboratory performs tests for physical, chemical, and microbiological integrity of raw materials, intermediates, and finished products. IMB uses compendial specifications and test methods of British Pharmacopoeia (B.P.), United States Pharmacopoeia (U.S.P.), or Romanian Pharmacopoeia (R.P.) for testing raw materials and finished products and have their own specifications for in process testing. In addition to testing the existing products, retaining samples for stability testing and quality assurance laboratories also develops new methods for various dosage forms.

At IMB the products made for export are scrutinized more vigorously than products for local use. Each batch of products for export tested at the plant is further tested by the Institute for Drug State Control and Pharmaceutical Research (ICRP), an agency of the Ministry of Health, responsible for the regulation and quality assurance of pharmaceuticals in Romania. The products made for multinationals for local use are tested in the factory and at the multinational's quality assurance laboratories before their distribution in Romania.

Quality control laboratory has some modern equipment like HPLC, GC, spectrophotometers etc., but not enough to perform adequate testing of such a large enterprise making a variety of products (Appendix VI). The laboratory has only one High Pressure Liquid Chromatograph (HPLC) and two apparatus for dissolution testing. Dissolution testing equipment is locally made and is not in compliance with international standards or compendia like B.P. and U.S.P. Additionally the spare parts and auxillary supplies like columns for the HPLC are scarce so even one HPLC is not adequately used. Most of the products are tested by the wet analysis and the testing is minimal. The laboratory performs few in process tests. The only in process test for tablets and capsules is weight variation and only four balances are available to perform the testing for the 153 products. In general the equipment is well maintained, but is old and additonal equipment and supplies are needed to do adequate testing of raw materials, in process and finished dosage forms.

IMB products for export have expiration of three years and the time is common for all the products. The expiration date is not validated by the laboratory test results and there is no protocol for stability testing. Secondly the Enterprise has not developed validated stability method of assay for the therapeutic agent in their formulations. The products distributed locally have no expiration date.

I discussed and advised them to follow the stability test protocol under the conditions of stress (high temperature and humidity) and ambient room temperatures, distributed to pharmaceutical manufacturers by the World Health Organization (WHO) and the United States Food and Drug Administration (USFDA).

IMB has poor documentation for the master and the batch records, good records for holding, warehouse, and finished product testing, equipment identification, process validation, in process

testing and sampling plans, written procedure deviation, material control, packaging control, finished product sampling plan. The IMB has only one record for master as well as batch record and that contains limited information. The Enterprise is inspected by regulatory agency regularly and has recalled products if asked to do so by regulatory agency. In general the Enterprise does not comply with Current Good Manufacturing Practices (CGMP) as described in "Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce." Failure to comply with CGMP would retard the growth of its export market.

7.6 Research:

IMB has a small research department responsible to design and develop various dosage forms. The research staff in the pharmaceutical product development department consists of 20 scientists and technicians. The development is divided into two groups, one responsible for the development of all solid dosage forms and the other responsible for the development of other dosage forms like liquids, semisolids, and injectables. IMB does not have in house expertise in the area of analytical method development which is an integral part of the product development and this function at present is performed by Quality Assurance Laboratories.

The research department develops generic dosage and scales them to production. To date the department has developed over two hundred products, a major accomplishment.

The scientists are not able to work at their maximum potential as they can only use a few excipients and are not exposed to new raw materials or technologies commonly available in western countries.

I worked with the research staff to improve stability of Ascorbic acid tablets. The present product changes its color from colorless to a brown colored product as the Ascorbic acid oxidizes

to dehydro ascorbic acid. The reaction is catalized by copper ions and the rate of reaction is dependent on the pH. Addition of a small amount of chelating agent like Ethylene Diamine Tetracetic acid (EDTA), small amount of citric acid and removal of moisture and air would probably resolve the problem.

The research laboratories have very limited laboratory equipment to develop pharmaceutical tablets and capsules or test them properly. There is no pilot plant facilities to validate the formula and process before preparing production lots of a dosage form. The research laboratory has no library with international journals and books and lack of ready accessibility to scientific literature has kept scientists unaware of many technological advances of recent years. Appendix VII has a list of books IMB should have as reference books.

The research staff at IMB has no appropriate education, training or experience with the science and art of new coating technologies like film coating, layered coating or enteric coating of beads, tablets or capsules, microgranulation, microencapsulation, intranasal drug delivery systems, transdermal drug delivery systems, or sustained release oral dosage forms.

The staff is educated, trained and has a familiarity with pharmaceutical processes and is capable of doing well and learning new technologies in a short period of time as demonstrated by their ability to produce good quality film coated tablets for multinationals.

The safety and efficacy testing of the finished dosage forms developed by the IMB is conducted by the ICCF.

The Chemical and Pharmaceutical Research Institute (ICCF) is involved in the research and development of pharmaceuticals and cosmetics. It is located in Bucharest and has branches in Iasi

for research in synthesis and isolation of antibiotics and for cosmetic formulations, in Brasov for cosmetics and pharmaceutical raw materials. The institute has laboratories and pilot plants to prepare modest size batches. The main activity of the institute is the preparation of chemicals and formulations of already marketed pharmaceuticals in the international market, but not produced in Romania. The institute is involved in the synthesis, and isolation from plants, or animals and the synthesis of new therapeutic agents, as well. The institute also develops new processes for wide variety of disciplines, development of high purity chemicals, biological reagents and diagnostic chemicals.

The institute has well developed complex departments involved with analytical and pharmacodynamic determinations of pharmacological testing and safety testing of drugs in animals. The main research interests of the institute are in the synthesis and testing of antimicrobial agents, hormonal and antihormonal substances, enzymes and enzyme inhibitors, metabolic substances, drugs for central nervous system, local anaesthetics, antihistamines, drugs for cardiovascular system and digestive tract.

Institute performs safety testing and clinical investigations in collaboration with ICSMCF.

The institute has pharmaceutical research laboratories capable of developing finished dosage forms such as tablets, capsules, semisolids (emulsion and suspension) and injectables for human and veterinary use. The pharmaceutical research laboratories develop and test cosmetics for local use, as well.

Conclusions

Based on my plant visit, meetings with scientists at various institutions, and examining various products and processes at IMB, I am convinced that IMB should utilize more efficient and cost effective modern technology of film coating, in place of sugar coating for most of its sugar coated products.

Drug Enterprise has adequate human resources with adequate education and experience to adapt to film coating technology and develop sustain release dosage forms after appropriate training. For a long term goal IMB needs to develop a research infrastructure of facilities, manpower, and testing equipment in laboratory and human clinical trials to develop new drugs for Romania and export.

At present IMB utilizes outdated old equipment, poor quality and limited raw materials in the formulation of various dosage forms. The present production system is in need of physical rehabilitation and replacement of most of the manufacturing, and testing equipment. All these and almost no adherence to Current Good Manufacturing Practices have resulted in poor quality of pharmaceuticals.

Recommendations

1. UNIDO should assist IMB in adopting efficient and cost effective film coating which would lower the cost of production of tablets significantly, but the economic impact of the change would be realized in 2-3 years.

2. UNIDO should send four scientists from IMB to study film coating at Rohm Pharma, Germany as soon as possible.

3. UNIDO should procure laboratory equipment to develop and test film coated tablets (Appendix VIII).

4. All equipment should be purchased with service contracts from the manufacturer for 3-5 years. Usually it is easy to procure equipment but difficult to maintain, since most of the equipment needs highly trained technicians to service it. A good service contract would save time and money in the long run.

5. Spare parts for 3-5 years should be ordered for all development as well as testing equipment.

6. IMB should procure various raw materials and auxiliary laboratory supplies to develop and test film coated tablets, conventional and enteric coated. (Appendix IX)

7. UNIDO should postpone the assistance to IMB for development of sustain release dosage forms for a two year period. IMB needs to select appropriate drug candidates and develop an infrastructure for research and testing of sustain release dosage forms in animals and humans.

8. IMB should initiate the implementation of CGMP and write Standard Operating Procedures (SOP) for cleaning, and maintaining all production and testing processes.

9. UNIDO should recruit a consultant to assist IMB to write SOP's and validate processes (4 months consultant time).

10. IMB should modify some of their current formulae of tablets to be film coated. The tablets should exhibit adequate hardness to withstand abuse of film coating. Modification of formulae may require change in quantity or specifications of raw materials.

11. IMB should investigate the use of corn starch as a binder (10-12% of formula) in place of potato starch to prepare tablets of adequate hardness.

12. IMB should develop second generation of cardiovascular drugs like Enalapril maleate and hypoglycemic drugs like Glyburide and anti-inflammatory drugs like Sulindac.

Appendix I

List of People Interviewed

1.	Ms. Cerasela Andrei	Interpretor, IMB
2.	Mr. Ion Arseleanu	Director IMB Bucharest
3.	Dr. D. Burghelea	Deputy Director I.C.C.F.
4.	Dr. A. Candidatu	Manager Analytical Services, I.C.S.M.C.F.
5.	Ms. Emilia Cheles	Sr. Research Pharmacist, IMB
6.	Dr. V.V. Cosofret	Manager Analytical Services, I.C.C.F.
7.	Yvonne U. Cretil	Sr. Research Pharmacist, I.C.C.F.
8.	Dr. Dumitru Dobrescu	Director, I.C.S.M.C.F.
9.	Dr. Lili Dobrescu	Head Quality Control, IMB
10.	Ms. M. Giuurgiu	Chemical Engineer, Armedio
11.	Mr. O. Jannone	Resident Representative U.N.D.P.
12.	Margreta Jurca	Production Engineer, IMB
13.	Gheorghiu Mihai	Manager Industrial Drug and Cosmetic Corp.
14.	Ms. Victoria Stacojiu	Production Supervisor, IMB

15.	Dr. V. Subtirica	Secretary Commision of Drugs, I.C.S.M.C.F.
16.	Teodor Teodorescu	General Manager, IMB

Appendix II

List of Places Visited

1. United Nations Development Program Offices
2. IMB, Bucharest
3. Institute for Drug State Control and Pharmaceutical Research ICSMCF
4. Chemical and Pharmaceutical Research Institute, ICCF
5. Ministry of Health, Bucharest
6. Sintofarm, Bucharest

APPENDIX III

LIST OF PRODUCTS

	1988 Quantity	1988 Value -thov lei-	1988 Pieces -thov-	1989 Quantity	1989 Value -thov lei-	1989 Pieces thov-	1990 Quantity	1990 Value -thov lei-	1990 Pieces thov -
0	1	2	3	4	5	6	7	8	9
Antimicrobial antibiotics and chemotherapeutic agents									
Ampicillin x 20 caps.	3170965	286021	63420	4073285	439570	97466	2923700	263798	58474
Oxacillin x 12	757000	46555	9084	569063	34997	6829	350699	20338	3963
Tetracycline HCl x 16 capsules	6415000	74735	102640	1089000	12687	17424	1480680	17250	23691
Total no.of capsules		407311	175144		487254	121719		301336	86133
Coly - Mycin x 20	169037	6237	5071	72140	2662	2164	-	-	-
Erythromycin ,ropionyl x 25	1726966	123910	43174	1386793	99502	34670	611480	43874	15287
Tetracycline HCl x 16 tablets	720930	7736	11550	5044609	59382	38715	2930451	32139	47687
Total no.of tablets		137933	59781		162046	125547		76063	62974
Tuberculosis preparations									
Ethambutol x 5o	240	14	-	151540	9130	7577	101370	6108	5069
Rifampicin x 1oo	-	-	-	58210	34053	5821	-	-	-
Sicordol x 1oo	34900	79682	3490	139960	86649	13996	44460	27525	4446
Total no.of.tablets		79696	3490		129352	27394		33633	9515

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Pyrazinamide x 2o	166630	3167	3334	190040	3611	3800	261640	4971	5233
Tebemycin x 2o	-	-	-	- 2o	- 1	-	-	-	-
Total no.of tablets		3167	3334		3612	3800		4971	5233
Antimycotic and antitrichomoniasis preparations									
Clotrimazole x 12	122721	2319	1473	137200	2593	1647	45760	165	549
Griseofulvin x 6o	149480	7877	8969	100680	5306	6041	29000	1528	1740
Stemycin x 2o	790470	21390	15809	1124480	30428	22490	133320	3608	2666
Fasigyn x 4	196179	4371	735	217320	4842	869	151554	4045	720
Metronidazole x 2o	420400	4162	8408	-	-	-	163817	1622	3276
Tricomycen x 15	217360	6249	3260	170520	4902	2558	161560	4245	2423
Total no.of tablets		46368	38704		48071	33605		15573	11380
Thyroid preparations									
Thyroton x 6o	140560	365	8434	157080	408	9425	35400	92	2124
Metabolic preparations-vitamins									
Nicotinic acid x 4o	53564	117	2343	132360	265	5294	17920	36	717
Vitamin B_1 x 4o	868330	1476	34733	809260	1374	32330	380960	648	23238
Vitamin B_6 x 2o	866751	26089	17335	370630	11157	7413	308520	9236	6170
Vitamin C 200 x 2o	3340500	12326	66810	8014725	29574	160295	4487975	16561	89760

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Electovit x 30	1504593	3761	45135	482539	1206	14476	624476	1561	18753
Viplex x 30	764235	2331	22927	1470800	4486	44124	403374	1230	12101
Vitamin A x 50	929792	2696	46490	235240	682	11762	250440	726	12522
Vitamin A + D_2 x 50	517340	1216	25867	503640	1184	25182	152880	359	7644
Polyvitamins x 100	185420	608	18542	343810	1128	34381	93120	305	9312
Total no.of tablets		51620	280182		51056	335267		30712	180198
Riboflavin phosphate 100/2	9980	818	998	7556	620	756	2250	484	225
Vitamin A palmitate 10/1	55750	412	557	90200	667	902	48100	356	481
Vitamin B_1 100 mg, 100/2	55310	9071	5531	122430	20087	12248	10300	1689	1030
Vitamin B_6 250 mg, 100/5	48920	6100	4892	15055	1775	1505	11100	1309	1110
Vitamin C 10 % 100/5	128810	10344	12881	58300	4547	5830	44590	3478	4459
Vitamin B_{12} 50 gama 100/1	73965	3903	7396	68150	3271	6315	45900	2203	4590
Vitamin B_{12} 1000 100/1	18015	4594	1802	16400	4100	1640	11520	2882	1152
Vitamin D_3 2,000 IU 1/1	153000	237	153	68500	106	68	269000	417	269
Vitamin D_3 6,000 IU 100/2	4570	634	457	4437	614	44	-	-	-
Vitamin A + D_2 1/3	95150	214	95	104700	236	104	72000	162	72
Vitamin D_2 400,000 IU 1/1	475200	486	475	593000	622	593	349400	306	349
Vitamin D_2 600,000 IU 1/1	246450	294	246	307800	325	307	148500	157	148
Vitamin D_2 600,000IU 1/3	263100	605	263	272750	627	273	186000	428	186
Vitamin E 3 % 5/1	93900	312	470	100000	333	500	54000	144	270
Vitamin E 30 % 5/1	5900	29	30	4100	21	20	7000	35	35

0	1	2	3	4	5	6	7	8	9
Vitamin B_1 1o mg, 1oo/1	3oo	32	3o	195o	211	195	454	49	45
Vitamin PP 1o/2	59oo	48	59	1125o	92	113	8ooo	66	8o
Total no.of ampoules		38133	36335		38254	31893		14165	14502
Calcium therapy									
Calcium, effervescent x 2o	1425734.	2o888	28516	1742940	25534	34859	559ooo	8159	11180
Calcium lactate x 1ooo	33903	1435	38903	52ooo	1919	52ooo	1221o	45o	1221o
Total no.of tablets		22323	67419		27453	86859		8639	23390
Calcium and magnesium gluconolactate 1o/2	62200	555	622	1o7o1o	955	1o7o	9415o	84o	942
Calcium gluconate 5o/5	124471	4o83	6223	98ooo	3214	49oo	675oo	2214	3375
Calcium gluconate 5o/1o	122800	5231	614o	72233	3o77	3611	51o15	2173	2551
Calcium pentotbenate 5/15	128500	869	642	13oo5o	879	65o	3394o	229	17o
Total no.of ampoules		1o738	13627		8125	1o231		5456	7o38
Tonic preparations									
Folic acid x 3o	22o86o	5o7	6626	267940	616	8o38	78800	181	2364
Aslavital x 25	23o14o	2385	7oo3	112590	1160	2815	142180	1464	3554
Energizing tablets x 2o	23o2co	3348	5604	173o96	2128	3562	173560	2074	3471
Gerovital x 25	532600	378	13315	428320	1042	1o7o8	41o64o	1766	1o266
Meclofenoxat x 2o	6o7755	2583	12155	823o8o	3oo4	16461	259320	946	5186
Pyrivin x 2o	1372o	27oo	274	-	-	-	1558o	3o66	311
Total no.of tablets		124o1	44977		8750	41584		9497	25152

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Aslavital 6/5	80400	567	482	122525	864	735	87178	615	523
Gerovital 6/5	150364	692	902	168000	773	1003	133396	614	800
Total no.of ampoules		1259	1384		1637	1743		676	1323
Hypnotics and Sedatives									
Bromoval x 2,000	2326	540	4652	2721	632	5442	31	7	62
Distonocalm x 30	2013340	16710	60400	1731000	14367	51930	1122760	9319	33633
Total no.of tablets		17250	65052		14999	57372		9326	33745
Calcium bromate 100/10	7700	852	770	5600	620	560	3000	332	300
Total no.of.tablets	7700	852	770	5600	620	560	3000	332	300
Neuroleptics									
Chlordelazine x 50	234760	739	11738	110040	347	552	18480	58	924
Thioridazine 0,005 x 30	130580	894	6529	79600	545	2388	55140	378	1654
Thioridazine 0,05 x 50	48100	1924	2405	34600	1384	1730	21000	840	1050
Trifluoperazine x 50	48520	269	2426	52920	294	2646	17757	98	883
Total no.of tablets		3826	23098		2570	7316		1374	4510
Raunervil 10/1	4500	29	45	3600	23	36	4000	26	40
Trifluoperazine 100/1	1100	40	110	1500	54	150	1800	65	180
Romergan 100/2	4550	421	455	4064	433	406	1960	209	196
Romthiazine 100/10	590	129	59	689	151	69	-	-	-
Total no.of ampoules		619	669		661	661		300	416

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Tranquillizers									
Meprobamate x 1,000	10128	757	10128	26690	1996	26690	7557	565	7557
Total no.of tablets		757	10128		1996	26690		565	7557
Antidepressive preparations									
Antideprin x 50	159540	766	7977	146280	702	7314	30960	149	1548
Total no.of tablets		766	7977		702	7314		149	1548
Antideprin 100/2	5050	291	505	1585	96	158	-	-	-
Total no.of ampoules		291	505		96	158	-	-	-
Analgesics and narcotics									
Sintalgon x 10	40080	110	400	39000	107	390	-	-	-
Total no.of tablets		110	400		107	390	-	-	-
Hydromorphone 100/1	-	-	-	958	137	95	320	46	32
Hydromorphone + Atropine 100/1	2632	377	263	7662	906	766	2206	317	220
Hydromorphone + Scopolamine 3/1	2800	10	8	11667	43	35	763	94	2
Mialgyn 100/2	6200	549	620	7717	630	771	6843	547	684
Morphine 100/1	3225	463	322	5017	720	501	3461	497	346
Morphine + Atropine 100/1	22	3	-	84	12	-	45	7	-
Total no.of ampoules		1402	1213		2448	2168		1508	1284
Analgesics,antipyretics, antirheumatics and antimalarials (synthesis)									
Aspirin x 2,000	246630	30335	493260	246400	30307	492800	193420	23791	386840
Algocalmin x 2,000	170900	126124	341800	134698	99407	269396	77498	57193	154996

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Aminophenazone 0.10 x 100	40446o	2123	40446	540720	2039	54072	45400	238	4540
Aminophenazone 0.30 x 100	336000	4305	33600	193000	2760	19300	-	-	-
Antinevralgin x 2,000	139185	32848	278370	137224	32385	274448	84351	19907	168702
Coffedol x 20	199000	3590	3980	214500	3869	4290	42240	762	845
Phenylbutazone x 20	162200	1022	3244	305960	1928	6119	36600	230	732
Total no.of tablets		200347	1194700		173495	1120425		102121	716655
Algocalmin 100/2	444125	54627	44412	254820	31343	25482	174000	21402	17400
Total no.of ampoules		54627	44412		31343	25482		21402	17400
<u>Local anesthetics</u>									
Procaine 1% 50/20	5750	496	287	6600	569	330	3410	294	170
Procaine 2% 100/2	790	68	79	920	79	92	550	47	55
Procaine 2% 100/5	320	27	32	228	19	23	170	14	17
Procaine 4% 100/5	310	27	31	300	26	30	270	23	27
Dixidextrocaine 100/2	164	15	16	370	33	37	-	-	-
Xylocaine 1% 50/20	30d00	3157	154o	4716o	4834	2358	13300	1363	665
Xylocaine 2% 100/2	42455	2437	424	47737	2740	477	19100	1096	1910
Xylocaine 4% 100/2	1430	147	143	3359	346	336	1600	165	160
Xylocaine + adrenaline 100/2	46310	2848	4631	48210	2965	4821	20100	1236	20l0
Total no.of ampoules		9222	7183		11611	8504		4238	5014
<u>Antihistamines</u>									
Chlorphenoxamin x 20	170400	588	3408	472400	1630	9448	130600	450	2612
Nilfan x 20	299520	2097	5990	70000	490	1400	61840	433	1237

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Tavegyl x 2o	94680	1775	1893	97800	1834	1956	80000	1500	1600
Total no.of tablets		4460	11291		3954	12804		2383	5449
Tavegyl 5/2	7000	92	35	14500	190	72	8000	105	40
Total no.of ampoules		92	35		190	72		105	40
Cardiovascular preparations									
Digoxin x 40	809360	3835	32374	778440	3736	31137	513440	2464	20537
Total no.of tablets		3835	32374		3736	31137		2464	20537
Digoxin 5/2	23900	81	119	49180	167	246	23500	80	117
Total no.of ampoules		81	119		167	246		80	117
Antiarrhythmics									
Propranolol o.o1 x 5o	820431	3692	41021	910260	4096	45513	376680	1695	18834
Propranolol o.o4 x 5o	804200	8404	40210	1021658	10676	51083	224940	2350	11247
Total no.of tablets		12096	81231		14772	96596		4245	30081
Propranolol 5/5	25200	87	126	11200	39	56	16000	55	80
Xylocaine 1% 100/1o	7462	734	746	12041	1185	1204	6827	312	683
Total no.of ampoules		821	872		1224	1260		367	763
Antihypertensives									
Guanethidine x 5o	22630	136	1134	22480	135	1124	-	-	-
Hyposerpil x 6o	1268000	2575	76080	1214440	2465	72866	202080	410	12125
Total no.of tablets		2711	77214		2600	73990		410	12125
Coronary vasodilators									
Agozol x 3o	69600	578	2088	143200	1188	4296	43640	362	1309

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Nyophillin x 2o	591120	1391	11822	287600	920	5752	162520	520	3250
Dipyridamole x 6o	2608000	69686	156480	5077756	135678	304665	1178139	31480	70638
Nitroglycerin x 4o	1083337	1863	43333	561200	965	22448	454520	782	18181
Total no.of tublets		74018	213723		138751	337201		33144	93428
Dipyridamole 5/2	53300	203	267	71000	269	355	49000	186	245
Nyopbilin 100/1o	46799	7534	4679	23491	1912	2349	10000	798	1000
Fosfobion 100/1	86585	9871	8658	51221	5839	5122	42900	4891	4290
Total no.of ampoules		17608	13604		8020	7826		5875	5535
<u>Medication of the blood and hematopoietic organs</u>									
Iron polymaltose 5/2	50500	778	253	30800	474	154	15000	231	75
Total no.of ampoules		778	253		474	154		231	75
<u>Coagulants and hemostatics</u>									
Epsilonaminocaproic acid 100/1o	1263	662	126	1900	996	190	1105	579	111
Venostat 5/1	100312	4213	502	142100	5968	711	114000	4788	570
Total no.of ampoules		4875	628		6964	901		5367	680
<u>Replacers of the circulating mass</u>									
Dextran 7o NaCl 6/500	4135	1526	-	5850	2159	-	1200	443	-
Dextran 7o Glucose 6/500	7180	2908	-	6850	2528	-	1700	627	-
Dextran 4o NaCl 6/500	4505	2261	-	4225	2120	-	2000	1004	-
Dextran 4o Glucose 6/500	3903	1959	-	3500	1756	-	1450	728	-
Total		8654	118	-	8563	122	-	2802	38

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Medication of the renal apparatus									
Nefrix tablets x 40	96d84o	2131	38754	1233140	2713	49326	27o04o	594	1o8o1
Furosemide ampoules 1oo/2	18625	1404	1862	28o37	2o26	28o3	1o5oo	758	1o5o
Urinary antimicrobial preparations									
Methenamine, tablets x 2o	138550	291	2771	1o702o	225	214o	78700	165	1574
Medication of the Digestive Tract									
Antacids and antiulcer preparations									
Dicarbocalm x 5o	1o7674o	5524	53837	11o522o	567o	55261	636250	3264	31313
Ulcerotrat x 2,ooo	17437	7149	54874	22ooo	9o2o	44ooo	5282	2166	12564
Ulcosilvanil x 6o	1o4oo	512	624	712o	35o	427	5ooo	285	348
Ulcostop x 4o	491oo	241	1964	6382o	314	2553	2552o	125	1o21
Trisilicalm x 5o	4354o	535	2177	25o8o	3o8	1254	53oo	65	265
Total no.of tablets		13961	93476		15662	1o3495		5965	46o51
Emetics and antinauseants									
Emetiral x 2o	632380	1o58	13648	438758	68o	8775	171920	266	3438
Torecan x 15	235280	2117	3530	211800	1906	3177	130520	1175	1958
Total no.of tablets		3175	17178		2586	11952		1441	5396
Torecan 5/1	7oooo	463	35o	96500	639	483	23950	159	12o
Magnesium sulphate 1oo/1o	1324o	114o	1324	11177	962	1117	924o	795	924
Total no.of ampoules		1603	1674		1601	1600		954	1o44
Purgatives and Laxatives									
Carbocif x 2,ooo	63oo	1o33	12600	2966	486	5932	8oo	131	1600
Dioctolax x 1oo	23061o	4774	23061	212099	4390	2121o	113400	2347	11340

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Laxamin x 20	494873	1089	9893	461800	1016	9236	110080	242	2202
Total no.of tablets		6896	45599		5892	36378		2720	15142
Intestinal antiseptics									
Saprosan 0.01 x 30	698982	1719	20970	729120	1794	21874	192240	473	5767
Saprosan 0.1 0 x 30	1158749	8551	34762	981120	7241	29433	302840	2235	9085
Total no.of tablets		10270	55732		9035	51307		2708	14852
Hepatoprotective preparations									
Mecopar forte x 20	535887	2519	11717	423530	1821	8472	55900	240	1113
Metespar x 40	267960	1322	10718	178960	1217	7158	102160	695	4086
Total no.of tablets		4341	22435		3038	15630		935	5204
Arginine sorbitol 12/250	6050	2124	73	6700	2352	80	5800	2036	70
Diagnostics									
Contrast agents									
Odiston 30% 1/20	900	8	0,900	530	5	0,530	4700	42	4,7
Odiston 75% 1/20	122500	2310	122,5	140600	2652	140,6	121800	2297	121,8
Pobilan 30% 1/20	-	-	1	300	4	0,3	2500	33	21,5
Pobilan 50% 1/20	37250	692	37,250	15842	294	15,842	8100	150	8,1
Total no.of ampoules		3010	160,65		2955	157,272		2522	136,75
Laboratory tests - chemistry									
Acetotest x 50	4320	16	216	2080	8	104	2240	8	112
Microtablets with bacitracin x 100	1152	19	115,2	1486	24	148,6	2200	36	230

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Microtablets for antibiotic sensitivity tests(local and digestive infections)	1456	64	1165	5090	226	4078	3900	173	3120
Microtablets for antibiotic sensitivity tests (staphylococcic infections)	809	34	323	-	-	-	-	-	-
Microtablets for antibiotic sensitivity tests (urinary tract infections)	2005	214	1042	7110	583	2844	3900	320	1560
Microtablets for antibiotic sensitivity tests - for current usage	3813	375	1525	10000	984	4000	7642	752	3057
Total no.of tablets		722	4386,2		1825	11174,6		1289	8129
<u>Dietetic products</u>									
Calcium lactate x 60	4218	30	253	4820	34	289	1540	11	92,4
Saccharine x 100	1469234	4261	146923	2764000	8016	276400	1025000	2973	102500
Total no. of tablets		4291	147176		8050	276689		2984	102592,4
<u>Solutions for infusion</u>									
Glucose 5% (vial + bag)	1637000	22193	1687	1481000	19282	1481	387400	5000	387,4
Glucose 10% (vial + bag)	1485500	23053	1485	1316000	20102	1316	489800	6848	439,8
Glucose 20% (bag)	142100	2213	142	118080	1838	118	96500	1505	96,5
Potassium lactate 100/10	120	17	12	140	20	14	120	17	12
Sodium lactate 100/10	70	9	7	180	23	18	-	-	-
Sodium chloride 0.9%,500 ml	1067700	10143	1067,7	1061000	10079	1061,0	347800	3304	347,8

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Sodium chloride 0.9%, 1000 ml	155500	2040	155,5	141400	1855	141,4	71000	932	71,0
Hamitol 20%, 250 ml	47300	609	47,3	41700	537	41,7	12000	154	12,0
Hamitol 20%, 500 ml	21050	406	21,05	21200	408	21,2	11000	212	11,0
Sorbitol, 500 ml	30500	300	30,5	36000	354	36,0	1848o	182	18,48
Physiological saline, 100/10	277970	18235	27797	105500	6921	1055o	79000	5182	7900
Total no.of infusions		79224	32458,65		61469	14798,38		23336	9345,98
Infusion Kits	2656000	44014	2656,0	3360990	53680	3360,99	1411000	21579	1411,0
Surgical catgut	159365o	16373	1593,65	978900	10127	978,9	512550	5244	512,55
Hormones									
Corticosteroids									
Superprednol x 40	181440	907	7257	78240	391	3130	74240	371	2670
Total no.of tablets		907	7257		391	3130		371	2670
Hydrocortisone 100/5	20054	16444	2005	20743	2801	2074	40800	5510	4080
Total no.of ampoules		16444	2005		2801	2074		5510	4080
Other products									
Distilled water 100/10	61453	4031	6145	54707	3589	5471	39162	2569	3916
Total no.of ampoules		4031	6145		3589	5471		2569	3916
Synthesis									
Vitamins									
Vitamin C	139887	17136		132000	70387		46500	7254	

0	1	2	3	4	5	6	7	8	9
Vitamin F	3150	180		5860	554		2450	232	
Total	143037	17516		137860	70941		48950	7436	
Sulphonamides									
Sulphonamide	162000	17859		168190	20603		79500	8220	
Sulphathiazole	73430	16722		53902	12985		6920	1147	
Sulphacetamide (acid)	18660	4814		8290	2139		4950	1277	
Sulphacetamide sodium	1500	75		-	-		190	-	
Sulphathiazole sodium	2430	-		1050	-		1625	-	
Phthalisulphathiazole	5040	695		2750	443		3820	360	
Total	263060	40166		234182	36170		97005	11004	
Antidiabetic agents									
Meugan	12830	2001		13533	211		5970	931	
Antipyretics									
Pyramidon	16325	234		15185	804		3000	273	
Chlorosulphonated preparations									
B S A	681500	20445		529180	15875		284000	8520	
Racelin x 5 l.	7610	3291		8900	3849		3550	1535	
	689110	23736		538080	19724		287550	10055	
Anthelmintics									
Refoxemid x 4,5 l.	45500	14332		32200	10143		20735	6531	
Odorants									
Total	232026	25723		202218	41163		151052	15255	
Antimycotic preparations									
Dimetridazole base	80500	55569		67500	46595		21300	14703	
Total		179077			225751			65091	

APPENDIX IV

INCOME STATEMENT

III. Summarized Income Statement

Revenues	1988	1989	1990(January to June)
Sales revenues	3351940	2318733	1297585
- domestic	3179824	2098784	1348759
- exports	172111	219949	48926
Other revenues	4237	299191	2999
Total revenues	3356177	2617924	1300684
	1644130	1215042	530495
Costs of production			
Materials	53643	64951	37808
Electricity	53643	64951	37808
Oil/natural gas	53643	64951	37808
Coal/lignite	53643	64951	37808
Wages and salaries	64973	63047	37412
Depreciation	-	-	-
Maintenance and repair	43246	99797	32787
Other costs	90148	75594	42570
Total operating costs	1856140	1518431	681072
Administrative and general expenditures	363151	271487	148281
Interest and other financial charges	17540	22008	11498
Net income/ loss	1079346	805998	459833
Taxes and obligatory contributions	784713	694161	149015
Net income (afetr tax)/ loss	294633	111837	310818

IV. Summarized Balance Sheet.

Assets	1988	1989	1990(January-June)
Cash and bank balance	29146	152545	16975
Trade receivable	203749	201135	106658
Other receivables	33222	180710	3500
Inventories	320447	291241	521559
- raw materials	122809	152124	348835
- work in process	17302	47626	35749
- finished goods	180336	91491	136975
Other current assets	49479	46465	46455
Total current assets	636043	872096	695157

	1988	1989	1990(January-June)
Medium and long term receivables	-	-	-
Investments	120338	170771	194575
Gross fixed assets	1416539	1473993	1417029
Less: Acumulated Depreciation	764076	811336	781317
Net fixed assets	652463	662657	635712
Total Assets	1410844	1705524	1525444
Liabilities			
Trade payables	105940	191651	113554
Other payables	4632	19641	2308
Short term loans	133442	194674	92612
Current portion of long term loans	-	-	-
Other current liabilities	43345	68386	40387
Total current liabilities	287359	474352	248861
Medium to long term debt	-	-	-
-domestic	-	-	-
-foreign	-	-	-
Investments by joint venture partners (if any)	-	-	-
Equity-type funds	989868	1060401	1041029
- statutory reserves	11279	-	40979
- Non statutory reserves	-	-	-
- enterprises'equity funds	-	-	-
- others	122338	17o771	194575
Total liabilities	141o844	1705524	1525444

V. Allocation of Profits

Please specify how profits are allocated to the various reserves and other categories.

	1988	1989	first half 1990
Profits	294633	111837	31o818
Budget tax	1o2472	17o35	221193
Investments	3o983		
Development funds	1557o	2o92o	1777o
Housing funds	16o6		
Circulation means	583o6	655o9	66455
Social activities	2157	162o	155o
Shares fund	5123	4581	3250
Prices raising	1910	445	-

	1988	1989	1990(January-June)
Additional wages and salaries	601	580	600
Crude oil	75000	-	-
Social portions	905	950	-

VI. Taxes and Obligatory Contributions

Please specify types and amounts of different types of subsidies received e/g. production, consumer, exports.

Land tax	2134	2137	1071
~~Taxes for goods circulation~~	~~716495~~	~~694144~~	149015
~~Drawing account~~	~~68218~~	~~17~~	-
~~Profit~~	~~294633~~	~~111837~~	310815

VII. Subsidies Received

Please specify amounts and basis of different types of subsidies received e/g. production, consumer, exports. —

VIII. Debt Service

Please provide details of typical terms and conditions of domestic and foreign short term and long term loans, indicating

	1988	1989	1990
- maturity terms		in 1999	8
- interest rates		5%	
- loan		89198 thousand lei for investmen	

IX. Working Capital Financing

Please specify the amount of working capital needed for normal operations. If a working capital financing is needed, please specify your source of financing and mechanisms and conditions of working capital financing.

1988	1989	1990
337405	397744	407417

X. Collection Record

Please specify the average period needed to collect your sales revenues (from the time a product is shipped from the factory to the time a payment is received) 10-20 days.

Appendix V

Major Production and Packaging Equipment

Equipment	Capacity	#
Glatt Fluid Bed Dryer Granulator (1967)	200 kg	4
Oscillating Granulator (Frewitt type)	MG 620, MG 203	6
Sigma Blade Mixer for Wet Granulation (Type Batagion)	200 kg	8
Cylindrical Tumbling Mixer	200 kg	7
Hammer mill		
Cutting Mill (APEX)		
Tray Dryer	200 kg	10
Hult Compactor (Granulation by Compression)		1
Sugar Coating Pans (made of copper)	25 kg	20
		30
Tablet Presses:		
Single Punch	50 kg tab/ hour	10
Rotary Press	2000 / hour	
Killian RF 6		
Russian		
Rumanian		
Manestry Express		
Killian Kiss NRD 33		
Eiffel		
Beta Press		
Manesty Express		
Manesty Rotapress T x 30		
T x 40		
		4
Capsule Filling		
H & K	75,000 / hour	
GKF 801	100,000 / hour	

Packaging	
Blister Pak (Uhlmann)	6
King	4
Noack (TN 220; BN 230)	6

APPENDIX VI

Major Testing Equipment

Name	Manufacturer	Quantity
High Pressure Liquid Chromatogram	Helwitt Packard	1
Gas Chromatogragh GCHF 183	Helwitt Packard	1
U.V. Spectrophototometer (Specord M 40)	Carl Lewis	1
IR Spectrophotometer (75IR)	Carl Lewis	1
Polarimeter	Carl Lewis	1
Spectrophotometer with Atomic Absorption	Carl Lewis	1
Mositure Determination		
Apparatus for Dissolution Testing	Romania	2
Apparatus for Disintegrateion Test	Romania	2
Apparatus for hardness Testing	Romania	1
Roche Friability Tester	Ciba-Geigy	2
Other Laboratory Equipmment		

APPENDIX VII
List of Books

1. Pharmaceutical Dosage Forms: Tablets Volume 1", H.A. Lieberman, L.Lachman and J.B. Schwartz, Editors; 2nd Edition, Published by Marcel Dekker, New York,NY USA, 1989.
2. "Pharmaceutical Dosage Forms: Tablets Volume 2", H.A. Lieberman, and L.Lachman, Editors; Published by Marcel Dekker, New York,NY USA, 1981.
3. "Pharmaceutical Dosage Forms: Tablets Volume 3", H.A. Lieberman, and L.Lachman, Editors; Published by Marcel Dekker, New York,NY USA, 1982.
4. "Pharmaceutical Dosage Forms: Disperse Systems Volume 1", H.A. Lieberman, M.M. Rieger, and G.S. Banker, Editors; Published by Marcel Dekker, New York,NY USA, 1988.
5. "Pharmaceutical Dosage Forms: Disperse Systems Volume 2", H.A. Lieberman, M.M. Rieger, and G.S. Banker, Editors; Published by Marcel Dekker, New York, NY USA 1989.
6. "Theory and Practice of Industrial Pharmacy", L. Lachman, H.A. Lieberman, and J. Kanig, Editors; Published by Lea and Febiger, Philadelphia, PA USA, 1986.
7. "Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences". A. Martin, J. Swarbrick and A. Cammarata, Editors, 3rd Edition, Published by Lea and Febiger, Philadelphia, PA USA 1983.
8. "Analytical Profiles of Drug Substances: Volumes 1-20", K. Florey, Editor;Published by Academic Press, New York, NY USA, 1975.
9. "AMA Drug Evaluations" Prepared by AMA Department of Drugs, Latest Edition; Published by John Wiley and Sons

Inc., New York, NY USA.

10. "The Pharmaceutical Quality Control Handbook" Rhys Bryant Editor; Published by Aster Publishing Corporation, Springfield, Oregon USA, 1984.
11. "Advances in Drug Delivery Systems", J.M. Anderson and S.W. Kim, Editors; Published by Elsevier Science Publishing Company Inc., New York, NY USA 1986.
12. "Microcapsules adn Microencapsulation Techniques", M.H. Gutcho; Published by Noyes Data Corporation, Park Ridge, NJ USA, 1976.
13. "Handbook of Powder Science and Technology" M.E. Fayed and L. Otten, Editors; Published by Van Nostrand Reinhold Company Inc., New York, NY USA, 1984.
14. "Handbook of U.S. Colorants for Foods, Drugs and Cosmetics, D.M. Marmion, Editor, 2nd Edition; Published by Wiley-Interscience, New York, NY USA, 1984.

Appendix VIII
List of Equipment

Item	Model	Vendor	*Price
Lab Devol. Coating System	LDC	Vector Corp	$37,500
Dissolution Apparatus	Model #SR2	Hanson Res.	7,465
Hardness Tester (Reconditioned)	Schleaniger2E	Vector Corp.	1,900
Desintegration Apparatus	Model # QC21	Hanson Res.	1,205
Rotating Bottle Apparatus	Model # 393	Hanson Res.	6,395
Vernier Calipers	Catalog#12-122	Fisher	38.60
Fluid Bed Lab Unit	Aeromatic Strea-1	Aeromatic	23,053
HPLC Columns	Open	Alltech (each)	250
Karlfisher Titrator	LTE AFS	Harvard	5,950
Viscometer	LVTDV-I	Brookfield	1,575
U.S. Standard Sieves	200#,100#,80# 60#,320#,10#	Fisher	450
Pycnometer	Catalog#03-247	Fisher	61
Spectrophotometer	Spectronic 601	Fisher	5,450
Oven	Precision Stm 80	Fisher	1,829
Moisture Balance	Cenco Model #26680	Fisher	1,375
Electronic Balance	Fisher XE-400	Fisher	695

*Based on U.S. prices valid for 90 days.

Vendor Locations

Aeromatic	9156 Rumsey Road	Columbia,MD 21045
Alltech	2051 Waukegan Road	Deerfield,Illinios 60015
Brookfield	240 Cushing Street	Stoughton,MA 02072
Fisher	461 Riverside Avenue	Medford,MA 02155
Hanson Research	9810 Variel Avenue	Chatsworth,CA 91311
Harvard	22 Pleasant Street	South Natick,MA 01760
Vector Corp.	675 44th Street	Marion,IA 52302

Appendix IX
Chemicals for Film Coating

Solvents:	Quantity	Vender
Methylene Chloride	5 gal	open
Acetone	5 gal	open
Methanol	5 gal	open
Isopropyl Alcohol	5 gal	open
Ethyl Alcohol	5 gal	open
Polymers:		
Hydroxy propyl methylcellulose (HPMC)		
Presto H	4 kg	IndoGerman Lab.
Presto HPMC	4 kg	IndoGerman Lab
Presto E (Enteric coat)	4 kg	IndoGerman Lab
Opadry	30 kg	Colorcon
Methylmethacrylate		
Eudragit L30D	4 kg	Rohm-Pharma
Ethylcellulose		
Surerelease	4 kg	Colorcon
Plasticizer:		
Triacetin	1 kg	Eastman Chem.
Dibutylsebacate (UNIFEX DS)	1 kg	Unioncamp
Dibutylphthalate	1 kg	Unioncamp
Glycerin	5 gal	Open
Propylene Glycol	5 gal	Open

1 Colorcon: 415 Boyer Blud West Point, PA 19486

2 IndoGerman Laboratories: 38-B G.I.E. Charkop Kandiuli, Bombay-67 India Fax # 91-22-6052-563

3 Unioncamp Chemical Products Div.: 1600 Valley Road Wayne,NJ 07470

4 Eastman Chemical Products: P.O. Box 431 Kingsport, TN 37662

11. Technical comments from Substantive Officer to Mr. Barghava's report on his first mission to Romania in November 1990

Proj. SI/ROM/90/801 - "Assistance in the adaptation of modern technologies for the production of oral pharmaceuticals".

Considering the present status of Romanian Pharmaceutical Industry, as described in the report and the urgent country's need for exports increase in order to help assurance of the required foreign currency, it is also UNIDO Backstopping Officer's point of view that some measures have to be taken previous to the assimilation of highly sophisticated slow release or sustained action new formulations.

Priority actions to be undertaken should be:

1.- Shift part of the present 53 sugar coated tablets, beginning as suggested in page 18 of the report to: non coated tablets and film coated tablets The savings in materials, manpower, time and energy, beside the increased quality of the final products will be of great significance and the time for obtaining practical results could be shortened if existing facilities for film coating can be utilized after formula development is finished at laboratory/pilot level.

2. Prepare a programme for and begin introduction of GMP in present production and quality control procedures. (mainly from the organizational point of view and as far as possible, improving the equipment and building conditions).

Above proposal will require some inputs that could be obtained from the projects'funds, even with reformulation of the former established objectives.

The new project objective that could be established is:

"Upgrade present condition of Romania pharmaceutical production (specially in the field of tablets) by means of improving materials and methods in present formulations as well as to introduce GMP in production and quality control procedures".

From the recommendations in Mr. Barghava's report, which are supported by the Substantive Officer, we have to choose first those that can be implemented within the projects' budget and will contribute more to fulfil the already mentioned objective. Nevertheless, also some cost sharing could be expected from the Government side, specially regarding the purchase of higher quality materials for better formulation of tablet cores.

Rec. 1,8,9, 10(modify some of the current tablets formulae, write sop and validate processes and adopt efficient film coating) could be achieved with expert(s)'s technical assistance within the 6 m/m (already included in the project document). Background and experts' duties have to be modified.

Rec. 2 - study tour. It can be readily implemented as foreseen and already negotiated with Rohm Pharma as the knowledge that could be obtained during this study tour visit will be also useful for the new objective.

Rec. 3,4,5 (lab. equipment for development of new pharmaceutical and coating techniques)

Major constraints regarding existing budget appears here as the total value of the list proposed (Annex VIII) is about US$ 100,000 and the available amount is only US$ 30,000

The priority criteria has to be discussed with the Romanian counterpart, as well as to analyze some additional possibilities to finance the difference.

Equipment cost for improving the quality control could be afforded by the project budget, but two critical pieces for the research of new formulations: Lab. Devol. Coating System and Fluid Bed Lab Unit would cost US$ 60,000 for both and a solution has to be found.

The list of suggested books (Appendix VII) represents an increase in the required budget in some additional US$ 5,000 and would be very convenient if it could have a solution as well as the remaining equipment.

As the result of the experts'mission indicates the need of reformulate the original project, as well as to obtain some additional funds, it will be required/convenient to call as soon as possible a meeting with UNDP, Government officials and UNIDO, in order to take decisions, prepare the new project document and continue with the most urgent actions.

The Government possibilities for financing raw materials for film coating experiments (Appendix IX) and for the possible use of present film coating facilities to introduce the research results, have to be clarified in advance. It would also be convenient to foresee the elaboration of a feasibility study, if possible by local experts, for the scale up of the research results to the industry in order to show explicitly, the economical convenience of changing to the new formulations/procedures.