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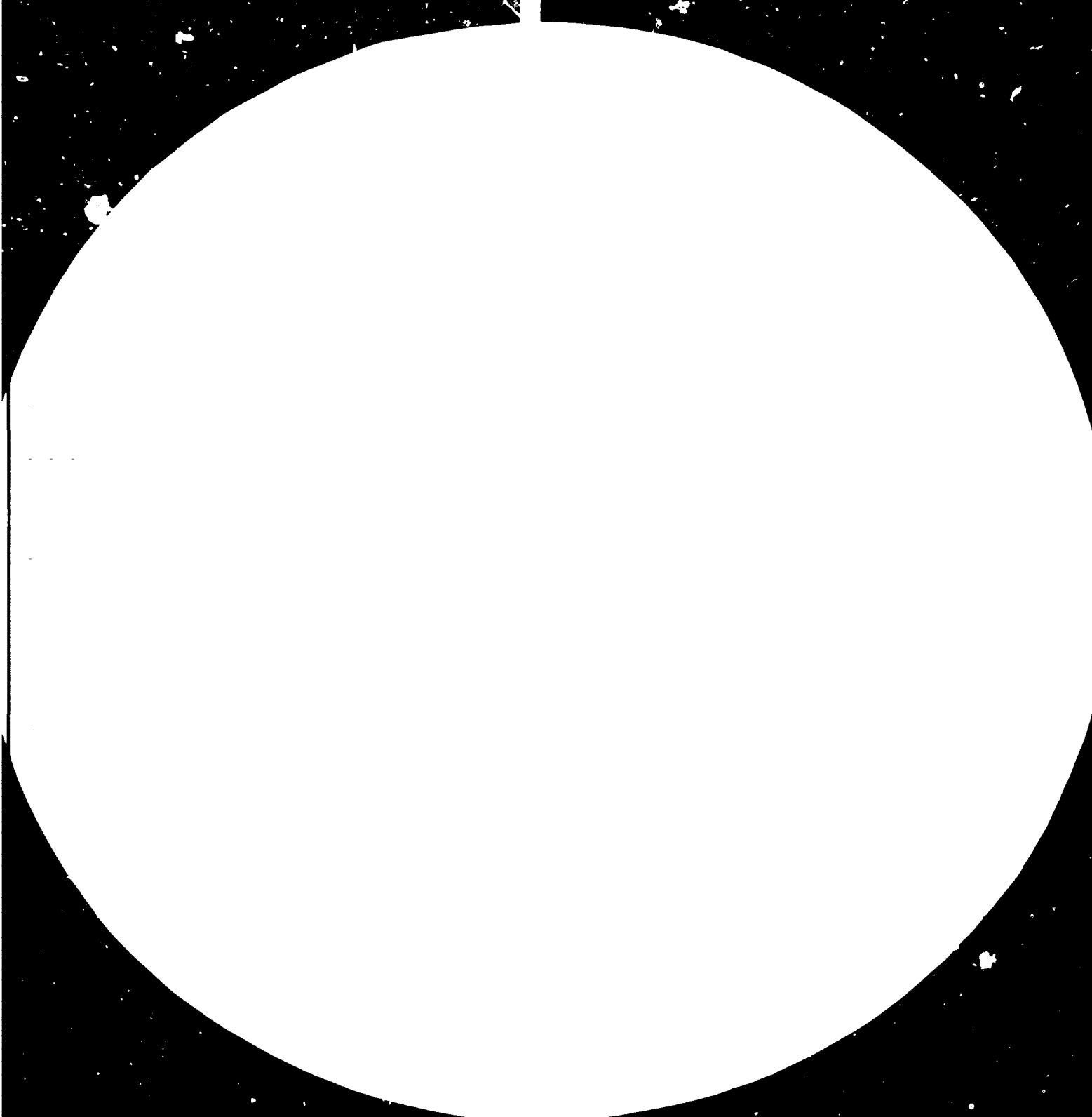

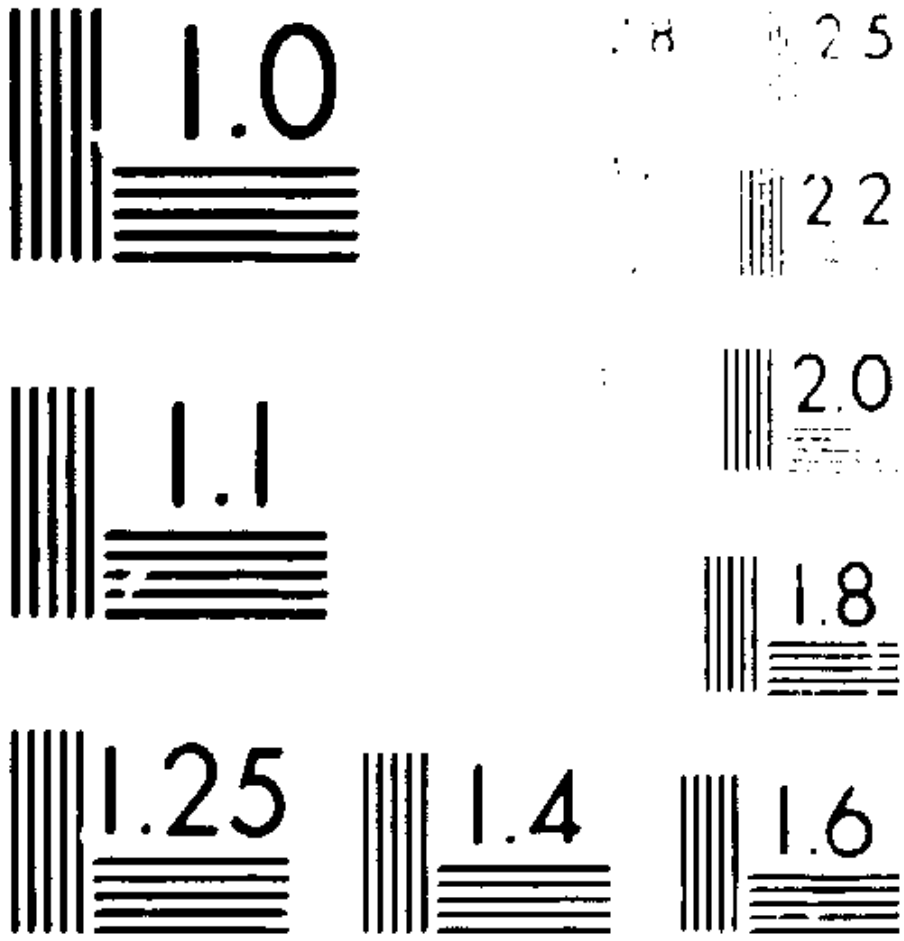
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Contractual Arrangements in the Pharmaceutical Industry

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# ARRANGEMENTS FOR THE TRANSFER OF TECHNOLOGY FOR THE FORMULATION OF PHARMACEUTICAL FORMS. CONTRACTUAL CONDITIONS AND BACKGROUND NOTES*

Prepared by

the UNIDO Secretariat



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# SUMMARY

Annexes

I. Process technology for the formulation of pharmaceuticals.

II. Details of equipment for formulation

III. Raw materials and auxiliary materials required for formulations

IV. Quality control

V. Packaging materials

## 1. Preface

In accordance with the recommendation No. 2 of the First Consultation on the Pharmaceutical Industry held in Lisbon (December 1980), UNIDO has been requested to prepare documents on the various contractual conditions, and variations thereof including background notes, related to contractual arrangements for the transfer of technology in the pharmaceutical industry.

The Morocco Round Table on the Pharmaceutical Industry (December 1981) further recommended that UNIDO prepare a document on contractual arrangements regarding the transfer of technology for formulations, taking the already large experience of developing countries in the matter into account (*).

In line with such recommendations, this paper provides general guidelines and concrete drafting proposals for the negotiation and conclusion of licensing arrangements related to the formulation of pharmaceutical forms. The preparation of this document has been premised on the assumption that the Licensee already operates a plant for formulations, or that the construction thereof is undertaken independently from the licensing agreement dealt with here.

## 2. Purpose, scope and content of this document

This document is primarily addressed to parties negotiating arrangements for formulations, and particularly to enterprises operating in developing countries. In its preparation, a number of principles have been taken into account, as described in a previous UNIDO document (**) and recommended at the Morocco Round Table:

(a) The transfer of technology should contribute to the identification and solution of economic and social problems related to the production and use of pharmaceuticals in developing countries, with an aim at substantially improving, at adequate costs and quality, the availability of essential drugs in developing countries;

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(*) See UNIDO PC/33, 21 January 1982.

(**) "Background paper for discussion on the relevant issues to be taken into account when negotiating transfer of technology agreements and the various terms, conditions and variations thereof that could be included in contractual agreements: possible scope, structure and content" PC.19, 17 October 1981.

(b) The parties to a transfer of technology agreement should be responsive to the health and other relevant policies of the receiving country, including import substitution, development of technical skills, promotion of local innovation, etc.;

(c) Licensing agreements should contain fair and reasonable terms and conditions, including payments, and be no less favourable for the recipient than the terms and conditions usually applied by the supplier or other reliable sources for similar technologies under similar circumstances:

(d) The agreement should, in particular,

(i) ensure the absorption of technology transferred by local personnel;

(ii) allow the use, as far as possible, of locally available materials and services:

(iii) facilitate and, in any case, do not restrict the adaptation and further development of technology received;

(iv) include adequate guarantees for the performance of the parties' obligations;

(v) provide full information on the characteristics of the technology and drugs to be manufactured, specially in respect of possible hazards and side effects;

(vi) do not contain unjustified restraints on the recipient's use of the technology.

The document deals with the main items to be negotiated when concluding licensing agreements of the type referred to. Where appropriate it includes:

i) Elements to be taken into account in the negotiation and drafting of the clauses;

ii) technical aspects, and particularly difficulties that may be faced at the negotiating phase and implementation of the agreement;

iii) concrete examples, wherever possible, indicating the technical implications of different pharmaceutical forms (injectables, tablets, capsules, etc.);

iv) recommendations as to how to deal with the particular issue;

v) possible clauses and variations thereof.

It is obvious that the recommendations made in the document as well as the clauses and variations proposed, can not cover all the possible alternatives available for dealing with each particular item. The document only includes those alternatives which are deemed more important or appropriate in view of the principles and objectives that preside its preparation. The importance and appropriateness of possible solutions have been assessed on the basis of four main criteria:

i) the likely acceptability of proposed solutions for both contracting parties;

ii) the compatibility of proposed solutions with existing regulations and positions on the matter, as described-for a number of issues- in an earlier UNIDO document (*);

iii) the practices which are generally accepted in international licensing and trade;

iv) the recommendations and suggestions of available model clauses/ contracts, or guidelines, as listed in document UNIDO PC.19.

As already indicated (**), the technology for formulation of final products is well-known and fairly well diffused. The transfer of techniques on formulation is likely to have a very limited impact as regards the improvement of the technological capability in the receiving country, without prejudice to its external effects as regards to the establishment of test laboratories and other facilities. In general, such technologies comprise of very little or no secret information, in contrast with technologies for the manufacture of bulk drugs.

For these reasons, and given the very limited technological contribution (with regard to production techniques) that such arrangements usually involve, arrangements on this matter might be limited (provided that the license of industrial property rights is not required) to the supply of technical assistance for a short period, or other type of agreements which do not imply for the recipient the obligation to effect continuous payments or observe restrictive conditions.

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(*) See "Preparation of Guidelines, Background paper", ID/WG.331/3, 23 September 1980.

(**) Ibidem.

In practice, however, arrangements for the formulation of pharmaceutical forms are very often framed as licensing agreements, involving the provision of active ingredients, the communication of medical and other scientific information needed for the registration of the products, the license of trademarks of the supplier, and eventually, the license of patents for covering imports of active ingredients from the supplier.

Following that practice, and in order to assist enterprises in developing countries, particularly in less developed countries among them, to improve the negotiation of that kind of arrangements, this document presents clauses and commentaries related to issues typically dealt with in licensing agreements for formulations.

For the purpose of collecting information on developing countries' experience in arrangements for formulations, UNIDO Secretariat has circulated a questionnaire,the reply of which by a number of pharmaceutical enterprises has been considered in the preparation of this document.

3. Licensing for production of dosage forms

After food and shelter, health care gets the top priority in any society. In the developing countries due to poverty and mal-nutrition, health-care assumes greater importance. Drugs and medicine plays a critical role without which health care becomes meaningless. Formulations are the products in the definite form ready to be taken or to be applied for treatment, mitigation, prevention or diagnosis of disease, an abnormal physical state or the symptom there of in man or animal or the restoration, correction or mitigation of organic functions in man or animal.

Formulations are made in various physical forms like tablets, capsules, liquid preparations, ointments and infusions. Similarly, packaging is also done in various forms. The tablet or capsules may be packed in bottles, tins or strips whereas ointments for commercial use is available in tubes and for hospitals etc. it is packed in glass jars. The infusions are put in ampules and antibiotic powder in vials.

Unlike other products, formulations being used for human consumption, are life saving, have to be produced under great care, proper mixing and dispersion is very essential. In case of antibiotics, infusions and injectables it is necessary to maintain sterile conditions to avoid contamination. Even all the ingredients including water must be pyrogen free. Very strict standards for manufacturing formulations have been established and it requires good manufacturing practices. The technology involved in the production of formulation is simpler as compared to the technology in case of bulk drugs and intermediates. Moreover, it is also repetitive because the formulation is the conversion of bulk drugs or mixture of bulk drugs into various physical forms, which can be easily taken or applied. Thus the same technology of preparation of tablets with minor adjustments of auxilliary materials and operations could be applied for production of tablets of any other drug. This also applies for preparation of infusion, ointments, capsules or any other form of formulations (see Annex I).

Formulations could be labelled under generic name or conforming to national formulary or under brand name. In a large number of developing countries, health care is being looked after by the State. Under such

circumstances, sometimes the State also takes the responsibility of production of drugs and medicines which is required for dispensaries, hospitals etc. These drugs are produced under generic neme or conform to national formulary.

The licensing arrangements for know-how may be linked to the setting-up of the new plants. The know-how is given by the agency or firm which is already producing these products. The licensee takes care of sub-contracting the civil construction and purchase of equipments and machinery under the expert guidance of the Licensor. Today, there are quite a few developing countries having well established modern formulation units which can offer know-how for setting-up of such units in other developing countries. This will give added advantage to such licensees in avoiding the initial mistake generally taking place while transfering technology from developed to developing countries.

It is observed that most of the State units continue for a longer period with the production of generic drugs, which are cheaper as compared to branded or specialities. Moreover, due to late payment by the Governmental institutions, these units are often put to heavy strain and some times their economic viability becomes a problem. It will be advisable that such units start production of generic drugs from the initial inception along with specialities for the market. Thus improving their economic viability and at the same time serving the State by supplying the generic drugs at cheaper prices.

The branded/speciality product licence agreement confine in some cases the Licensee mainly to the production role under the expertise, know-how and supervision of the licensor and the licensor mostly takes care the function of promotion and distribution, that is marketing. As marketing is the key to the success of pharmaceutical industry, most of the developing countries are deprived of this aspect, thereby these brand and speciality licences are getting extended. The manufacturer in a developing country gets only a marginal benefit out of such transactions. As continued dependence of marketing promotion remains in the hands of the licensor for years together, it would be fair both for the licensor and the licensee to get the equal benefit out of such contractual agreements by passing the marketing know-how as a part and parcel of such agreements.

Chemical and bulk drug production units are located invariably depending upon the source of raw materials, intermediate and energy whereas formulation units are generally located in big cities and towns which are consuming centres and also have facilities for getting auxiliary and packaging materials produced in those places. Moreover, formulation units do not pose any environmental problem, both affluents and air pollution. Most of the equipments and machinery required in case of formulations are standard one and can be placed as soon as civil builders are ready. The piping network is also simple. However, for maintaining good manufacturing practices, lay-outs, air-conditioning, ventilation, designing of sterile area, flooring, movement of raw materials and storing assume greatest importance. It is for these factors that some of the countries which have pharmaceutical production require expertise even in civil designing. Therefore, the basic design data and information has to be supplied by the Licensor in a precise manner.

In case of basic drugs, most of the developing countries venture for well-known established drugs which have been in use in developed countries for long times whereas in case of formulations, even the latest formulations used in developed countries find its way in the developing countries. Though the technology of production of formulation is simpler as compared to the basic drug industry, yet stability studies, especially in case of combination drugs are very important. The compatibility of various drugs in combination could have interaction and effectiveness has to be determined by clinical trials. Similarly besides the stability, economical data, the storage conditions etc. are part of technological data experiences which have to be transferred to the Licensee. In case of specialities, it is the manufacturing aspect, which plays an important role and therefore the promotional and medical literature including any adverse observations and the precautions, which have been taken, should also be intimated to the Licensee so that he could take precautions whenever such eventualities arise. Both in case of new drugs as well as formulations, every country has their own laws for registration. In case of well-known drugs, the clinical data produced in the Licensor's country have to be submitted to the drug authority before permission for marketing of such products are given and in case of completely new drugs/formulations in some countries it is necessary that the clinical trials be also carried out

after which the permission for manufacturing/marketing of such drugs is given by the Government. For the successful operation of the agreement, it is necessary that both Licensor and Licensee exchange complete information pertaining to procedures and rules existing in their respective countries.

4. Major and Special Equipment Required

Some of the developing countries are ar present self-sufficient in production of various equipment and machineries for the production of Formulations in dosages form in a batchway operation. Efforts are being made in such countries to produce continuous and automatic production line for liquid filling antibiotic filling stations.

Annex II gives the list of major equipment and machinery required for a formulation unit having the following capacities based upon two shifts working, whereas the packaging will be in the general shift.

Formulation Unit capacity per annum

| | | | |
|---|---|---|---|
| a. | Tablets and Coated Tablets | : | 350 Million |
| b. | Capsules | : | 30 Million |
| c. | Liquid Orals | : | 100 ML |
| d. | Injectables (Ampoules) | : | 4.5 Million |
| e. | Ointments | : | 4.4 MT |

The Annex also gives the detail specifications, material of construction, numbers of equipments required and probable ruling prices in 1981 and early 1982 in India.

5. Raw Materials Required

According to the type of formulations to be manufactured, a number of raw materials and auxiliary materials are required. An illustration on this point is presented in Annex III.

6. Quality and Process Control

Drugs and medicines are organic and inorganic chemicals, biological products, plant products, as single or in combination. With the advent of Organic Chemistry, large number of organic compounds could be synthesised and tested for drug activities. It is done with the co-operation and participation of scientists from many disciplines, such as Pharmacy, Medicine, Chemistry, Pharmacology, Microbiology etc. The interactions of these chemical compounds are studied with a wide variety of living organisms to find out the therapeutic actions. Once proved promising, the biological effects of these new medicines must be tested on the human beings commonly known as "Clinical Trials". Thus, the doses, the side effects etc. are determined and ultimately the specifications, chemical array and physical characteristics are laid down. Being a sensitive and a lifesaving item, many countries have framed their rules, regulations and acts, regarding preparation, use, standard and specifications of drugs. These informations are compiled in the form of pharmacopoeia, which lays down the monographs on most of the drugs detailing their descriptions, solubility, identification, melting range, reactions, on drawing of preparation. The pharmacopoeia also lays down the standards regarding reagents used for testing these drugs, indicators, methods of analysis, limiters for various harmful metals, salts, etc.

Many countries have their own pharmacopoeia. These pharmacopoeias are prepared by eminent persons in the profession and have legal sanction. Similar standards have been prepared by the World Health Organization in the Internal Pharmacopoeia, to ensure the quality of the products.

a. Quality Control

Quality control requires two elements:

i. Personnel

Personnel must be well-trained in Chemistry, Biology, Microbiology, Toxicology, Pharmacy, etc. In some of the developing countries where new plants are being set-up, it is essential that the above personnels are given training by the Licensor.

ii. Laboratory

Laboratory is the place where the scientists perform the tests as prescribed in the pharmacopoeia or by a drug development group of the producer under the conditions approved by the local drug authorities. The analytical laboratory must be equipped with all the instruments, apparatuses and chemicals prescribed or required for carrying out these tests. Many of the equipments and instruments used are quite sophisticated, e.g. micro-processors, HPLC, MV, IR etc. The laboratory carries out chemical analysis, instrumental analysis, micro-biological testing, package testing, pharmacological and toxicological tests.

Functions of Quality Control

The main function of quality control is to ensure that every product manufactured in the company is the quality it has designed to be. Some of the companies have drawn in-house standards, which are higher than even the pharmacopoeial standards for purity, etc. In order to achieve this, it is essential that the quality control laboratory perform the following functions from the stage of receipt of raw material to the release of finished products:

1. Testing of finished products according to the standards and specifications.
2. Testing of raw materials, auxiliary materials, packaging materials, according to standards and specifications.
3. Preparation, updating, improvement of standards and specifications, which are most stringent than even pharmacopoeia.
4. Procedures for testing, including those for manufacturing and allied departments for process control.
5. Proper documentation for tracing manufacturing history.
6. Inspection and control in the manufacturing section for maintaining good manufacturing practices and standards.

Quality Control personnel draw a representative sample from in-coming lots and test the same. If it complies with the standard and specifications, test report is submitted. In fact, once the material is under test, the quality control personnel puts the material under quarantine and sometimes the label is pasted indicating that the material

is under test. If the material passes, the label mentioning "Passed" is put on the container and sent to the warehouse. If it is rejected, again different label indication "Rejection" is put on the container and sent back to the production unit for reprocessing, if possible. These three labels are made of three different colours to identify whether the (i) "material is under Test" (ii) "Passed" or (iii) "Rejected". A similar procedure is adopted in case of raw materials, packing materials etc.

b. Process Control

In order to achieve the desired quality, it is necessary that the quality of the product be tested and controlled at each and every stage of manufacture. In a well-established pharmaceutical manufacturing unit, there is the practice to have a separate laboratory, known as "Process Control Laboratory" to perform the above functions. Thus, from incoming raw-material up to the end-product are being tested by the Process Control Laboratory and once they get satisfied the product is submitted to the quality control laboratory. In case of tableting, various tests are carried out at the stage of mixing, granulation and after compression. Most of the earlier tests are physical ones; only at the end the chemical assays are also carried out. The double checking system ensures the best quality of the products.

c. Organization of the Quality Control Department

Given the crucial role of a Quality Control (Q.C.) Department, it should be independent from the production unit and should only report to the general manager of the Licensee.

It should also be free to exchange information without restriction with the Licensor's Q.C. Dept. Thus both Q.C. Dept. should be able to speak the same technical language. The function of the Q.C. Dept. is very important since its approval may be required for the implementation of the transferred technology, including Licensee's payments in some cases.

Although it is an obvious security for both parties and patients that the Licensee's Q.C. Dept. exists, operates correctly and is able to control the required specifications, and the technology implementation, there is a tendency in some developing countries to underestimate its importance and goals.

To some extent, it also exists a temptation among certain licensors to put aside the key role of the licensee's Q.C. Dept. in order to possibly minimize the vigilance of such Dept.

In the interest of all parties involved, a license agreement for the manufacture of medical products should contain specific provisions for the creation or adaptation of an efficient Q.C. Dept. The methods used and the operations performed by the licensee's Q.C. Dept., as long as records and samples are kept, are the only way to eventually detect the responsibility of the Licensor in case of production problem.

For cases where the Licensee does not possess, at the time of signing the licensing agreement, a Q.C. Dept. a number of specimen clauses are presented in Annex IV.

7. Packaging

Packaging of the pharmaceutical products, owing to its inherent importance deserves special mention. From the very beginning of the civilisation, packaging in some form or the other was in practice. It has become more and more scientific and sophisticated and has gained status of a technological entity. This applies as much to the pharmaceutical industry as to any other. Because of its relation to health, packaging in pharmaceutical industry is emphasised, though more upon functional efficiency, yet it should have a consumer appeal. Besides, this packaging is essential to impart longer shelf life of the product by protecting it from environmental deterioration. The primary objects of packaging are: -

i) Protection from water, moisture, light and heat, aerial oxidation etc.

ii) Prevention of contamination and mixing.

iii) Prevention of breakage, material losses and loss of potency.

iv) Protection from deterioration and even formation of toxic and antagenic substance which are hazardous to health.

v) Identification of the product.

vi) Convenience of transport.

vii) Presentation to the Consumer.

During the last decade, tremendous progress has taken place in the field of packaging materials as well as types and modes of packing. Various types of packaging materials available today are given below: -

a. Glass - neutral, sulphated, amber

b. Metals - stainless steel, mild steel, tin-plates, aluminium in the form of containers, foils, collapsible tubes etc.

c. Plastics - polythylene, polyprosylene, PVC, polymethylpentene, saran, nylon, polycarbonate, polystyrene, polyurethane, cellulose and cellulose derivatives, gelatin, urea formaldehydersin etc.

d. Paper and Cardboards.

The availability of suitable packaging material may adversely affect the type of formulation or even the productivity. Packaging development may therefore proceed parallel with the stability, shelf life of the product. It may some times even be expendient to modify the formulation to suit the container or packaging medium provided it does not adversely affect the product. If plastic containers are to be used, it is necessary to avoid the use of bacteriostatic preservative which is absorbed by the plastic materials. A metal container may necessitate the addition of a corrosion inhibitor or a screening agent or application of a suitable inert coating. The choice of packaging material and also the type of packaging depend upon the following factors:

1. Physical nature of the product - solid, liquid, paste etc.

2. Chemical nature - corrosiveness, sensitivity of the product to water, moisture, light and heat, oxidation, putrefication, reactiveness.

3. Possibility of deterioration, decomposition, formation of toxic substances.

4. Mechanical strengh of the package and product during transportation and storage.

5. Ultimate use.

6. Degree of protection required.

7. Compatibility

8. Customers convenience - size, weight, opening and reclosing, legibility of printing.

9. Presentation - particularly for those products which may be the subject of impulse buying.

10. Filling method

11. Cost.

Based upon the physical nature of the product various medicinal preparations may be categorized as below: -

The list of packaging materials for these products is given in Annex V.

## 8. Marketing

Marketing is the kingpin of the Drug and Pharmaceutical Industry. It is their function to see that the Drugs are made available where they are needed and when they are needed and also make the profit to plough back them for expansion dividends and research and development which are the basic features of the industry.

Formulations are of three categories, namely (i) Generic, (ii) Specialities, (iii) Over the countrer products.

### i) Generic

The Generic products are named after the official pharmacopoeial name or some of the countries have their own national formularies which also include mostly the pharmacopoeial name and in case of certain combination, the name given also become generic. Most of the formulations required by the institutions are generic and packed in bulk. These are cheaper as compared to specialities. Besides, the Government, such practising doctors who also dispense the medicine to the patients, purchase generic formulations in bulk.

ii) Specialities

Unlike other consumer products, formulations marketing is more sophisticated and unique in its character. there is very little contact between the consumer and producers, as formulations are PRESCRIPTION product and hence has to be prescribed or recommended by the medical professionals. Moreover, same product is being marketed by large number of companies,thus it involves system of conviction and promotion of product by each company, which could be achieved easily by identifying the product by giving it a branded or proprietory name called "Speciality". Thus the marketing of specialities require a very large network of medical representatives backed by promotional and medical literature, samples, gifts, participation in seminars, inviting medical professionals to visit their production centres, research and development and quality control units. Most of the sale of formulations in the trade is of specialities whereas generic product constitute very small percentage. Reverse happens in case of institutions, hospitals and general practitioners requirements. Initial sale of the specialities depends upon the reputation of the firm.

iii) (OTC) Over the Counter Product - Household Remedies

(OTC) or household remedies are such products, the efficacies of which are well known and is advertised through newspapers, periodicals, radio and television. Thus marketing of OTC product is almost similar to any consumer product.

Marketing Organization Structure and Functions

Marketing Organization is headed by the Marketing Director supported by various functional departments below: -

1. Marketing Research: (a) Market Demands/Potential studies (b) Retail Chemist Survey; (c) Stockist survey; (d) Study of competitors sale; (e) Sale analysus; (f) Region and country-wise, productwise sale: (g) Incentive scheme; (h) Sale forecasting. (i) Fixation of targets and performance evaluation of stockists, retailers.

2. Market Planning: This department discharges a staff function, which includes planning, co-ordination and monitoring activities.

Preparation of Sale Programme based upon optimum utilization of Production capacities, growth rate of the industry. Preparation of sale budget and its month to month monitoring, inventory control, monthly reviews, co-ordination with production.

3. Distribution: The distribution department discharges a wide range of activities which include: (i) Stock requisition, allocation, supply position; (ii) Inventory management through weekly stock statements; (iii) Pursuance of transport bottlenecks, (iv) Monitoring of short dated products; (v) Review of stockist performance; (vi) Legal and administrative proceedings of depots; (vii) Depots inspection; (viii) Formulation of price-lists; (ix) Complaints on non-availability and sub-standard quality.

4. Supplies to Hospitals: The Government is always the biggest single buyer and distributor of drugs. These are supplied in mostly in generic form in bulk in special packagings, with special markings on credit and at highly competitive rates. Most of the supplies are made direct by the manufacturers without middleman agency. Either central agency after calling the tender fixes the rate and various institution or Government department can directly put the indents directly to the manufacturers, or the central agency fixes the rate and assumes the function of purchase and distribution.

5. Trade Sale: It is done through the wholesale dealers or distributors particular territory, who supplies the material to the retailers as well as to the practising doctors, clinics and small hospitals.

6. Sales Promotion/ Sales promotion is done by the sales representatives, who details his product to the medical professional. To achieve this efficiency, the department has to prepare: -

1. Latest technical information from a promotional dimension rather than restrict the interpretation of same to the therapeutic and clinical aspects.
2. Regular procurement and supply of Promotional literature to the Representatives.
3. Training of Sales Representatives and refresher courses and training programme.
4. Co-ordination with medical and distribution department.

7. Medical Department:(i) supply of latest therapentic information to the field force; (ii) conduct training programme; (iii) collection of scientific data - national, internal; (iv) to attend and take-up company view point in medical conferences and seminars; (v) to establish good contacts with the health and drug control authorities; (vi) preparation of medical literature with due weightage to therapentic and commercial aspects; (vii) timely investigation of complaints; (viii) development of infrastructure for clinical trials and other scientific activities.

8. Finance: Besides liiking the general aspects of financing salaries, realisation, inventory control, fixation of targets, evaluation of performance and profitability, it should get remunerative prices fixed from the authorities.

9. Personnel and Administration: Manpower planning recruitment promotional policy on which the success of the organization depends.

Registration of new drugs

In order to enable the Licensee to obtain the registration of the products, the Licensor should provide a set of informations, such as:

1. Chemical description of the drug/drugs, declaration of the internationally or nationally accepted generic name or the name under which it is proposed to be sold:

   a. description
   b. full chemical composition, if not known, such other details are known.
   c. description of pharmaceutical form/forms in which it is proposed to be marketed and the root of administration, the proposed doses and the claims to be made for such a drug.

2. Composition of the drug giving the amount of each ingredient.

3. Details of the method of production.

4. Analytical specification, chemical as well as physical, taste for proper identity, purity and quality. The methods of assay including analytical methods for determination of active ingredients.

5. Details of stability studies.

6. Details of investigations regarding safety and effectiveness for use.

   a. efficacy invitro and invivo studies.

   b. pharmacological and pharmacogynamic studies on laboratory animals pertaining to physiological systems such as cardio vascular system, respiration system, central nervous system, urinary nervous system, and enotomic nervous system.

   c. bio-chemical studies showing detailed observations, distribution, metabolism and excretion of the drug.

   d. depending upon the type of drug to acute toxcity, toxicological studies, sub acute and chronic toxcity. corsenogenecity and drug dependence and teratogenic studies.

7. Details regarding clinical trials.

Data to be Supplied for Marketing Promotion

1. Besides the data referred to collected by the Licensor in the country of origin or in other countries, it is obligatory in some countries to carry the clinical trials for latest and new drug and in case of well-established drug and combination, published data is to be submitted to the drug authority before obtaining marketing permission.

2. Copies of published or unpublished reports of clinical trials pertaining to and evaluation of the safety and effectiveness of the drug.

3. Certificate of approval or free sale certificate issued by the Health Authorities in the country of manufacture and the names of the countries where this drug is being marketed.

4. Drafts or specimen of lable, adopted literature etc. proposed to be adopted for marketing.

The full insert should have correct information about the contents, food therapatic as well as toxic or communication of the drug.

5. Literature for medical profession giving factual data, general specimen, supported by acceptable scientific evidence.

6. Whether the drug is approved by Food and Drug Authority Aministration USA or any drug Authority in other countries, if so, whether any restrictions are imposed on sale, way of labelling etc. (a copy of the literature including, if any, side effects, contra communication, precaution, warning etc. as approved by these authorities.)

Medical Information

As part of promotional strategy for specialities, it is necessary that the manufacturer educate or elaborate various scientific and medical information given below to the medical professionals: -

I. History

II. Structural Formula

III. Pharmacological aspects.

i) Serum levels; ii) Kinetics; iii) Distribution of drug in the body: iv) Mode of Anti-microbialaction; v) Therapentic uses of the product.

IV. Comparison with known drugs and its advantages.

V. Toxicity and side effects.

a) Hypersensitivity; b) Nephrotoxicity; c) CMA toxicity; d) Haematological toxicity.

1. Recitals

The inclusion of "recitals" or a "preamble" to the contract, is a quite common practice and may be useful for stating the premises of the contract and the objectives of the parties.

These clauses may include, for instance, reference to the business background of the parties, the willingness and intention thereof to enter into and execute the agreement, and their desire to observe the health and other relevant policies of the country of the Licensee.

It should be noted that in case of discrepancy between the recitals and the substantive provisions of the agreement, the latter prevail.

Specimen clauses

1. Recitals

WHEREAS the Licensor .....

(Alternative a: has manufactured and sold the Products defined below for several years).

(Alternative b: is in the possession of technology for the manufacture and sale of the Products defined below)..... and owns patents in the Licensee's country related to the Products:

AND WHEREAS the Licensee has facilities for the manufacture, packaging and marketing of pharmaceutical products;

AND WHEREAS the Licensor is able to transfer technical information and to provide, if requested, basic drugs for the manufacture of the Products:

AND WHEREAS the Licensee desires to obtain a license for the manufactur and sale of the Products;

AND WHEREAS the Licensor and the Licensee intend to conclude and execute this Contract in a manner that is beneficial to the development of the pharmaceutical industry in the country of the Licensee and in conformity with the health regulations in force in that country;

NOW THEREFORE the Licensor and the Licensee hereby agree as follows:

2. Definitions

While not indispensable, a cluase containing the definitions of the main terms and expressions used in the agreement may avoid repetition and misinterpretation.

Such a clause would usually define, in a licensing agree for formulations, terms such as "Technical information","Medical . ientific information", the Products (i.e. the medicines to be formulate the "Basic Drugs" (i.e. the required ingredients) etc.

Specimen clauses

2. Definitions

In this agreement the following words will have the following meaning:

2.1. "The Licensor" will mean the party named as such in this Contract, or its successor or legal assignee;

2.2. "The Licensee" will mean the party named as such in this Contract, or its successor or legal assignee.

2.3. "The Contract" will mean this agreement together with all its annexes and any subsequent amendment made thereto in accordance with the provisions of the Contract.

2.4. "The Licensor's plant" will mean the plant of the Licensor located at .....

2.5. "The Licensee's plant" will mean the plant of the Licensee established at .....

2.6. "Technical information" will mean all formulae, process, technical and scientific knowledge necessary for the manufacture and marketing of the Products, including but not limited to production process, quality control methods, packaging methods and materials, machinery and equipment needed, stability data and full specification of the Products, raw materials comprising bending, flavouring and dying materials.

2.7. "Medical and scientific information" will mean all the medical, scientific and related literature and data on pharmacological and clinical trials on the Products, including information, reports, samples and documents required for the registration of the Products with the Health Authority of the Licensee's country.

2.8. "The Products" will mean .....

2.9. "The Basic Drugs" will mean the following drugs entering into the formulation of the Products .....

2.10. "Improvements" will mean any technological advance developed or otherwise acquired by the Licensor or developed by the Licensee related to the manufacture or packaging of the Products.

2.11. "Effective Date of the Contract" will mean the date on which this Contract will come into force in accordance with provision ..... thereof.

3. Medical and scientific information. Registration of Products.

The communication of medical and scientific information related to the Products to be licensed [illegible] on the main objects of agreements for formulations. It generally permits the Licensee to obtain most of the information required for the approval of the Products by the competent authority in its own country, and save the money and time that would require the gathering of data and testing of the specialities.

In addition to such information, the Licensor would be normally asked to provide a sample of the Products, in order to make the laboratory tests as required in the country of the Licensee.

In a situation where the Licensor itself manufactures and sells the Products, the communication of medical and scientific information will not imply other expenses than the limited costs of reproducing the pertinent documentation.

On the other side, the obtention of such information is for the Licensee the first step on the basis of which he will be able to request the authorization of the Products before the competent authority. Failing such an authorization, there would be no further reason to receive other supplies from the Licensor (technical information and assistance, etc.).

Given these characteristics of the contracts for formulations, it is usual that the Licensee does not effect any payment (or even undertake to do it) until the authorization of the Products has been obtained. Lacking the authorization, the contract remains without object and may therefore be declared terminated without responsibility for any of the parties.

If the Licensor does not receive payments, as it is usual, until the Products have been approved or are on the market (when remuneration is based upon royalties on sales (*)), he may refuse to provide information other than that already available to him, except if the Licensee agrees to bear the costs for obtaining any additional information. Such an additional information may be necessary to meet requirements imposed by the competent authority of the Licensee's country.

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(*) This is the main form of payments suggested in the specimen clauses attached here. See "Remuneration".

It is important that the Licensor disclose to the Licensee all information known to him on the actual or possible adverse or side effects of the Products, both at the time of signing the agreement as well as during the lifetime thereof, including information on changes in the registration status of the products in other countries (for instance, if the authorization for sale has been cancelled or restricted the therapeutical uses of the Products, due to new determined or alleged adverse effects). The due observance of such an obligation is not only in the interest of the Licensee, but primarily in the interest of the patients and the health authorities of the Licensee's country, and will contribute to avoid the situation where products banned in developed countries due to their verified or presumed adverse effects are sold, without appropriate limitations, in developing countries.

A product may have several medical applications. Some of them may not be suitable at all in the Licensee's country. Besides, many active principles have both human and veterinary applications and very little difference in specifications. The Licensee should be duly informed by the Licensor, and under the Licensor's responsibility, on the limits to be observed in the use of the product.

Finally, the Products are normally registered under the Licensee's name.

Nevertheless, for the case of termination of the Contract by reasons attributable to the latter, it may be stipulated the Licensee's obligation to transfer the respective certificate to the Licensor or any person designated by him.

Specimen clauses

3. Medical and scientific information

3.1. Within ..... days from the Effective Date of the Contract, the Licensor will supply the Licensee with all the Medical and Scientific Information related to the Products, available to the Licensor, including samples thereof, and all details known to the Licensor on adverse or side effects of the Products.

3.2. If during the proceedings before the competent authority of the Licensee's country for the authorization of sale of the Products, that authority requires new laboratory, specifications or additional information, the Licensor will supply them, .....
(Alternative a: at the Licensee's cost)

(Alternative b: at its own cost)

3.3. During the lifetime of the Contracts the Licensor will promptly communicate to the Licensee any new data known to the Licensor concerning adverse or side effects of the Products, as well as any changes in the registration status of the Products in the Licensor's country or in other countries where such Products are marketed, where such changes have been determined by the actual or possible adverse or side effects of the Products.

3.4. The applications of the Products are the following: .....
.....

3.5. The documentation referred to in this article will be .....
(language).

3.6. The Products will be registered under the Licensee's name. However, if this contract is terminated by reasons for which the Licensee is responsible, the Licensee will transfer the certificate of registration to the Licensor or a person designated by him, subject to the legislation in force in the Licensee's country.

4. Technical information

The content of the know-how or technical information to be supplied for the formulation of pharmaceutical products, strongly depends upon the technical capacity of the Licensee. For some firms in developing countries, which already possess experience and skills in this field, the transfer of such information may be unnecessary or required to a very limited extent. In other cases, particularly in the less developed among developing countries, the transfer of such a knowledge may have considerable importance, at least at the initial stages of development of a pharmaceutical industry.

The know-how necessary for formulation is generally simple, and may be handled without great difficulty. However, technical assistance and training may be convenient when the Licensee has a low technical capacity.

The expression "know-how" is rather imprecise and ambiguous, both in commercial practice and in legal terms. It is advisable, hence, to avoid the use of the expression, and replace it (as suggested in the attached specimen clauses) by "technical information".

The technical information related to formulation may eventually include some pieces of confidential knowledge. In that case, the Licensor should identify such pieces and the Licensee observe an obligation of confidentiality (see point 12, "Confidentiality", below).

The Licensee will be interested in receiving technical information which is the most updated and which has been commercially proven by the Licensor. Its description should be sufficiently clear and comprehensible, correct and complete (see also point 14 "Guarantees"). The contract should also determine the form in which it is to be transferred (specifications, instructions, etc.) and the language in which it should be drawn up.

Technical information generally consists of one formula, some manuals and other written documents, or explanations, plus some complementary informations related to the environment of the production process, such as input, maintenance, storage and basic design.

The contract should contain a detailed and exhaustive list of what the technology to be transferred is precisely composed of. The content of the list depends on the drug and the process concerned. It is highly probable that any point left aside from such list and later requested by the Licensee will be refused by the Licensor. The list will also be helpful for the itemization of the contract's price.

The components of the technology to be transferred may include (depending on the Products and the object of the contract):

- process (if any)
- specific know-how developed by the Licensor
- required raw materials, specifications and consumption of same
- equipment and materials and lay-out
- utilities and their specifications
- operations to be performed in the course of the process
- basic design and basic engineering
- storage of raw materials, semi-finished and finished products
- quality control techniques
- treatment of effluents (whenever applicable)
- recovery of solvents (whenever applicable)
- requirements of qualified personnel
- safety instructions; protection of the personnel
- strain specifications (whenever applicable)
- sampling; keeping of samples (up to 10 years).

Once the complete list of the components to be transferred has been established and each component has been defined, the contract should include the identification of the support (manuals, drawing, charts, computerized documents, tapes, training sessions, demonstration sessions, etc.,) which shall contain said component of the technology.

The strict definition of components and the corresponding way of transfer, should prevent the Licensee from receiving unadapted documentation. In too many instances, documentation is mostly composed of internal manuals for the Licensor's personnel use only. The documentation as well as training sessions should be a "product" specific for exportation, adapted

whenever necessary to the requirements of the Licensee. In too many opportunities, this aspect of the transfer is unformally treated alledgely not to "complicate" the Contract because the parties have so many opportunities to meet that these "details" shall be solved personally by both representatives on a punctual basis. Experience has shown this lack of foresight may cause many problems.

Specimen clauses

4. Technical information

4.1. (Alternative a: Within ..... days from the communication of the Licensee that the authorization for sale of the Products has been obtained).....

(Alternative b: Within ... days from the Effective Date of the Contract) the Licensor will provide the Licensee with the latest commercially proven Technical Information, as defined in 1 above ("Definitions") required for the manufacture, quality control and packaging of the Products, including the following: .....
.....
.....
.....

4.2. The aforesaid documentation will be furnished in the form of .....
.....

4.3. All documentation referred to in 4.2. will be drawn up in ..... (language) and be presented in a clear manner comprehensible for a normally skilled professional in pharmaceuticals, using ..... (units system).

4.4. The following documentation will be considered as confidential, in accordance with art..... of this Contract ("Confidentiality") .....
.....
.....

4.5. The documentation will be .....
(Alternative a: sent by registered air mail to the following address. The Licensor will confirm by telex to the Licensee the expedition date of each lot of documentation expedited).

(Alternative b: handed over to ..... at .....)

4.6. Upon reception the Licensee will issue a "reception certificate" stating that the documentation has been received, indicating eventually the missing documents.

4.7. The documentation transferred will become the property of the Licensee..... days after the issuance date of the "reception certificate" and will remain the property of the licensee even if the Contract is terminated before the expiration date, whatever the cause is.

5. Technical assistance

If the Licensee has limited experience in the formulation of pharmaceutical products, it may require the advice of the Licensor by means of technical assistance provided for by the latter's personnel. The Contract may determine the number and category of the personnel to be deputed, as well as the time of their work, or leave the Licensee the possibility to request the supply of the assistance, should it deem it necessary, up to a maximum of man-months specified in the Contract.

The determination of the schedule and program for the technical assistance may be left to an agreement between the parties to be made reasonably in advance from the date where the assistance is expected to start.

The Licensee will normally bear, in addition to a fee, a subsistence allowance for the deputed personnel consisting either in the direct coverage of accommodation, meals, etc. or in a fixed amount of money (normally payable in local currency) per each day of presence in the Licensee's country.

Specimen clauses

5. Technical assistance

5.1. (Alternative a: The Licensor will make available at the Licensee's Plant a total of ..... man-months of technical assistance, in order to provide advice and assistance to the Licensee in connection with the manufacture and packaging of the Products. The personnel to be provided by the Licensor and the duration of their assignment will be as follows:

| Category | Duration of assignment |
|---|---|
| ..... | ..... |
| ..... | ..... |

(Alternative b: The Licensor will, at the Licensee's request, send qualified technicians to the Licensee's Plant, in order to provide technical advice and assistance to the Licensee with respect to the manufacture and packaging of the Products. In accordance with this provision, the Licensor will provide up to a maximum of ..... man-months of technical assistance).

5.2. The Licensee will pre-pay to Licensor an economy class round trip air ticket for the personnel deputed to Licensee's Plant.

5.3. (Alternative a: The Licensee will provide accommodation, meals and transport for official work all free of charge at the Licensee's country).

(Alternative b: The Licensee will pay a subsistence allowance of ..... ..... (local currency) for each calendar day of presence in Licensee's country of Licensor's personnel, on the date of beginning of their duties.

5.4. The schedule and programme for the technical assistance will be agreed upon between the Licensor and the Licensee in due time but at least ..... month before the start of its provision.

6. Training

In some cases, the Licensee may consider convenient to ensure the learning of the production techniques by means of the training of its personnel. In that hypothesis, there might be substantial advantages if the training takes place at the Licensor's premises, including on-the-job experience in the production, quality control and packaging of the products.

Preferably, the on-the-job training should also comprise the manufacture and control of a certain number of batches, or for a determined time.

The Contract should establish the number and qualifications of trainees, and refer to the determination, in due time, of the schedule and specific content of the training programme.

The costs of travel and subsistence of Licensee's personnel being trained are normally covered by the Licensee. It may be also advisable to take out an insurance policy covering any injury or damage to persons or property that may be caused by the trainees during their stay at Licensor's plant.

Specimen clauses

6. Training

6.1. The Licensor will provide training to qualified employees of the Licensee at the Licensor's Plant, with respect to the manufacture, quality control and packaging of the Products, including on-the-job training for .....
(Alternative a: the production and control of at least ..... batches from the beginning to the end)

(Alternative b: no less than ..... weeks)

7.2. The number and qualifications of the trainees will be as follows:
.....
.....

7.3. The schedule and contents of the training programme will be agreed upon in due time between the Licensor and the Licensee.

7.4. The costs of the trainees' travel as well as food and board whilst in Licensor's country will be borne by the Licensee.

7. Patents

Patent protection in pharmaceuticals, wherever it is recognized, concerns the process of manufacture (process patents) of a drug or the drug itself (products patents).

In the case of process patents the manufacture of a pharmaceutical form does not imply the use of the patent, which always refers to a basic drug and not to a formulation. Therefore, the existence of such patents is, in principle, irrelevant to the licensee in an agreement concerning only formulation.

Instead, if product patents exist (*) the Licensee will need a license to use the patent covering the drug entering into the formulation, even though the Licensee will not manufacture the drug itself.

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(*) A large number of developing countries presently do not recognize product patents in pharmaceuticals. They are:

Upper Volta
Argentina
Benin
Bolivia
Brazil
Cameroon
Chad
Chile
Colombia
Congo
Ivory Coast
Korea
Ecuador
Egypt
Gabon
Ghana
Guyana
Honduras
India
Indonesia
Iran
Irak
Kuwait
Lebanon
Lybia
Morocco
Mexico
Nigeria
Paraguay
Peru
Central African Republic
Senegal
Syria
Thailand
Togo
Tunisia
Uruguay
Venezuela
Yugoslavia

A licensing agreement for formulation may, wherever product patents are involved (*), include the following stipulations:

(a) specification of the number, and eventually date of granting and expiration, of the patents licensed;

(b) Licensor's warranties regarding its title to the patents and their validity;

(c) the action to be undertaken in case of infringement of licensed patents. That action may be jointly assumed by both parties, or left to only one of them (normally the licensor);

(d) the obligation (normally at the Licensor's charge) to maintain in force the licensed patents, by paying the renewal fees, if required.

The Contract may also include in connection with this issue a "patent immunity" clause, under which the Licensor undertakes not to use the patent rights it may own in countries other than the Licensee's country to prevent Licensee's exports of the Products to such countries. The negotiation of such a clause will normally be a part of the discussion on the right to export recognised to the Licensee (see point 19 below).

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(*) The same would apply if the protection conferred by process patents, is extended to the products manufactured with that process, for instance, if the patent owner is entitled to prevent imports of such products into the country where the patent is in force.

Specimen clauses

7. Patents

7.1. The Licensor hereby grants the Licensee, with effect from the Effective Date of the Contract, a license of use under the following patents as registered in (country of the Licensee) .....
.....

7.2. The Licensor warrants that:
(a) it owns the listed patents and that it has the right to grant licenses for the sale of the Basic Drugs in (country);
(b) to the actual extent known to him, there is no limitation, including any pending official procedure or litigation, which adversely concerns the validity of the aforesaid patents.

7.3. The parties will promptly inform each other on any infringement of patents listed above which became known to them.....

(Alternative a: The parties shall jointly undertake the proceedings against infringers, and determine their respective responsibilities and the distribution of expenses and costs.).

(Alternative b: the Licensor shall undertake at its own expense the pertinent proceedings against infringers, and will enjoy the benefits of any sum payable by the infringer in concept of royalties, license fees or damages. In the event that the Licensor fails to undertake the proceedings as stipulated, the licensee will be entitled to take all appropriate legal actions against infringers on the basis of powers or authorizations provided by the Licensor. In this case any sum payable by infringers will correspond to the Licensee).

7.4. The Licensor will pay any renewal fees necessary for the maintenance of the patents listed above.

7.5. The Licensor or any person holding rights from it will not use any patents that it holds under the laws of (country or countries), and which corresponds to the patents listed above, to prevent the exports of the Products by the Licensee to said countries.

8. Trademarks

Licensing agreements for formulations sometimes comprise the license of trademarks owned by the Licensor. Such a license does not create special problems from a legal point of view, but gives rise to a number of economic and enterpreneurial consequences that potential licensees should carefully take into account.

For the Licensor, the use of its own trademarks on the Products sold under license, permits it to acquire control over the market developed by the Licensee: expired the agreement, the licensor may agree to renew it or to exploit the market himself, or grant a license to a third party. The Licensee on its side, becomes completely dependent upon the Licensor's decision and may be forced, if it wants to continue in the use of the trademark, to the acceptance of very disadvantageous terms.

Further, the license of trademarks implies additional payments by the Licensee which, in the absence of specific legislation on the matter, may continue as long as the market product retains its commercial value. Finally, the acceptance of such a license would also lead in general to greater controls of the Licensor as regards to the quality of the Products and may be a justification for requiring that the basic drugs that enter into the formulation be purchased only from the Licensor or other source designated by it.

In view of the problems referred to, and except where very special circumstances justify it, it would seem advisable that the Licensee uses its own trademarks or other trademarks determined by it on the Products formulated under license. Eventually, the Licensor may be accorded the right to question the choice of a given trademark, on reasonable grounds.

Specimen clauses

8. Trademarks

8.1. The Licensee will be free to choose the trademarks to be used on the Products, in accordance with the law of the Licensee's country.

(Alternative a: The Licensee will inform the Licensor, in due time, the trademark the Licensee intends to use on the Products. Within ..... days from receipt of such communication the Licensor may communicate and substantiate any objection concerning Licensee's choice).

9. Supply of basic drugs:

The manufacture of the Products will in most cases require the purchase of the basic drugs that enter into their formulation by the Licensee. In many cases, particularly in developing countries, such drugs are not produced locally and hence need to be imported from external sources.

An obligation imposed on the Licensee to acquire basic drugs from the Licensor or other source designated by it, will be regarded in many developed and developing countries as a restrictive business practice and held illegal.

There is only one situation where the Licensee may be legally bound to buy the basic drugs from the Licensor. It is the case where the latter holds product patents in force in connection with basic drugs in the Licensee's country, on the basis of which it can legally prevent the importation of the drugs by third parties. However, even in this situation, the agreement should not contain a clause stating the Licensee's obligation to buy from the Licensor, since that restriction should only apply to the extent and as long as imposed by the patent in force.

In both situations described (either if there are product patents or not) the drugs should be supplied by the Licensor at a reasonable price non less favourable than the price usually charged, for similar supplies, by the same Licensor or other alternative sources.

In cases where no product protection exists, from the Licensee's point of view it is advisable to ensure in the Contract as much freedom to purchase as possible. One of Licensor's interests in granting a license for formulations is usually the possibility to sell the Licensee the required basic drugs. A reasonable compromise between the parties interests may be to grant the Licensor a preference in the acquisition of basic drugs, if the latter offers at least the same price, quality and delivery conditions as the Licensee can secure from other alternative sources.

The use by the Licensee of Licensor's trademarks should not be deemed as sufficient ground for imposing the acquisition of basic drugs from the Licensor itself or other source designated by it. The Licensor's interest or public (*) interest in ensuring the quality of products which bear a licensed trademark may be satisfied by requiring that the basic drug used by the Licensee strictly corresponds to the specifications supplied by the Licensor. The latter may also be authorized to require samples of the products, and the Licensee prevented from selling, with Licensor's trademarks, Products in respect of which it has been proven that they do not comply with the specifications set forth in the Contract.

Eventually, the Licensee may agree to purchase exclusively the required basic drugs from the Licensor. In this hypothesis, some safeguards should be provided for as regards to the prices to be charged, the amounts to be purchased and the consequences of any interruption in delivery.

In cases where there is one supplier, a special provision should carefully stipulate a maximum percentage of price increase per year during the purchasing period allowed to the licensor. If no agreement can be reached on that point and if no other firm gurarantees are given to the Licensee, then it would be advisable not to enter into a license and purchase agreement, which is extremely risky for the latter.

The contract may detail the conditions for delivery of the basic drugs, and the procedures to be followed in cases where differences arise out as regards to the compliance with the minimum specifications agreed upon.

As far as payments and credit terms are concerned, it is advisable to stipulate that payments and credit terms are linked to the date of the conformity certificate issued by the Licensee's Quality Control Department, and not to the date the basic drugs reach the delivery point.

As far as prices are concerned, the contract may determine that prices are fixed and unrevisable for a minimum period, for instance, 12 months, and that, once revised, prices are again unrevisable for the same minimum period. When applicable an indexation clause, if any, it should not apply if the resulting increase of price is below a certain percentage. Such a clause must be linked to at least one official or governmental index.

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(*) In some countries, the law itself establishes the obligation of the Licensor to ensure the quality of the products sold under a licensed trademark.

Specimen clauses

9. Supply of basic drugs

9.1. The Licensor will, upon the Licensee's request, supply the Licensee with the Basic Drugs (as listed in .....) produced by the Licensor and entering into the formulation of the Products, at a price non-less favourable than the price usually charged by the Licensor or other suppliers for Basic Drugs in conformity with the specifications set out by the Licensor under the Contract.

9.2. (Alternative a: i) The Licensee will be free to buy such Basic Drugs from any sources, provided that if the Licensor is willing and able to offer the Licensee such Basic Drugs at least at the same price, and with the same quality and delivery conditions as the Licensee could obtain from other sources, in this case the Licensee will grant preference to the Licensor.

ii) If after comparing the offers of various sources, including the Licensor, the Licensor's offer is less favourable than other offers, the Licensee will communicate to the Licensor the terms of the best offer it has obtained. The Licensor will indicate within ..... days from the receipt of Licensee's communication whether it will modify its offer in order to meet the better terms that the Licensee could obtain from the source).

(Alternative b: If the Licensee receives a quotation, under similar purchasing conditions, from an alternative supplier, which is at least .....% below the Licensor's price, the Licensor must then adjust his price to the level of this quotation, otherwise and for the time of this quotation, the Licensee may purchase without prejudice from the alternative supplier).

(Alternative c:

(i) The Licensee accepts, under the conditions stated in the present article, to exclusively purchase from the Licensor the Basic Drugs, and the Licensor agrees to supply the Licensee during the lifetime of the Contract, starting on....., under the following preferential conditions he usually grants to his licensees and subsidiaries.
(ii) The minimum yearly quantities of Basic Drugs to be delivered by the Licensor to the Licensee are: .....

Quantity

Year 1

Year 2

(iii) The above mentioned quantities being the result of forecasts established jointly by the Licensor and the Licensee at the time of signing the present license agreement, it is agreed upon by both parties that ..... month(s) before the beginning of each calendar year, said forecasts may be revised in order to adjust them to the real requirements of the Licensee.

(iv) The Licensor guarantees the Licensee he shall take all necessary measures to that the forecasted, eventually revised, and agreed upon quantities of Basic Drugs will be timely available for delivery to the Licensee.

(v) The Licensor recommends and the Licensee accepts to maintain, for each Basic Drugs considered, a minimum security stock as follows .....
.....

(vi) The Licensor guarantees the Licensee he shall take all necessary measures in order to be able to immediately replace the eventual loss of the Licensee's security stock(s); as well as the eventual loss of any delivery, whatever the cause of the loss.

(vii) Within each year and per each Basic Drug, the split quantities to be delivered by the Licensor are stated in Annex..... However, upon..... month(s) written notice given to the Licensor, the Licensee may request, and obtain, modifications in quantities to be periodically delivered within a year, as long as the yearly total agreed upon for that year in Annex ..... is not changed.

(viii) In the case the Licensor would not be able to comply with one (or more) delivery, as stated and agreed upon in Annex..... the Licensor binds himself to immediately inform by telex the Licensee, indicating the reasons of the interruption; duration, or estimated duration, of the interruption and the alternative sources of supply he recommends.

(ix) During the interruption, the Licensee shall have the right to purchase the missing Basic Drugs from any alternative source of supply recommended or not by the Licensor. The eventual price increase, under the same purchasing conditions, paid by the Licensee to an alternative supplier will be reimbursed up to a maximum of .....% per KG for Basic Drugs, upon

presentation by the Licensee of the corresponding paid invoice and debit note.

(x) In the case there is no possible alternative supplier, the Licensor will pay to the Licensee a penalty amounting to .....% of the ex-factory value of the interrupted delivery. The payment of this penalty will take place, the case being, at the date the delivery should have taken place. The maximum accumulated amount of these penalties to be paid by the Licensor to the Licensee is fixed at ..... (amount and currency).
Once this amount reached, the Licensee shall have the right, giving written notice to the Licensor, to terminate the present Contract.

(xi) Furthermore and at his sole judgement, the Licensee may take all appropriate steps for obtaining indemnities due to the impossibility to carry out his activities. The above mentioned penalties and indemnities do not apply in case of force majeure, duly and timely notified to the Licensee by the Licensor.

(xii) The price of the Basic Drugs will be as follows for .....
(period). This price will be revised ..... annually and adjusted in accordance with ..... (index or formula).

(xiii) The increase resulting from the application of the precedent clause will not be applied if the increase is below .....%.

(xiv) Above .....% of resulting price increased, the Licensee will not be any longer obligated to exclusively purchase from the Licensor.

9.3. (*) If the Licensee intends to purchase the Basic Drugs from sources other than the Licensor, within ..... days from the communication of the Licensee indicating such decision, the Licensor may require that samples of the Basic Drugs to be purchased be sent to it for analysis in Licensor's laboratories to ascertain their conformity with the specifications provided for by the Licensor.

The samples will be considered approved if the Licensor does not communicate and duly substantiate its objections within ..... days from receipt of the samples. The Licensee will not put on the market products bearing Licensor's trademarks with respect to which it has been determined that they do not conform to the specifications set out in the Contract. Any dispute arising from differences in analytical results of samples will be finally decided by .....
.....(**))

---

(*) This clause would only apply in cases where Licensor's trademarks are used on the Products.

(**) A neutral drug control institute should be indicated here, preferably the State laboratory for control of drugs in the country

9.4. (i) The specifications of the Basic Drugs to be delivered are stipulated in Annex ..... The Licensor guarantees that the specifications of all Basic Drugs delivered by him to the Licensee will, at least, meet the minimum specifications stipulated in that Annex.

(ii) The Licensor will replace, free of charge, the Basic Drugs which will not meet these minumum specifications and rejected by the Quality Control Department of the Licensee.

(iii) The Licensor shall forward to the Licensee, together with the shipping documents, one certificate of analysis per batch, or fraction of batch, composing each delivery. The analysis corresponding to such certificates shall be performed by the Licensor according to the methods and operational modes stated in the present Contract.

(iv) The storage conditions concerning the Basic Drugs, recommended by the Licensor are stipulated in Annex ..... They take into account the specific conditions prevailing at the Licensee's facilities and in the Licensee's country.

(v) Within ..... days after reception of the Basic Drugs at Licensee's facilities, the Licensee will perform analysis of these Basic Drugs according to the methods and operational modes stated in this Contract.

(vi) The date of the conformity certificate issued by the Licensee will be the date of final acceptance of the received Basic Drugs.

(vii) In case of rejection by the Licensee's Quality Control Department, a sample of the rejected Basic Drug will be sent to the Licensor together with the analysis certificate.

(viii) Any disagreement concerning the results of Licensee's analysis shall not stop the future deliveries by the Licensor.

(ix) If such a disagreement is not settled within .... days/months, both parties agree they shall accept the final decision of the expert (company or individual) mutually designated below:

.....
.....
.....
.....

committed to that effect by the most diligent party. The cost of the expertise will be paid by the faulty party according to the final decision of this expert.

(x) All costs, charge, taxes, occuring before the delivery point will be at Licensor's expense, and those occurring after such point will be at the Licensee's expense. However, when such costs, charges, taxes occur because of a proven fault of the other party, then the latter will be responsible for the payment or reimbursement to the former.

(xi) The conditions under which the Licensee orders required Basic Drugs and the conditions under which the Licensor confirms, ships and invoices are detailed in Annex .....

10. Improvements

The access to improvements made by the Licensor may be of interest for the Licensee, particularly if they imply an increase in yield or reduction of costs of production.

It is convenient that the Contract defines what is meant by "improvements" either in a general clause on definitions or in the clauses specifically dealing with that issue.

In general, the price for the transfer of Licensor's eventual improvements is deemed to be comprised in the global price of the Contract. However, if the Licensee assumes reciprocal obligations as regards to the transfer of improvements reached by it, the parties should agree upon the terms for the transfer, including the price. Such a clause should be of a non-exclusive character, i.e., the Licensee should have the possibility to transfer its improvements to parties other than the Licensor.

Specimen clauses

10. Improvements

10.1. The Licensor will promptly inform the Licensee on any Improvements available to the Licensor during the lifetime of the Contract, and will provide the Licensee with full documentation necessary for the putting into practice of such improvements at Licensee's Plant.

10.2. The Licensee will inform the Licensor on any Improvements made by the Licensee during the lifetime of the Contract and, upon the terms and conditions to be agreed upon, will provide the Licensor, on a non-exclusive basis, with full documentation necessary for the putting into practice of such Improvements.

11. Exclusivity

In general, it is in the mutual interest of the parties that the agreement for the formulation of pharmaceutical forms be of an exclusive nature, since the dimension of the national market (particularly in developing countries) and the competitive patterns generally prevailing in pharmaceuticals, would make it uneconomic to grant more than one license.

The exclusivity may be limited to the sole country of the Licensee or to a larger territory, for instance, including some neighboring countries.

The molecule of one active principle is composed of a certain number of atoms displaid according to a specific structure. Generally a part only of this structure is at the origin of the action of the active principle. The remaining atoms have no medicamental effect; they may be replaced and other atoms may be added without changing the medical applications of the active principle.

The results of modifying the "secondary" part of the molecule reside in the side effects of the active principle. Considerable investigation is being presently undertaken to minimize side effects of drugs which sometimes also prevent the use of said drugs in association with other drugs. The modified active principle is more attractive than the initial one.

Consequently, it is important that the Licensee be protected against the granting by the Licensor of licence agreements related to said modified active principles. Other wise this Licensee would soon have acquired an obsolete product.

Specimen clauses

11. Exclusivity

11.1. The Licensor shall provide the items comprised in this Contract exclusively to the Licensee and to no other party .....

(Alternative a: in the Licensee's country)
(Alternative b: in the territory comprising the Licensee's country and .....)

11.2. (i) In case the Licensor shall have the intention, in the Licensee's country, to grant a licence for the manufacture of a variety of ..... (product name), that is a product with the same basic molecule and the same medical applications but with different side effects, then the Licensee shall be given a first refusal right by the Licensor.
(ii) The validity of the present Article is extended for a period of ..... years after the expiration date of the Contract.

17. Confidentiality

If the information transferred to the Licensee comprises data of a confidential nature, the Licensor should be bound to indicate which parts of the information it considers falling under that category, and the Licensee should undertake the appropriate measures in order to avoid their unauthorized disclosure.

The confidentiality obligation should not apply to the extent necessary for subcontracting or procurement, or for complying with governmental regulations requiring the approval or registration of the agreement or of the Products sold thereunder.

The confidentiality obligation should normally expire on the date of expiration of the Contract stipulated by the parties. Exceptionally, it may be established that said obligation be extended for an additional and reasonable period after that date, if the novelty of the product justifies it.

Conversely, the confidentiality obligation may expire before the date of termination of the Contract, if the secret information becomes publicly known during the lifetime thereof. In this hypothesis, the Licensee may also require the renegotiation of the terms (e.g. reduction of royalty rates agreed upon) of the Contract, as far as the loss of secrecy has deprived the information from the basic element justifying its remuneration.

Specimen clauses

12. Confidentiality

12.1. The Licensee will, upon the terms set out below, keep confidential all informations transferred by the Licensor and specifically indicated by him as being of secret character. The Licensee will take all proper steps to comply with this obligation and, in particular, will require his employees to give written undertakings not to disclose the information referred to in this clause.

12.2. The obligation of confidentiality will not apply to disclosure:
(i) by the Licensee to third parties to the extent necessary for subcontracting, procurement or other legitimate reasons related to the manufacture or sale of the Products;

(ii) to governmental authorities to the extent required for approval or registration of the Contract or the Products.

12.3. The obligation of confidentiality set forth in article 12.1. above will extend.....

(Alternative a: ..... until the expiration of the agreement, as provided for in article ..... ("Duration").

(Alternative b: for a period of ..... after the expiration of the agreement).

12.4. The obligation provided for in this article will cease at any time before the date specified in 12.3. above when the relevant information has become publicly known independently of the Licensee.

13. Remuneration

The remuneration to be paid by the Licensee is the main contractual obligation at its charge.

As a rule, agreements concerning formulations provide for the payment of a royalty applicable on the sales of the licensed Products. One of the advantages of this method in the context of these agreements, is that the Licensee only starts payments once the Products have been registered or approved by the competent health authority and production and sales have begun (*).

In case royalties are provided for, the Contract should regulate the applicable rate, the basis of calculation, the form and time of payment and the means of control at the Licensor's disposal. As regards calculation, in order to avoid duplication of payments, it may be advisable to deduct therefrom, among other things, the price of basic drugs supplied by the Licensor or its designee.

Eventually, the Contract may stipulate a lump sum payment in instalments to be made, for instance, on the dates at which the medical, scientific information and technical information is delivered; and upon satisfactory completion of the first batches of the Products.

If, as assumed in this document, the Contract comprises different supplies, it may be advisable to itemize the different components and establish the part or the price corresponding to each of them. This procedure would permit to easily solve situations that may arise during the agreement's lifetime and which would lead to a reduction of the level of payments, for instance if a licensed patent is invalidated.

The Contract should establish which of the parties will bear the taxes and levies applicable to the remuneration provided for.

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(*) For other considerations on the relative advantages and disadvantages of royalties vis-à-vis other forms of payments, see UNIDO, Guidelines for the evaluation of transfer of technology agreements, Development and Transfer of Technology Series, No. 12, New York, 1979, p.47.

Specimen clauses

13. Remuneration

13.1. In consideration for the supply of technical information, medical and scientific data and license as provided for in this Contract, the Licensee will pay to the Licensor .....

(Alternative a: .....% of the net ex-factory sales price of the products, after deduction of allowances, discounts, rebates, taxes and the price of Basic Drugs supplied by the Licensor or other source indicated by it and incorporated in the Products.

(i) The royalties will be payable ..... (period) in ..... (currency), according to a statement drawn up by the Licensee and certified to be correct by a chartered accountant;

(ii) The Licensee will furnish the Licensor with sales reports for ..... (period) containing information on the number of Products sold of each type manufactured by the Licensee and the respective date and price of sale. The Licensor may appoint an auditor or delegate at its own expense for checking the information referred to and the correctness of the statements mentioned in (i) hereinbefore).

(Alternative b: A lump sum of ..... (currency) as follows:

.....% on the date of receipt of medical and scientific data for the approval of the Products;

.....% on the date of receipt of technical information;

.....% on the date of satisfactory completion of the first ..... batches, as provided for in ....., but not later than ..... from the Effective Date of the Contract).

(Alternative c:*) The price estipulated hereinbefore is composed as follows:

.....% for the supply of medical and scientific information;

.....% for the supply of technical information and improvements thereof;

.....% for training of personnel;

.....% for license of patents;

(....% for license of trademark).)

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*) This clause may apply in connection with alternative "a" or "b".

13.2. In addition to the sums referred to above, the Licensee will pay to the Licensor for each Licensor's expert deputed to the Licensee's Plant for the supply of technical assistance, the sum of ..... (currency) per day of absence from the Licensor's Plant.

13.3. All taxes and/or levies under any existing or future law of the Licensee's country applicable to the sums stipulated in this caluse will be borne by .....

(Alternative a: the Licensor. Upon request, the Licensee will provide the Licensor with the receipts of payments or deductions made by the Licensee in concept of such taxes or levies).

(Alternative b: the Licensee.)

14. Guarantees

(a) Suitability for use

Amont the responsibilities of the Licensor, it should guarantee that the patents and technical information transferred, if used in accordance with its specific instructions, is suitable for manufacturing the Products in conformity with the specifications set forth in the Contract. Though such a guarantee may be deemed implicit in some countries, its express stipulation in the agreement may be advisable, particularly if special performance guarantees are not provided for.

(b) Correctness and completeness of documentation

Similarly, it is convenient to stipulate in the contract the almost obvious obligation that the documents supplied by the Licensor be correct and complete, in order to permit the full transfer and application of the technology.

(c) Performance guarantees

The provision of performance guarantees in agreements for formulations may have some advantages for the Licensee, particularly those with scarce experience and skills in the matter. Such a provision may, however, increase the total price of the Contract, at least as far as the Licensee will have to bear the costs reuqired for ensuring the presence of Licensor's personnel during the test run.

If the test run fails and the Licensor is not willing or able to rectify deficiencies which are attributable to it, the Licensee may have the right ot terminate the Contract, except if the results obtained satisfy certain minimum parameters defined therein. In this situation, the Licensor may be liable to pay penalties.

The Contract (or an annex thereto) should specify with precision the guaranteed parameters, the method of evaluation and duration of the test run. It may also indicate the term within which the altter should be carried out; however, it may be advisable to keep flexible the Contract on this point since the registration or approval of Products depend upon the issuance of an administ·tive authorization which may be granted with varying delays outside the control of the parties.

Specimen clauses

14. Guarantees

Suitability for use

14.a. The Licensor guarantees that the technical information transferred if used in accordance with the Licensor's specific instructions, is suitable for manufacturing and packaging of the Products as stipulated in this Contract.

Correctness and completeness of documentation

14.b. All the documentation supplied by the Licensor under this Contract will be correct and complete, and presented in a comprehensible manner for a normally qualified personnel in the field.

Performance guar ·tee

14.c.1. The Licensor guarantees that the Products to be obtained by the Licensee will meet the unit ratio of raw materials and quality, purity and stability standards specified in ..... provided that (i) the technical information is properly used in accordance with Licensor's instructions; and (ii) intermediates, basic chemicals and other inputs employed meet the specifications agreed upon as indicated in ..... Within ..... months from the Effective Date of this Contract or when otherwise agreed upon by

the parties, tests will be carried out, in the presence of authorized representatives of the Licensor and the Licensee, in ..... consecutive batches. The Licensor will be deemed to have fulfilled this guarantee if the average of the ..... batches produced meets the guaranteed parameters and standards evaluated as specified in .....

14.c.2. Should the test run fail to conform to the guaranteed parameters by reasons attributable to the Licensor, the Licensor will provide the additional information and changes necessary to achieve such parameters, within ..... from the end of the test run.

14.c.3. If the Licensor does not provide the information referred to or after the second test run the guaranteed parameters are not demonstrated, the Licensee will have the right to terminate this Contract, except if the reuslts obtained are not less than .....
In this latter case, the price provided for in this Contract will be reduced as follows:
(Alternative a: The royalty rate will be reduced in % per each .....% of deficiency in .....)

(Alternative b: The lump sum will be reduced in .....% per each .....% of deficiency in .....)

15. Warranty against infringement

The Licensee may request the Licensor to provide a warranty against infringement of third party's patents, when using the technology transferred.

One alternative found in some licensing agreements is a full obligation of the Licensor to indemnify and hold harmless the Licensee against such claims, including the Licensor's obligation to undertake the defense of the Licensee. In other cases, Licensors are reluctant to take such a wide responsibility, on the ground that it is very difficult to ascertain whether in the Licensee's country problems of that nature may arise. In this hypothesis a limited warranty is generally granted, by means of Licensor's representation that to the best of his knowledge there are no third party's patents infringed by the use of the technology transferred or the importation of the basic drugs.

Specimen clauses

15. Warranty against infringement

15.1. (Alternative a: The Licensor warranties that, to the best of his knowledge, the use of the information transferred and of the importation of the Basic Drugs do not infringe any patent in ..... (country) on the date of signing of this Contract.)

(Alternative b: (i) The Licensor will indemnify and hold harmless the Licensee against any claim or suit for infringement of any patent against the Licensee which is based upon the use, in accordance with this Contract, of any patent licensed or of the technical information received from the Licensor. (ii) The Licensor will upon receipt of such notice, undertake at its own expense the defense of any such suit or action. The Licensor will have sole charge and direction of the defense of any such suit or action and the Licensee shall have the right to be represented therein by advisory counsel of its own selection at its own expense. The Licensee will co-operate to the extent possible in the defense of any such suit or action and furnish evidence in its control.)

16. Liability

The manufacture of the Products, or the use thereof by patients, may eventually derive in damages to property or injury to persons. Who will be responsible for such events?

The question may be left to the solution applicable in accordance with the law governing the Contract, or the parties may attempt at establishing some general clauses regulating the matter.

The Licnesor may be deemed liable only if the damage or injury has been produced while using the information it has supplied strictly in accordance with its instructions. If the event was in connection with manufacture, the Licensor could only be held liable if the Licensee consciously followed the Licensor's operative instructions. If injury derives from the adverse or side effects of the Products, the Licensor may exclude its liability if they were not sold or advertised with the precise therapeutical indications and warning timely communicated by the Licensor.

Licensors may be reluctant to accept a wide or unlimited liability emerging from the causes referred to, except perhaps if a higher price is accepted by the Licensee. A possible compromise may be reached by limiting the liability of the Licensor either in scope, for instance, if it only applied in cases of negligence, or in extent, by putting a limit to the total liability of the Licensor.

Specimen clauses

16. Liability

The Licensor will hold the Licensee free and harmless from any third party claim for injury to persons or damage to property resulting from the proper manufacture or use of the Products and will indemnify the Licensee for such damage as Licensee may be held legally liable to pay in respect thereof and for Licensee's reasonable legal and other expenses made in connection therewith, provided that the Products have been produced and packaged strictly in accordance with Licensor's technical information, and sold and advertised with appropriate indication of the hazards and side effects timely informed by the Licensor.....

(Alternative a: This clause will apply if it is proven that the damage or injury was a direct consequence of negligence of the Licensor in the execution of its obligations under the Contract.)

(Alternative b: The total liability of the Licensor under this clause will amount to .....)

17. Insurances

It is up to the parties, according to their evaluation of risks, to decide what kind of insurance policies should be taken out in connection with agreements concerning formulations.

As a minimum, the Contract should contemplate coverage regarding acts of Licensor's personnel at Licensee's plant (if technical assistance is provided for) and, symmetrically, of Licensee's personnel at Licensor's plant (if the supply of training has been agreed upon)..

Specimen clauses

17. Insurances

17.1. The Licensor will take out and maintain in force an insurance policy to cover any injury or damage drived to persons or property caused by acts or ommissions of Licensor's personnel deputed to the Licensee's Plant.

17.2. The Licensee will take out and maintain in force an insurance policy concerning any injury or damage derived to persons or property caused by acts or ommissions of the Licensee's personnel trained at the Licensor's Plant.

18. Duration

The duration of the Contract will depend upon the interest of the parties. The longer the term thereof, the better are Licensee's chances of having access to improvements, if they are likely to be of nay importance with respect to the specific Products licensed. Likewise, if royalty payments are stipulated, the longest duration of the Contract benefits the Licensor, since the total price of the Contract increases in direct relationship with its duration.

Though in view of differing circumstances, it is difficult to suggest a reasonable general duration for this type of Contracts, a duration of up to five years may be recommended here.

Specimen clauses

18. Duration

This Contract will last for ....., counted from .....
(Alternative a: the Effective Date of the Contract.)

(Alternative b: the date on which the first sale of the Products has been effected.)

19. Use of the technical information and patents

It has been common, particularly when there is a substantial disparity in the bargaining power of the parties, that agreements for formulations include a number of restrictive (business practices, such as non-contest clauses, field of use restrictions, tying clauses, etc.

Some of such restrictions or modalities thereof have been dealt with in other sections of this document, in a manner that excludes their imposition (see, e.g. points 7, 8 and 9 below).

In general terms, the LIcensor should refrain from requiring obligations or imposing restrictions which unjustifiably limit the entrepreneurial freedom of the Licensee and the use of the information it receives. Though it is not appropriate to deal here with all such practices,*) it may be advisable that the Contract make reference to some hypotheses which may be relevant, according to the circumstances of the particular case.

(a) Field of use restrictions

The Licensee may wish to sell the Products for purposes other than those set forth in the Contract (for instance, for veterinary, when the Contract refers to use in human medicine). The Licensee should not be prevented from doing so, but the Licensor may rightly request the inclusion of a reservation limiting the applicability of guarantees and warranties granted by it to the uses specifically stipulated in the Contract.

(b) Restrictions on the use of information and patents after the expiration of the agreement

This type of restrictions is one of the most harmful encountered in transfer of technology agreements.

If the Contract involves patents granted for a term that extends beyond the date of termination of the Contract, once expired the latter, the Licensor might use it exclusive rights against the Licensee, as against any third party. As indicated before, the license of patents in an agreement for formulations only means that the Licensee is thereby authorized to import the protected drugs and put them on the market incorporated in a pharmaceutical form.

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*) For a comprehensive proposal on a regulation of restrictive practices at the international level, see UNCTAD, Draft International Code of Conduct on Transfer of Technology, TD/CODE TOT/33.

Hence, it would be advisable for the Licensee to take the post-expiration situation into account, and negotiate terms that permit it to continue in the use of the licensed patents until their expiration. While such an unconditioned right is the best alternative for the Licensee, other possibilities may be subject to such a right to conditions determined in the same Contract (e.g. provision of the drugs by the Licensor at international prices and payment by the Licensee of a reduced rate of royalty) or to be negotiated once the Contract comes to an end.

As regards technical information for formulation on the other side, the Contract should not limit, in any manner, the right of the Licensee to continue in its use, since it has paid the price required for its disclosure and there is no exclusive right thereon.

(c) Exports

Another delicate question is often that of the treatment of exports that might be made by the Licensee. The importance of this issue obviously depends upon the size of the markets at stake and the feasibility of exports of the Products to third countries.

Between the complete freedom of the Licensee to export and the complete prohibition thereof, a wide range of alternatives exist and may be negotiated in accordance with the circumstances. The Contract should not contain, as a principle, export restrictions,*) but exceptions may be included, for instance, in the form of a list of countries where exports should not be made, or of countries where the Licensor or his licensees are formulating and selling the Products.

Specimen clauses

19. Use of information and patents

19.1. Nothing in this Contract will be interpreted as directly or indirectly:
(a) limiting the field of use by the Licensee of the patents licensed and the technical, medical and scientific information supplied by

*) In many developing countries which have enacted regulations on transfer of technology such restrictions are deemed objectionable.

the Licensor, being understood, however, that the guarantees and warranties granted under this Contract by the Licensor are limited to the use of such information in accordance with the terms and conditions set out thereunder;

(b) restricting the use of such information after the expiration of this Contract;

(c) preventing the Licensee from exporting the Products .....
(Alternative a: to any country or region.)
(Alternative b: except to the following countries .....)
(Alternative c: ..... except to the countries where the Licensor or his licensees are formulating and selling the Products. At the date of signing this Contract, such countries include the following .....)

19.2. (Alternative a: The Licensor will not use the licensed patents to prevent the Licensee from formulating and selling the Products after expiration of the Contract as provided for in ..... ("Duration").)

(Alternative b: The Licensee will have the right to continue in the use of the licensed patents until their expiration after the termination of the Contract as stipulated in ..... ("Duration"), on the terms and conditions to be agreed upon with the Licensor in due time.)

(Alternative c: After the termination of the Contract as stipulated in ..... ("Duration"), the Licensee will have the right to continue in the use of the licensed patents until their expiration against payment of a reduced royalty rate of .....%, and the Licensor will uspply the Basic Drugs at a price non less favourable than the price usually charged by it or by other suppliers in the international market.

## 20. Effective Date of the Contract

In order to avoid misunderstanding and ensure the timely execution of the Contract, it is important that the time for the performance of the parties obligations be clearly determined, for instance, counting from the "Effective Date of the Contract". In countries where the Contract needs registration or approval by a competent authority, it is advisable to take the date of that event into consideration.

Specimen clauses

20. Effective Date of the Contract

20.1. This Contract will become valid upon its formal signing by duly authorized representatives of the Licensor and the Licensee.

20.2. (Alternative a: The Effective Date of the Contract will be the date of signing thereof by Licensor and Licensee.)

(Alternative b: The Effective Date of the Contract will be the date upon which this Contract has been registered or approved by the competent authority of the Licensee's country.)

21. Termination

Clauses on anticipated termination of the Contract will normally vary according to the applicable law, particularly as regards the qualification and legal consequences of defaults by the parties.

In agreements related to formulations, an automatic cause of termination may be the lack of registration or approval of the Products in the Licensee's country, or a subsequent restriction of sales thereof. In these situations, the main purpose of the Contract is frustrated and there is no reason for its continuation.

The Contract may determine the causes that authorize any of the parties to terminate it (e.g. failure to affect payments, lack of supply of technical information, etc.) or leave such a determination to the law applicable to the Contract.

In the case of Licensor's default, the Licensee may be authorized to continue in the use of all items supplied and of licensed rights until the date provided for the normal expiration of the Contract. If the Licensee is responsible for the termination, it should in principle cease in the sale of the Products.

In any case, the parties should be given a reasonable term, after due notice by the other, to remedy the alleged default.

As regards the termination by the Licensor, it may be unfair that he makes use of such right once the Licensee has effected all payments due (for instance, if a lump sum has been provided for) or lacking a short period for the normal termination of the Contract. In order to avoid this situation, the Contract may limit such Licensor's right, without prejudice to its right to undertake all other legal actions as appropriate according to the nature and extent of the default.

Specimen clauses

21. Termination

21.1. This Contract will automatically terminate if the competent authority of the Licensee's country does not authorize the sale of the Products or if, after approval, subsequently revokes or substantially restricts the sale of the Products in that country.

21.2. (Alternative a: This Contract may be terminated by either party for any cause sufficient under the proper law of the Contract, if the party in default has not remedied its fault within ..... from receipt of the other party's notice.)

(Alternative b: Without prejudice to any express clause relating to termination contained herein,

(i) this Contract may be terminated by the Licensor if the LIcensee fails to effect the payments provided for in this Contract within ..... from receipt of the Licensor's notice thereon;

(ii) this Contract may be terminated by the Licensee if the Licensor fails to perform its obligations under clauses ("Technical information", "Medical and scientific information", "Technical assistance", "Training"), and the default is not remedied within ..... from receipt of the Licensee's notice thereon.)

21.3. If the Contract is terminated by the Licensee for reasons for which the Licensor is responsible, the Licensee will have the right to continue in the use of all items supplied and rights licensed by the Licensor, until the date of expiration as stipulated in ..... ("Duration").

21.4. If the Contract is terminated by the Licensor for reasons for which the Licensee is responsible, the Licensee will cease the production and sale of the Products.

21.5. However, the Licensor cannot terminate this Contract .....
(Alternative a: if the Licensee has effected all payments provided for.*)
(Alternative b: after ..... years from the Effective Date of the Contract.)

22. Exoneration (force majeure)

According to the traditional conception of force majeure a contracting party is not deemed to be in default of its obligations if the performance thereof is prevented by contingencies which are unforeseeable (at the time of the contract's signing), unavoidable and independent of the parties, and which render impossible the further execution of contractual obligations.

International contractual practice has generally attenuated the strict requirements of such conception. The unavoidableness is, thus, substituted by a reference to events beyond the control (or the reasonable contro) of the parties. Likewise, instead of the extintive effect traditionally accorded to force majeure, the practice recommends to suspend the Contract until the disturbing contingencies are overcome.

Provisions on this issue may include:

(a) Definition of exonerating circumstances and enumeration of contingencies that may be comprised, such as, force of nature (acts of God), acts of war (whether declared or not), strike, lock-out, governmental order or regulation, etc.;

(b) Notification of the occurrence of such circumstances and proof thereof;

(c) Effects of the force majeure:

(i) exclusion of responsibility for non-performance;

(ii) consultation between the parties in case of continuation of circumstances.

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*) Applicable in cases where a lump sum has been established.

Specimen clauses

22. Exoneration (Force Majeure)

22.1 Neither the Licensor nor the Licensee will be deemed to be in default of their contractual obligations whilst performance thereof is prevented by circumstances which were beyond the control of the party concerned and which by the exercise of due diligence and reasonable foresight it could not have prevented or overcome, including in particular war or hostilities, riot or civil commotion, natural physical disaster, strike, lock-out or concerted acts of workmen, accidents, fire or explosion.

22.2. The affected party will give notice as soon as possible to the other party, with evidence that a contractual obligation is prevented or delayed, and if the Force Majeure lasts continuously for a period of ....., the Licensor and the Licensee will consult together regarding the future execution of the Contract.

23. Sublicensing and assignment

Given the nature and content of agreements concerning formulations, neither the Licensor nor the Licensee will be normally interested in sublicensing. For the latter, sublicensing in its own country would imply the emergence of a competitor, while sublicensing in other countries may be less interesting than direct exports of the Products, if they are feasible.

However, if the Licensee expects that certain sublicenses in its own or other countries may be granted, a clause might be negotiated for that purpose.

Assignment of the Contract will not normally be permitted (unless with the prior consent of the other party), since it is usually deemed to be intuitu personae, i.e. entered into taking the solvency, capacity and ...tation of the counterpart into account.

Specimen clauses

23. Sublicensing and assignment

23.1. This Contract is not assignable, unless with the prior and express consent of the other party.

23.2. (Alternative a: The Licensee will not grant sublicenses based upon this Contract).

(Alternative b: The Licensee may grant sublicenses under this Contract, with the prior consent of the Licensor, and provided that the licensor will receive .....% of the price agreed upon with the sublicensee. The Licensor will have no obligations or responsibility with respect to the sublicensee).

24. Applicable law and settlement of disputes

It is advisable that the Contract indicates the law which governs it, and the authorities that will be competent for solving any disputes arising out between the parties.

Some developing countries require or favour the position that the law be that of the licensee's country and that any dispute be submitted to the judicial courts of that country.

With respect to the applicable law, the parties may choose a different country's law, which has a close and real connection with the Contract, or stipulate (if controversies are submitted to arbitration) a judgement "ex accuo et bono". In any case, decisions should take into account the public policy rules (ordre public) of the concerned countries.

If arbitration is provided for, the respective clauses should indicate, inter alia, the seat of the tribunal, the procedure to be applied, the number and method of nomination of arbitrators, the language to be used and the character of the final award. For the sake of simplicity and clearness, the Contract may refer to the arbitration rules of an international organization, such as to the Rules of Conciliation and Arbitration of the United Nations Commission on International Trade Law (UNCITRAL).

Specimen clauses

24. Applicable law and settlement of disputes

24.1. (Alternative a: This Contract will be construed under and governed by the law of the Licensee's country).

(Alternative b: This Contract will be construed and governed by the law of .....(country) except as to matters relating to public policy of ..... (Licensor's or Licensee's country) which will be decided in accordance with the applicable law of the country concerned).

24.2. All disputes arising out of or in connection with this Contract, which the parties hereto are not able to solve by negotiations within a reasonable period, will be finally settled .....
(Alternative a: by the competent courts of the Licensee's country).
(Alternative b: by the competent courts of .....).
(Alternative c: under the Rules of Conciliation and Arbitration of the United Nations Commission on International Trade Law by three arbitrators appointed in accordance with such Rules. The arbitration will take place in .....(city) and all proceedings will be in .....(language). The award of the arbitrators will respect the public policy rules of .....(Licensor's and Licensee's country) and will be final on the parties hereto).

ANNEX I

## PROCESS TECHNOLOGY

### Tablets

Tablets are used in oral dosage forms and are produced by various degrees of compression. They can be of various types e.g. plain, chewed, sugar coated, enteric coated, film coated, layered and sustain release tablets.

The flow-chart in Appendix describes the various steps in the manufacture of tablets. Following are major unit operations carried out in the manufacture of tablets.

(a) Milling and shifting

Basic ingredients are pulverised and sieved.

(b) Mixing

Depending on the batch size, carefully weighed quantities of various ingredients like active components diluents, binders, blouring agents etc. are mixed in a mass mixer or planetary mixer as per the requirement.

(c) Preparations of paste

The solution for granulation is prepared separately.

(d) Dry and wet mixing

The granulation solution is added to the mass and fixed thoroughly.

(e) Wet granulation

The wet mass is granulated in a machine to required mesh size.

(f) Drying

The wet granules are dried in a thermostatically controlled dryer so that the potency of the drug remains uneffected.

(g) Granulation

The dried or partially dried granules are again passed through a smaller mesh in a granulator. Dry granulation is required in case of single action component comprising the major part of the product.

(h) Blending

The granules are blended with the lubricating and disintegrating agents.

(i) Tabletting

The lubricated granules are fed to tabletting mchine where tablets are formed by compression. During tabletting quality control tests for disintegration, hardest fri

(j) Inspection

Tablets are passed through inspection belts for checking of uniformity, coating etc.

(k) Packing

Depending on the requirements, tablets are packed either in glass, plastic, PVC or tin containers or strip packed or blister packed in suitable foils mad of paper, plastics, alumirimu, etc. counting is done either manually or by machine.

(l) Labelling

The packed tablets are labelled properly by putting the batch number, manufacturing and expiry dates - in case of Vitamins, antibiotics etc. The pack should indicate the composition of active ingredients and average doses.

## COATED TABLETS

There can be sugarcoating, compression coating, or dry coating, enteric coating, film coating. The tabletting and packing process is the same as described in case of tablets except -

(a) Sugar coating

The coating is applied in successive layers to the tablets by deposition from a solution of sucrose. The coating shall be chiefly of sucrose together with purified talc, starch and shellac.

(b) Dry coating

The granules of different substances are prepared separately and fed to rotary machine, the core from one rotary machine is being transferred to the other rotary machine by transfer mechansim, and further compressed with the granules of second active drug more stable for atmospheric conditions or with the granules of inert auxiliary material forming the outer layer of the tablet.

(c) Enteric coating

A suitable coating is applied such that the tablets comply with the disintegration test for enteric coated tablets, i.e. delayed release in the gastric juice.

(d) Film coating

The coating which normally comprises less than 10 per cent by weight of the finished tablet is applied by deposition from a suitable solvent. It may consist of any suitable synthetic or nautral filming form.

## CAPSULES

The capsules are used for keeping the potency of the drug. It protects the same from atmosphere and also masks the taste and odour of the drugs. It is easier to be swallowed. The capsules are of three types - hard gelatine, soft gelatine and seamless capsules.

As capsules are made out of gelatine, these have to be stored in a dry and cool place. The flow charts in Appendix ... describe the various steps in the manufacture of capsules. The following major operations are involved in filling the empty hard gelating capsule: (a) sieving and powdering, (b) blending, (c) sealing, (d) filling, weighing and blending, (e) packing and (f) labelling.

(a) Milling and sieving

Basic ingredients are powdered and sieved through suitable mesh.

(b) Mixing

As per the batch size, the required ingredients are wighed and mixed thoroughly in mass mixer or plentary mixer.

(c) Preparation of solution

If small granules are required the granulation solution is prepared separately.

(d) Wet mixing

The solution is added to the mass and mixed thoroughly.

(e) Wet granulation

The wet mass is granulated to required mesh size.

(f) Drying

The wet granules are dried in a thermostatically controlled dryer without affecting the potency of the drug. Steps (e) and (f) are not commonly followed unless otherwise required for special type of preparations. However, granulation is done in all cases.

(g) Blending

The granules are blended with the lubricants.

(h) Sorting and cleaning of empty capsules

The empty hard gelatine capsules are stored in humidity-controlled air-conditioned area. They are sorted out and cleaned before filling.

(i) Filling of capsules

The empty gelatine capsules are taken in the hopper of automatic capsule filling and closing machine and after adjusting the weight, the mass is filled in the machine. Hand-operated machines are also used for filling the capsules. These operations require humidity-controlled air-conditioned area. Weight variations are to be eliminated by properly adjusting the machine.

(j) Polishing and inspection

The filled and sealed capsules are put in polishing pans and after that, the capsules are subjected to inspection and quality control before packing.

(k) Packing

Depending on the requirements the capsules are filled in glass, plastic, PVC or tin containers or strip-packed in suitable foils made of aluminium or paper. Counting is done either manually or by machine.

(l) Labelling

The packed capsules are labelled properly by putting batch number, manufacturing and expiry dates in case of vitamins and antibiotics. This also should indicate the composition of active components and average doses. The finished products after quality control tests are transferred to commercial stores. Steps (h) to (l) and storing require a humidity-controlled air-conditioned area.

## LIQUID ORALS

The liquie preparations are also oral dosage forms of single or combinations of drugs. These preparations include syrups, elixirs and suspensions. Appendix ..... shows the folow-shart for the manufacture of liquid orals. The following operations, in principle, are followed in the manufacture of liquids.

(a) Preparation of demineralized water

All the liquid preparations require demineralized water of particular specifications with respect to ionic concentrations, pH and conductivity. This is produced by passing the potable water through a series of ion-exchange columns and finally degassing the water.

(b) Preparation of solution or suspension

The active ingredients are weighed carefully. The base materials are measured carefully and demineralized water, if reuqired, added into the solution preparation tank. The active ingredients are also put into the tank fitted with stirrer and mixed thoroughly. In case of suspensions, the product is passed through colloid-mill or homogenizer. For preparation of ethical products, percolators or extractors are used. Depending on the process-permitted preservatives, stabilizers, colouring and flavouring materials are added during mixing.

(c) Adjustment of parameters

To get the suitable quality of product, the pH, viscosity and volumes are adjusted as per the requirements.

(d) Filtration

In case of solution - the mixed mass is filtered through suitable filter media. Suspension do not require filtration. Samples are given for quality control.

(e) Transferring the mass

The final mass is transferred to the vessles for filling.

(f) Washing and cleaning of bottles

The suitable containers are cleaned and washed thoroughly with demineralized water. If required, they are dried in ovens or continuous driers.

(g) Washing and cleaning of PP caps

The rubber caps are cleaned and washed thoroughly.

(h) Filling

The liquid preparations are filled into bottles or jars to uniform volume by a suitable filling machine.

(i) Capping

The filled containers are capped properly and sealed. In case of delicate preparations, inert gas sparging is necessary for storage capacity of the product.

(j) Labelling

The containers are labelled by putting batch number, manufacturing and expiry dates. The label also should indicate the composition, average doses, storage conditions etc.

(k) Packing

For transportation, suitable number of containers are packed in cartons and transferred to commercial stores after quality controls. All illustration of ..... syrup is presented in appendix .....

## PARENTERALS (Injectables)

Parenterals preparations are used in internal dosage forms - intermuscular, intravenous etc. The flow-chart in appendix ..... describes the overall operations involved in the manufacture of injectables.

In the case of ampoules or vials, utmost care has to be taken for preparation of pyrogen-free distilled water as well as perfect sterile conditions in the manufacturing areas to ensure non-contaminated product. Air-conditioned and sterile zones are obligatory for the parenteral preparations. Following operations are followed in the production of ampoules and vials.

(a) Preparation of pyrogen-free distilled water

Suitable equipment is used for preparation of pyrogen-free distilled water.

(b) Preparation of solution

Carefully weighed quantity of the active ingredient is put into the solution preparation tank, stirred well in the solvent to ensure the homogeneous solution.

(c) Filtration

The solution is then filtered through aseptic filters in case the produce is thermolabile. For thermophilic products, ordinary filtration is used. The solution is ready for filling after quality control tests for sterility, concentration etc. and kept in pressure vessels.

(d) Washing and dry heat sterilization of ampoules an vials

The ampoules or vials are cleaned, washed thoroughly with pyrogen-free distilled water and flushed with compressed filtered air, if required. These containers are then sterilized by indirectly heated dry sterilizaters. The stoppers are also washed and sterilized in autoclaves.

(e) Filling

The ampoules or vials are filled with the solution in suitable filling machine and sealed. The filling room must be sterile and air-conditioned with the flush of filtered air under positive pressure. U.V. lamps, laminar flow hoods etc. are used to maintain aseptic condition in the filling area.

(f) Sterilization by autoclaving

The sealed containers are then sterilized by autoclaving with direct steam at particular steam pressure and time. The heat sterilization depends on the particular type of products.

(g) Leak testing

The ampoules or vials are tested under vacuum for leak test. Rigorous quality control tests are carried out for sterility. Visual inspection is conducted for visible impurities.

(h) Labelling and packing

The containers are labelled by putting batch number, dates of manufacture and expiry etc. Isolated area is required for penicillin group of products.

## TRANSFUSION LIQUIDS

These preparations are menat for intravenous use and hence utmost care is taken for preparation of pyrogen-free distilled water and sterility of the product. The flow-chart in appendix ..... describes the manufacturing steps. All the procedures are similar to those for injectables. Strictly maintained sterile conditions are required in the filling and sealing area.

## OINTMENTS

Ointments are meant for external use and hence these are non-sterile preparations. However, sterile preparations are required for special use, e.g. opthalmic ointments. The flow-chart for the manufacture of ointments is shown in appendix .....

In broad, the following steps are involved in the manufacture of ointments.

(a) Preparation of base

The ointment base is prepared in the jacketted vessels with the provision of heating and stirring.

(b) Incorporation of ingredients

Carefully weighed quantities of active ingredients (as per the quantity of base) are added slowly into the base under continuous stirring and mixed thoroughly. Permitted preservatives, stablizers are added here. For sterile preparations, the base is sterilized in dry heat sterilizer in suitable container and the ingredients are also added under aseptic conditions as described in the paranteral section.

(c) Smoothing

The mixture is passed through a colloid mill/triple roller mill and sampled for quality control tests.

(d) Filling

The ointment is then filled into the collabsible tubes by automatic filled and crimping machine. For sterile preparations, smoothing is done under sterile condition and tubes are also sterilized after filling.

(e) Labelling

Apart from the tubes are printed with the necessary information like composition, warning etc., these are labelled after filling with batch number, date of manufacture and expiry.

## POWDERS AND GRANULES

Powders and granules are used for oral, external or parenteral use. The flow chart for the manufacture and filling is shown in appendix ..... The major operations are similar to those for tablet manufacture. After milling, sieving, granulation, drying, blending, quality control tests are conducted. The granules are then filled into bottles by automatic filling machine and capped. Sampling is done for weight variations. The bottles are then labelled and packed. After quality control tests they are stored. Depending on the nature of product and final use, sterile and air-conditioned areas are required for final product and filling.

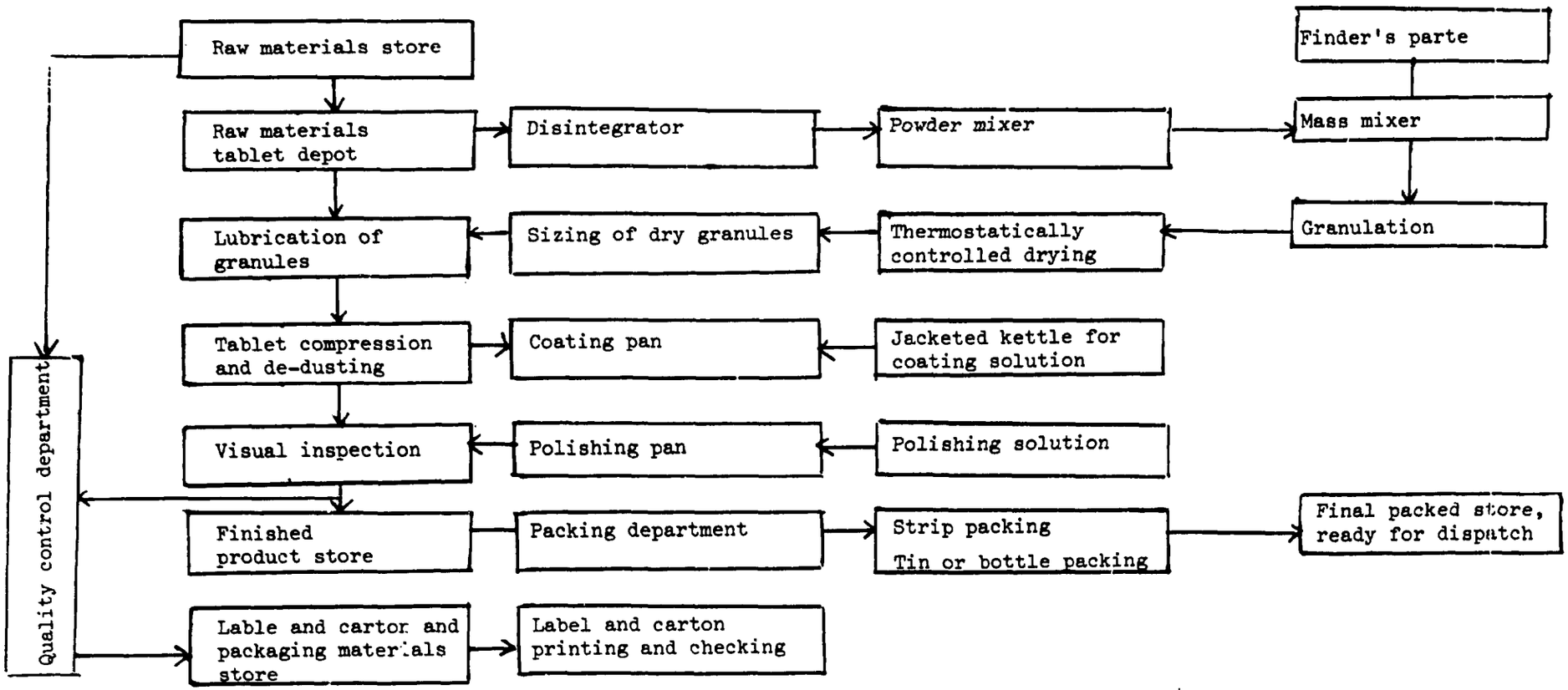



Figure I Flow chart for manufacture of tablets

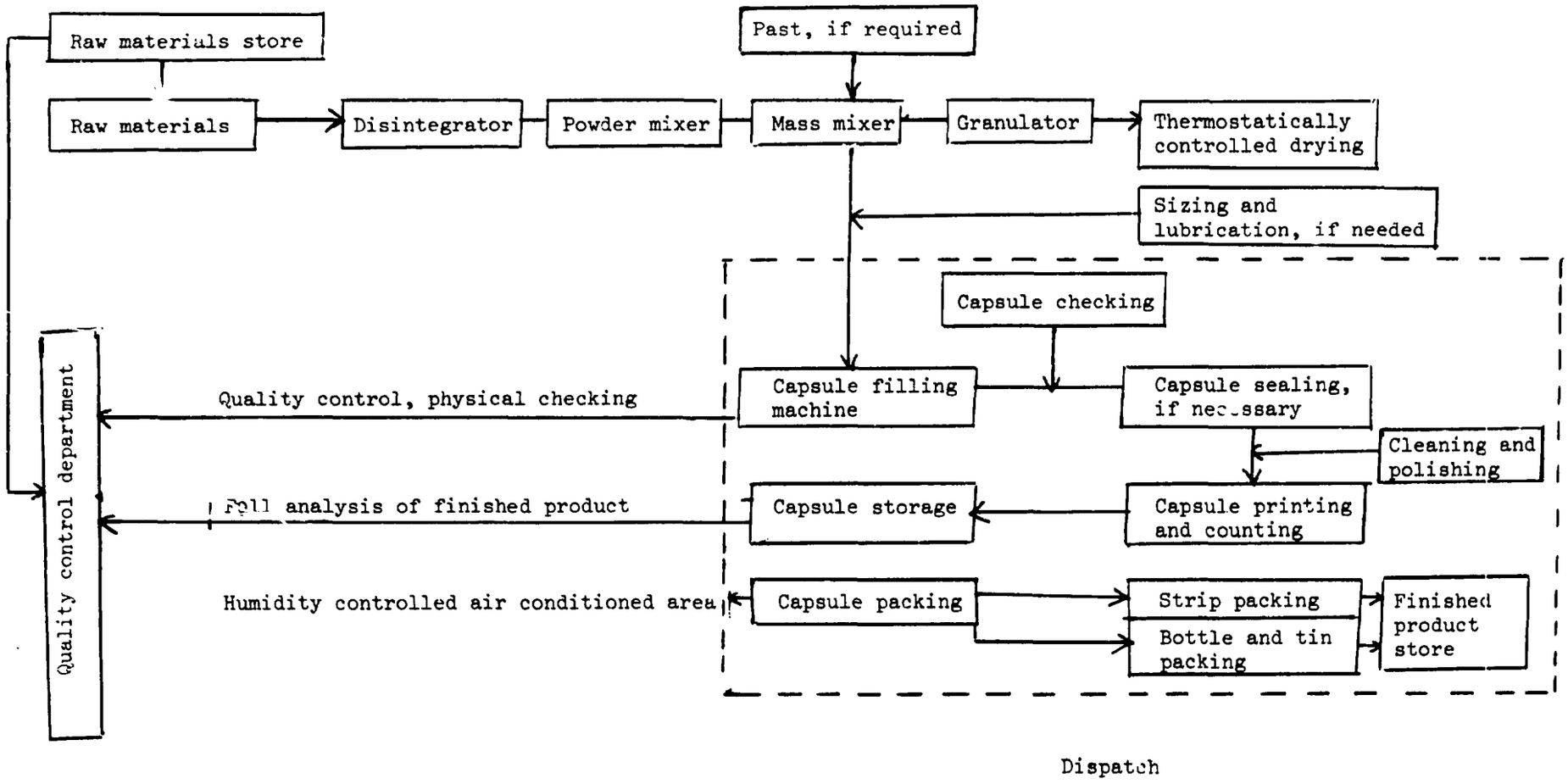



Figure II Flow chart for the manufacture of capsules

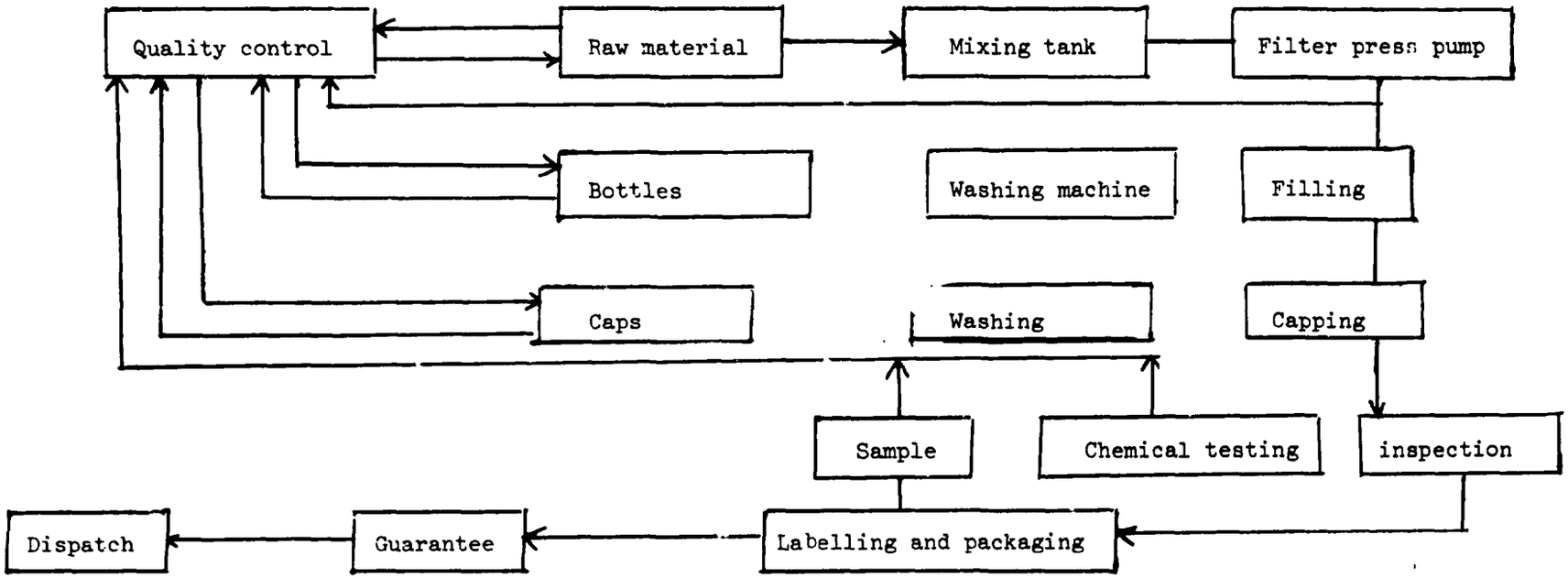



Figure III Flow chart for the manufacture of syrups, elixirs and solutions

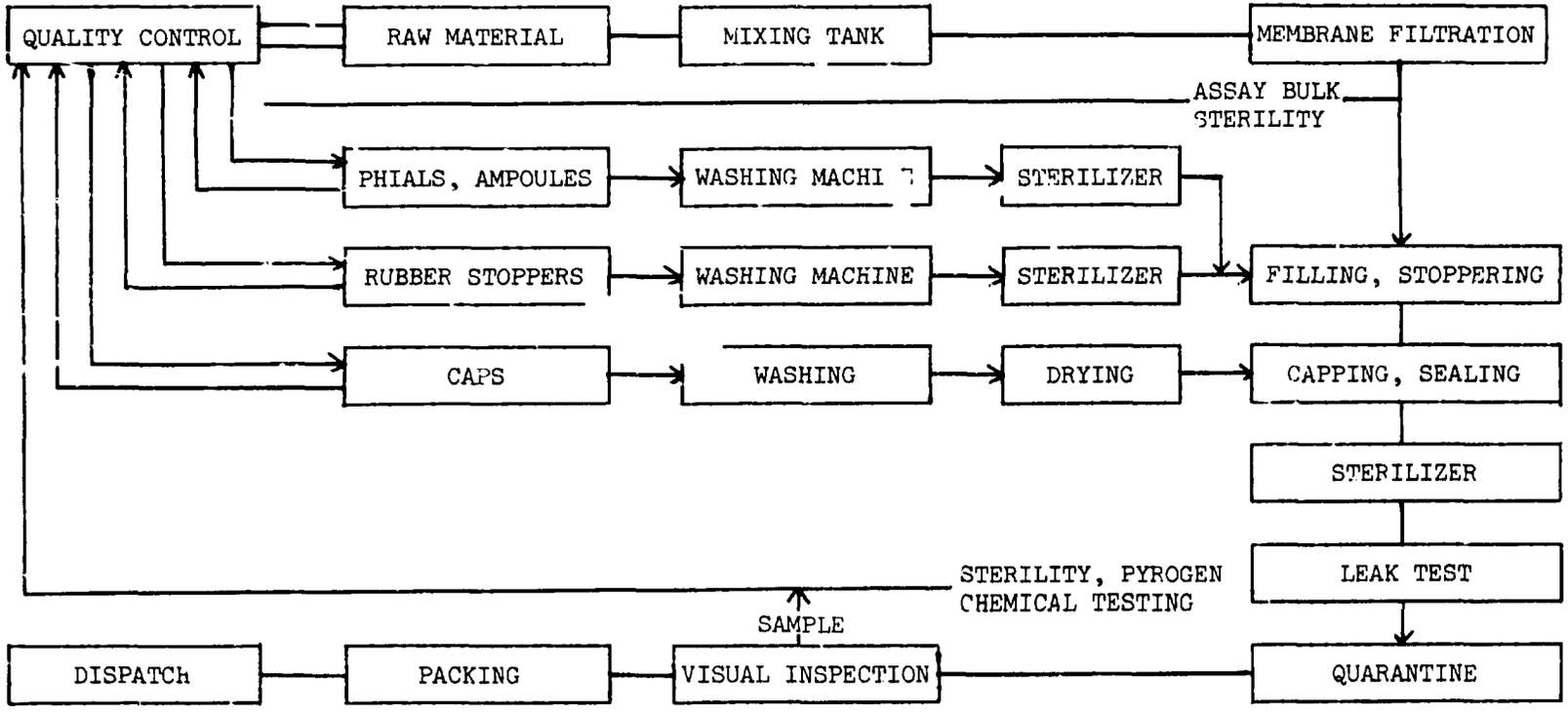



Figure IV: Flow chart for parenterals

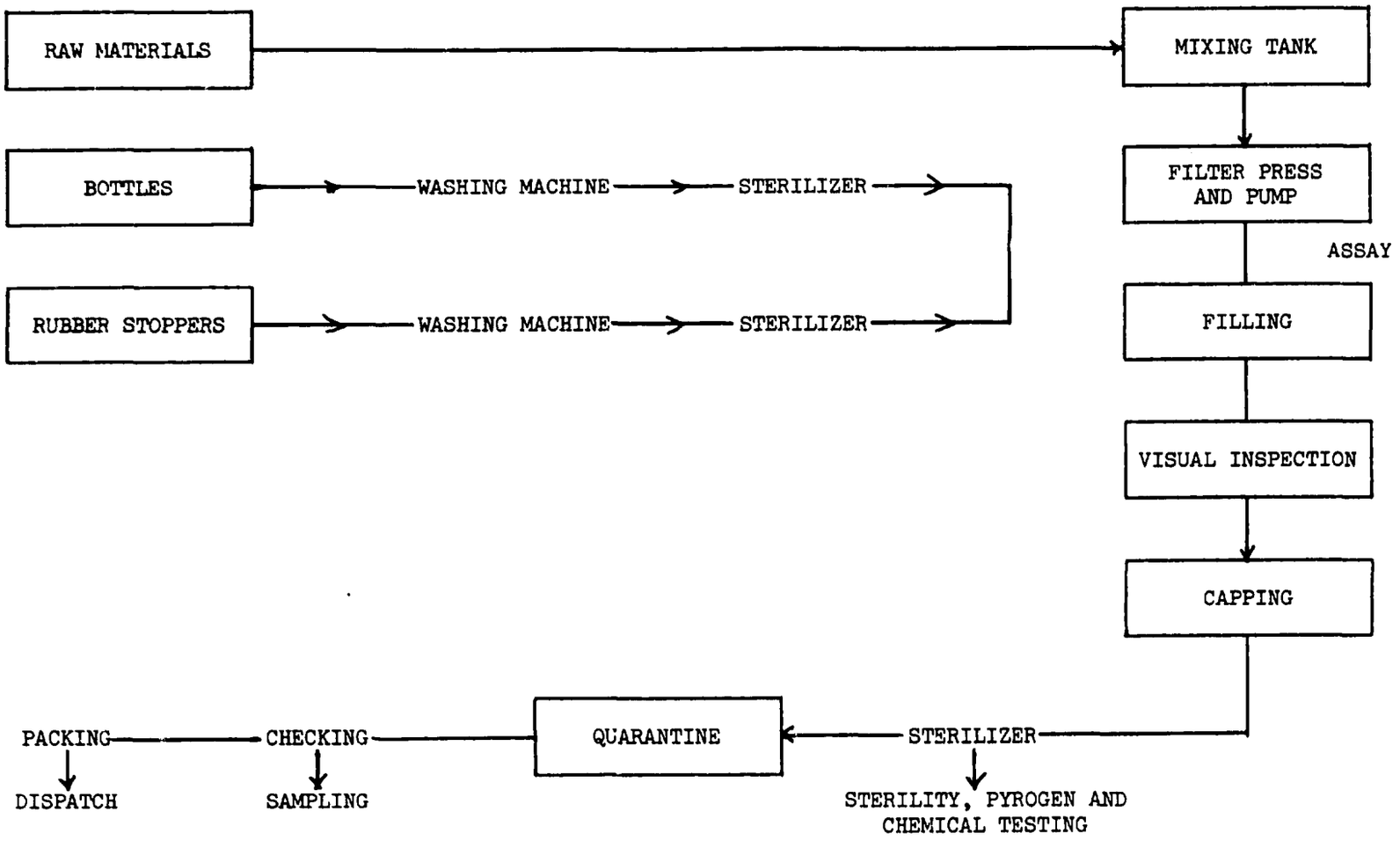



Figure V: Flow chart for transfusion fluids

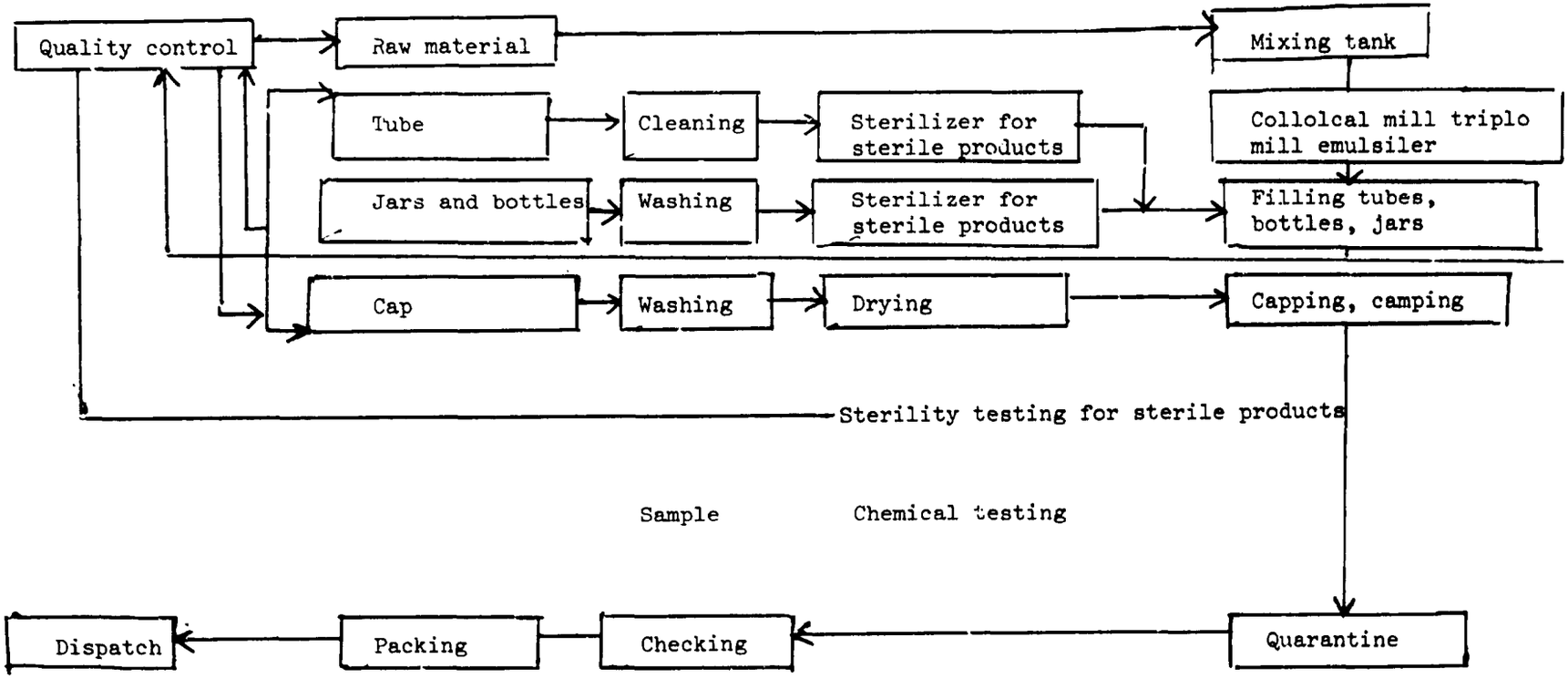



Figure VI Flow chart for the manufacture of ointments, emulsions, lotions and suspensions

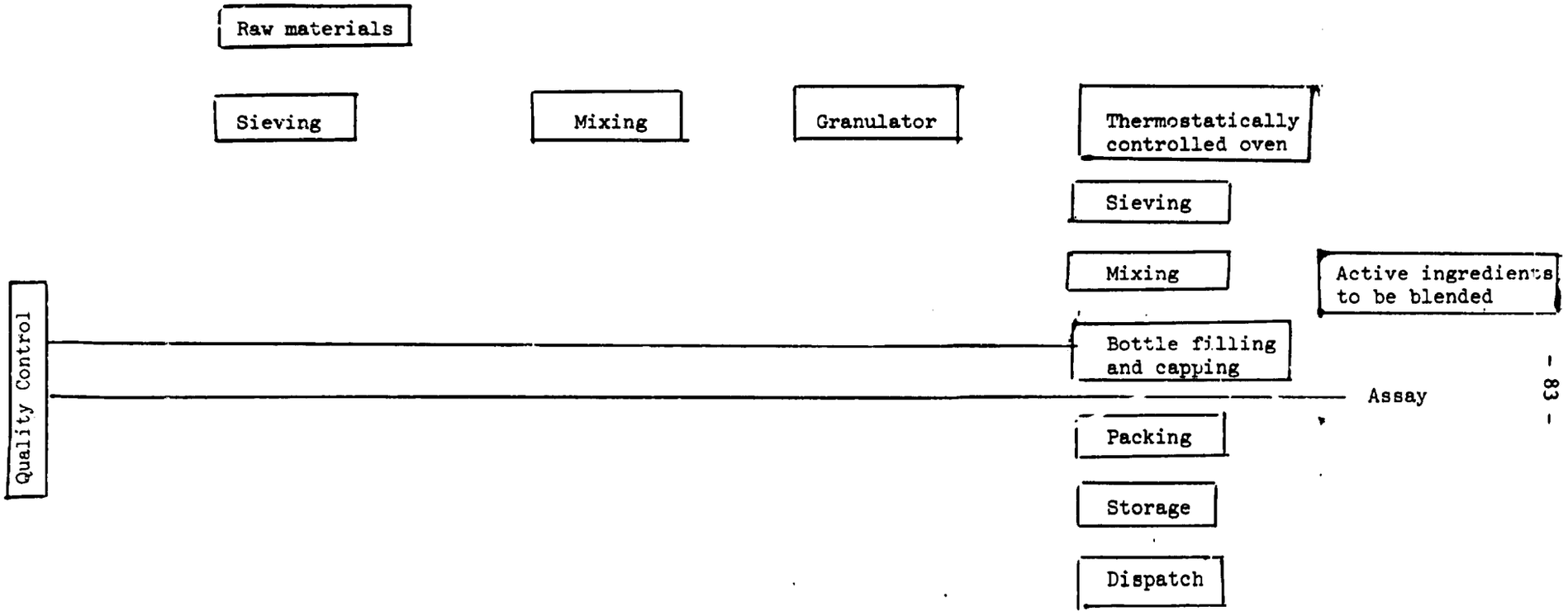



Figure VII Flow chart for powder filling

Annex II

DETAILS OF EQUIPMENT FOR FORMULATION

| S. No. | Description | Material | Capacity | Qty | Total cost (Rs.) |
|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 |
| A. | TABLETS | | | | |
| 1. | Mechanical shifter (portable type), single desk, with variable meshes 12-120, starter, TEFC motor, 1.8 kW, direct on the line. | S.St.AISI 304 | 30" dia | 1 | 27,500/- |
| 2. | Tilting pan, flat lid on top (openable), jacketted. | S.St.AISI 304 | 63 lit. | 1 | 10,000/- |
| 3. | Planetary mixer, complete with bowl, top disc. agitation assembly, drive mechanism for both, motorized lifting arrangement with drive, TEFC motor alongwith a spare bowl. | S.St.AISI | 380 lit. | 1 | 1,27,000/- |
| 4. | Comminuting mill, 600-4600 rpm for wet granulation and powdering, TEFC motor 5.7 kW variable screen. | S.St.AISI 304 | - | 1 | 45,000/- |
| 5. | Fluid bed dryer, steam heated with steam heater, product container, flame proof vertical motor and with a spare container. | S.St.AISI | 100kg/hr | 2 | 2,55,000/- |
| 6. | Air circulation dryer, steam heated, fibre glass body, insulated, 2 nos. 12" diameter fans with 0.5 HP EPM, trays other accessories, 24 trays of dimensions 32" x 10" x 1.25". of S.St.AISI 304. | MS.S.St. 304 | 24 trays | 1 | 1,05,000/- |
| 7. | Multi-mill with motor on a shaft having 12 blades with knifedge and 2 scraper blades TEFC motor, 2.2 kW, variable speed 750-3000 rpm direct on line. The unit should have 6 different perforated screens. All contact points S.St.AISI 304. | S.St.304 | - | 1 | 30,000/- |

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| 8. | Oscillating granulator with 1 H.P. TEFC motor. | S.St.304 | 50kg/hr | 1 | 19,500/- |
| 9. | Drum blender | S.St.304 | 200 lit. | 1 | 15,000/- |
| 10. | Rotary Tabletting machine 27 stations with suitable TEFC motor, direct on line. | SSt.304 | 70,000 tabs/hr | 2 | 1,95,000/- |
| 11. | Rotary tabletting machine 16 stations with suitable TEFC motor, direct on line. | SSt.304 | 17,000 tabs/hr | 2 | 90,000/- |
| 12. | Coating pan, vibration free, Manesty CP-4, 36" model with variable speed 10 to 30 rpm, drive-EPM 1 H.P. alongwith SW, hot air blower of 0.5 H.P., EPM to provide thermostatically controlled hot air at 70°C. | SSt.304 | 36" dia | 5 | 1,85,000/- |
| 13. | Polishing pan with continuously variable speed reducer 12-36 rpm with worm reducing gear box, with a suitable EPM. | SST-304/ 316 | 700 mm | 2 | 42,000/- |
| 14. | Tablet inspection belt with S.St. hopper, magnetic vibrator, conveyor, with adjustable speed. | - | 1 lakh tabs/hr | 2 | 30,000/- |
| 15. | Strip packing machine, 4 Track model, vibratory feeder, batch printing attachment, special conveyor belt of 3M length with all controls. | - | 48000/hr | 2 | 1,95,000/- |
| 16. | Batch counter with an electromechanical system coupled with electronic unit. | - | 2000 tabs/hr | 2 | 45,000/- |
| 17. | Tin sealing machine, semi-automatic with 1.5 kWh TEFC motor. | - | 1000/hr | 1 | 22,400/- |
| 18. | Semi-automatic roll sealing machine for bottles of different sizes and caps of sizes ranging from 12 to 70 mm dia. | - | 2000-2500/ hr | 1 | 33,000/- |
| 19. | Conveyor belt, double side, 5 metre length (operating), variable speed with 1 kW TEFC motor. | - | - | 2 | 34,000/- |

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| B. | CAPSULES | | | | |
| 1. | Multimill | SST-304 | 36" dia | 1 | 35,000/- |
| 2. | Shifter | SSt-304 | 36" dia | 1 | 27,500/- |
| 3. | Mixer | SSt-304 | 50 lit. | 2 | 50,000/- |
| 4. | Clearing and shorting machine | - | - | 2 | 75,000/- |
| 5. | Capsule filling machine | SSt-304 | 3600/min | 2 | 36,000/- |
| 6. | Strip packing machine | - | 2400/hr | 1 | 62,500/- |
| | | | | | 2,86,000/- |
| C. | LIQUID ORALS | | | | |
| 1. | Tank for solution preparation, jacketted, openable lid, dished bottom, bottom outlet, propeller agitator with 0.75 kW TEFC motor. | SSt-316 | 250 L | 1 | 35,000/- |
| 2. | Tank for solution preparation, openable top lid, flat bottom, propeller agitator with 0.75 kW TEFC motor. | SSt-316 | 560 L | 1 | 38,000/- |
| 3. | Holding tank, openable flat lid on top. | SSt-316 | 675 L | 3 | 78,000/- |
| 4. | Centrifugal pump, complete SSt-304 with 0.75 kW TEFC motor mounted on base, covered with SSt-304. | SSt-304 | $1m^3/hr$ H=30m | 1 | 10,000/- |
| 5. | Filter press, horizontal, 8 plates of 8" dia. Gear type transfer pump with 0.75 kW TEFC motor with suitable starter, mounted on trolley. | SSt-304 | 500 L/hr | 1 | 30,000/- |
| 6. | Bottle washing machine fitted with a tank for soaking the bottles, double ended brushing unit with a suitable TEFC motor, rinsing arrangement. | - | 1000 btls./ hr | 1 | 22,500/- |
| 7. | Vacuum filling machine with automatic "return to source" device to prevent overflow. Adjustable device to accommodate different sizes of bottles. | - | 1000 btls./ hr | 1 | 22,500/- |
| 8. | Semi-automatic roll sealing machine. | - | 2500 lit/ hr | 1 | 33,000/- |

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| 9. | Conveyor belt with 1 kW TEFC motor. | - | - | 1 | 25,500/- |
| 10. | Percolator. | SSt-AISI 304 | 350 lit. | 1 | 18,000/- |
| 11. | Demineralized water unit to give 500 lit/hr. DM water with pH 7.0 and conductivity 14 micromhos/cm, $CO_2$ free. | St.-rubber-lined | 500 lit/hr | 1 | 30,000/- |
| 12. | Storage tank for DM water. | ST-RL/HDPE | 1500 lit. | 1 | 15,000/- |
| 13. | Portable stirrers 170 and 360 rpm with 0.5 HP motors. | SSt-304 | 63 lit. | 1 each | 18,000/- |
| 14. | Movable vessles. | SSt-304 | 63 lit. | 2 | 30,000/- |
| 15. | Tank, jacketted. | SSt-316/304 | 63 lit. | 1 | 12,500/- |
| | | | | | 4,18,000/- |
| D. | INJECTIBLES | | | | |
| 1. | Distilled water unit to produce pyrogen free distilled water. The unit is complete with still, condenser, steam regulator, strainer, safety valve, pressure gauges etc. | SSt-304 | 300 l/hr | 1 | 1,00,000/- |
| 2. | Storage tank. | SSt-304 | 1000 L | 1 | 32,000/- |
| 3. | Centrifugal pump all SSt-304 0.75 kW TEFC motor | SSt-304 | $1m^3/hr$ H=20M | 1 | 10,000/- |
| 4. | Solution preparation tank, jacketted, openable top lid, propeller agitator, 0.75 kW TEFC motor, 720 rpm. | SSt-316 | 630 L | 1 | 60,000/- |
| 5. | Holding tank, flat openable top lid, flat bottom. | SSt-316 | 675 L | 1 | 26,000/- |
| 6. | Solution preparation tank, completely removable top lid, agitator. | SSt-316 | 63 L | 1 | 15,000/- |
| 7. | Horizontal plate type filter press, 8 plates. | SSt-304 | 500 L/hr | 1 | 30,000/- |
| 8. | Centrifugal pump with 0.75 kW motor. | SSt-304 | $1m^3/hr$ H=20M | 1 | 10,000/- |
| 9. | Pressure vessels for aseptic filtrations, complete with all accessories. | SSt-304 | 50 L | 1 | 10,000/- |
| 10. | Pressure vessels for aseptic filtration, compelte with all accessories. | SSt-304 | 100 L | 1 | 16,000/- |

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| 11. | Membrane filter holder with teflon gaskets to be used with pressure arrangement along with air escape valve. | SSt-304 | - | 2 | 24,000/- |
| 12. | Seitz filter holder for aseptic filtration to be used either for pressure or vacuum filtration. | SSt-304 | - | 1 | 15,000/- |
| 13. | Double door leak proof dry heat electro-sterilizer, 760 x 760 x 1200, with 1.5 kW TEFC motor. | SSt-304 | - | 1 | 1,20,000/- |
| 14. | Horizontal rectangular autoclave 600 x 600 x 1200, complete with all accessories and fittings. | SSt-304 | - | 1 | 1,50,000/- |
| 15. | Horizontal rectangular autoclave double door, 1550 x 1200 x 2100, steam heater, complete with all accessories and fittings. | SSt-304 | - | 2 | 9,00,000/- |
| 16. | High speed rotary automatic ampoule washing machine complete with 0.5 HP motor and all other accessories and fittings. | SSt-304 | 3000/hr | 1 | 42,000/- |
| 17. | Bottle washing machine with suitable TEFC motor and accessories. | - | 1000 btl/ hr | 1 | 22,500/- |
| 18. | High speed double stroke automatic ampoule filling machine, 0.5 HP motor, syringes with SSt drip proof needles, no ampoules, no liquid device to handle 1 cc to 10 cc and with spares to handle 10 cc to 25 cc ampoules. | SSt-304 | 3500/hr | 1 | 38,000/- |
| 19. | High speed double stroke automatic ampoule filling machine, 0.3 HP motor, syringes with SSt drip proof needles, no ampoules, no liquid device to handle 1 cc to 10 cc and with spares to handle 10 cc to 25 cc ampoules. | SSt-304 | 3500/hr | 1 | 38,000/- |

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| 20. | Vacuum filling machine. | - | 1000btl/hr | 1 | 22,500/- |
| 21. | Automatic ampoule labelling machine. | - | 3000/hr | 1 | 50,000/- |
| 22. | Conveyor belt, 1 kW motor. | - | - | 1 | 25,500/- |
| 23. | Vacuum vessels for leak test of ampoules and with vacuum gauge. | Steel | 100 lit. | 1 | 12,500/- |
| 24. | Semi-automatic roll sealing machine. | - | 2500/hr | 1 | 33,000/- |
| | | | | | 16,68,500/- |

D. OINTMENTS

Complete series of equipments like blender-kneader, filling machine, roll sealing machine, labelling, testing etc. (tentative) 2,50,000/-

## Annex III

## RAW MATERIALS AND AUXILIARY MATERIALS REQUIRED FOR FORMULATIONS

### Raw materials

Tetracycline hydrochloride, chloroquine phosphate, thiamine hydrochloride or mono-nitrate (Vit. $B_1$), Ampicillin-trihydrate etc. the specifications of the drugs are given in most of the pharmacopoeia.

### Diluents

Lectose, sucrose, dextrosemonohydrate, starch, sodium chloride.

### Moistening agents

Purified water, alcohol of suitable strength, iso-propyl alcohol, mucilage of India gum or guar gum or starch, aqueous solution of liquid glucose or dextrosemonohydrate or sucrose or gelatine or their mixtures.

### Lubricants

Stearic acid, sterates, finely powdered talc and liquid paraffin.

### Sugar coatings

When tablets are directly to be sugar-coated, coating shall be chiefly of sucrose together with purified talc, starch or other suitable innocuous substances.

### Enteric coating

Where the drug may be destroyed or inactivated by the gastric juice or where it may initiate the gastric mucosa, the use of enteric coating is indicated. Such coatings are intended to delay the release of the drug until it passes through the stomach.

### Colouring and flavouring agents

The addition of colouring and flavouring agents unless permitted in the monograph is not official.

Disintegrating agents

Starch, cellulose derivatives etc.

Emulsifying agents

Tween 80, Span 20, benzal monium-chloride, glyceryl-mono-stearate, gum acacia.

Suspending agents

Gum acacia, gum tragacanth, chemicals like sodium-carbo-osy-methyl, cellulose, methyl-cellulose, polyacrulic acid, sodium-alaginate etc.

Sweetening agents

Sugar, saccharin, sodium saccharin, dextrose, glucose.

Diluents or base for ointments

Paraffin, lard, oleio or cotton seed oil, absorption base, hydrophilic substances like wool-fat, linolin, washable base, polyethylene glycols, emulsion base, sodium lauryl sulphate, hydro-wool-fat, stearic acid, sodium emulsion, silicon base, bentonite, veegum.

Anti oxidants

Butylated hydroxy toluene, butylated hydroxy anisole, propyl-gallate.

Preservatives

Parahydroxy benzonic acid, methylorpropyl ester, sorlic acid.

The monographs of the above products are available in most of the pharmacopoeia giving specification - essays and other analytical procedures including physical properties to identify the product and determine the purity.

Annex IV

QUALITY CONTROL

1. Both parties do hereby recognize that the successful transfer of the technology concerned by the present Contract cannot be achieved without the existence at the licensee's facilities of an efficiently operating Quality Control Department. The licensor shall fully assist the licensee to constitute such a Quality Control Department or, if already existing, to adapt and check the efficiency of said Department to meet the specific requirements of the transferred technology and to achieve the expected results.

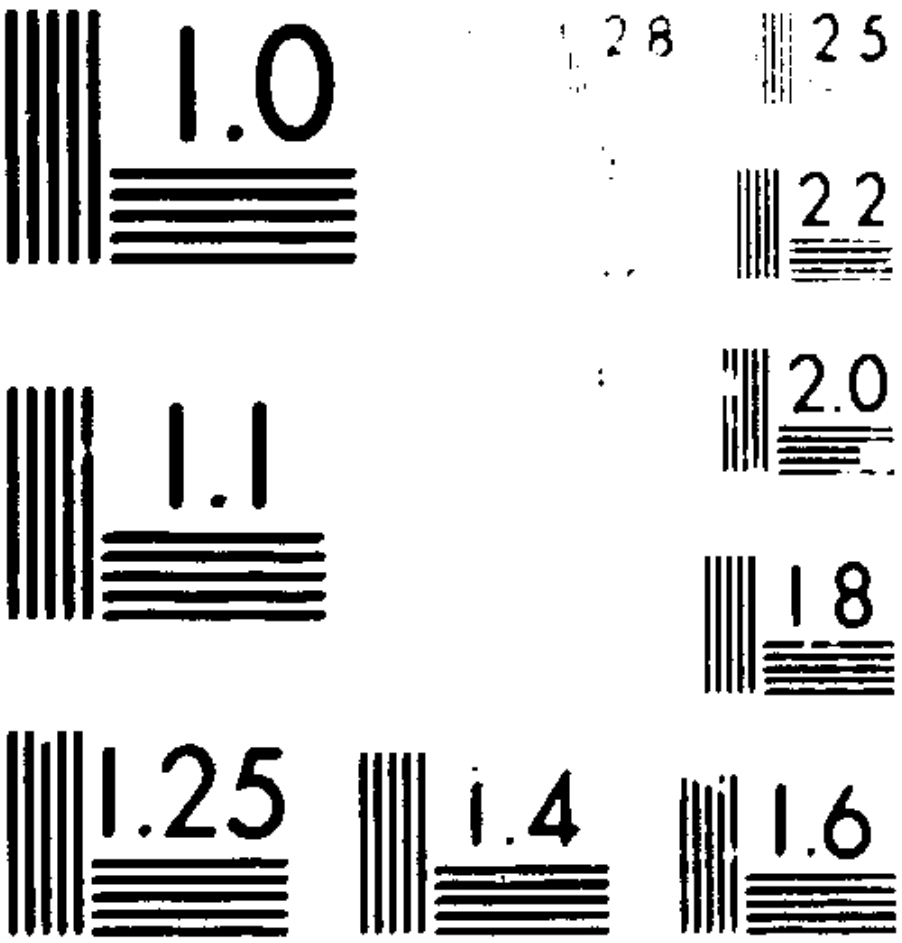
The licensee hereby agrees to implement the recommendations of the licensor in that respect.

These recommendations shall take into account the financial, technical and human resources of the licensee as well as the specific conditions prevailing in the licensee's country.

2. To implement point 1 above, the licensor and the licensee shall constitute within ..... days after the Effective Date of Contract a "joint committee for quality control". The representatives of the licensor belonging to that committee shall belong to the licensor's Quality Control Department in charge of controlling at licensor's facilities the production technology being transferred under the licence agreement.

3. Both parties recognize that due to their specific function and responsibilities each Quality Control Department shall have the largest possible autonomy.

Consequently, the Quality Control Department shall only report to the top managerial level and not to the production management. They shall be free to mutually exchange scientific and technical information related to the drug(s) production controls referring to the present Contract. The conclusions they shall jointly reach shall bind both parties.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4. The information to be transmitted and the verifications to be operated by the licensor shall concern, but not be limited to:

4.1 Internatl organization, qualification, and responsibilities of licensee's personnel (for example, those in charge of sampling should be distinct from those in charge of the analysis).

4.2 Space availability and location at the disposal and under the sole responsibility of the Quality Control Department (quarantine).

4.3 Identification (labelling) of the raw materials, semi-finished products and finished products according to their respective step in the production process.

4.4 Equipment, materials, chemicals and reactive agents as well as their respective maintenance.

4.5 The sequence according to which quality control operations shall be performed and said operations.

4.6 Records of controls performed and samples to be kept.

4.7 Conformity of the licensor's assistance with the quality control regulations in force in the licensee's country.

5. During the course of the Contract, the licensorr shall fully assist the licensee to allow (whenever applicable) the integration of local products instead of imported products and/or to allow modifications incurring cost reductions proposed by the licensee's Quality Control Department.

6. It shall be the responsibility of the licensor to certify that the licensee's Quality Control Department is operational after the provisions contained in point 4 have been performed as well as it shall be the responsibility of the licensee to keep records and samples (whenever applicable) of all operations undertaken by the licensee's Quality Control Department, as stated in point 4.6.

7. The licensor shall have free access to these records and samples as well as, whenever applicable, to the RM/1 supplied by the licensor and rejected by the licensee's Quality Control Department.

8. Considering that free exchange of information is profitable to both parties and to the users of their product, the licensor and the licensee hereby agree not to limit to the duration of the present licence agreement the relations between their respective Quality Control Departments.

## Annex V

## PACKAGING MATERIALS

SOLIDS

(i) Powders: electrolytes - antibiotics and other biological preparations, lyphilized powder, have to be protected from moisture.

(ii) Effervescent granules: to be protected from moisture.

(iii) Tablets: In the case of hospitals, those are packed in containers of 1000 to 5000 tablets to avoid excessive breakages, whereas coated tablets can be packed in large quantities.

(iv) Capsules: Hard gelatine: for hospital can be packed in tins or amber glass bottle. Soft gelatine: are packed in smaller quantities in amber glass bottles.

(v) Suppositories and pessaries: made out of glyco-gelatine bases with active ingredients incorporated in a suitable soft base. These are to be kept at low temperatures and are packed in PVC cavities.

Strip packing or blistes packaging of tablets and capsules are becoming more and more popular due to hygenic storage and handling conditions, as well as smaller packages unit available for sale.

SEMI-SOLIDS - Ointments and creams:

Collapsine metal tubes are mostly used and give good protection from oxidation and contamination. For bulk quantities required by the institutions and hospitals, these can be safely packed in plastic containers.

LIQUIDS

(a) Aqueous oral preparations: Infusions, extracts, syrups, alixers, linctures are mostly packed in glass bottles whereas for bulk quantities plastic containers have also been commonly used besides large size glass bottles.

(b) Aqueous non-oral preparations: Eye-lotions, eye-ear drops; amber glass bottles sterilized before filling are fitted with plastic nozzel; lately single one shot-type rubber packs are coming in the market.

(c) Emulsions: mostly glass bottle, plastic containers are on the trial.

(d) Injections: are packed in glass ampoules; electrolyte solution as well as glucose solution is packed in glass bottles, however they are increasingly being replaced by disposal plastic bags.

NON-ACQUEOUS LIQUIDS

(i) Oils - vegetable oils, castor oil, olive oil .. packed in glass, metal or plastic container.

(ii) Essential oils - organic solvents are packed in glass bottles.

(iii) Inhalers: The active material comes out of metal, glass or plastic containers in the form of spray caused by pressure created by liquified gas known as propellant mostly chloro-fluor-organic compounds. The valve used is of plastic like dichlorodifluoromethane, trichloromonofluoromethane.