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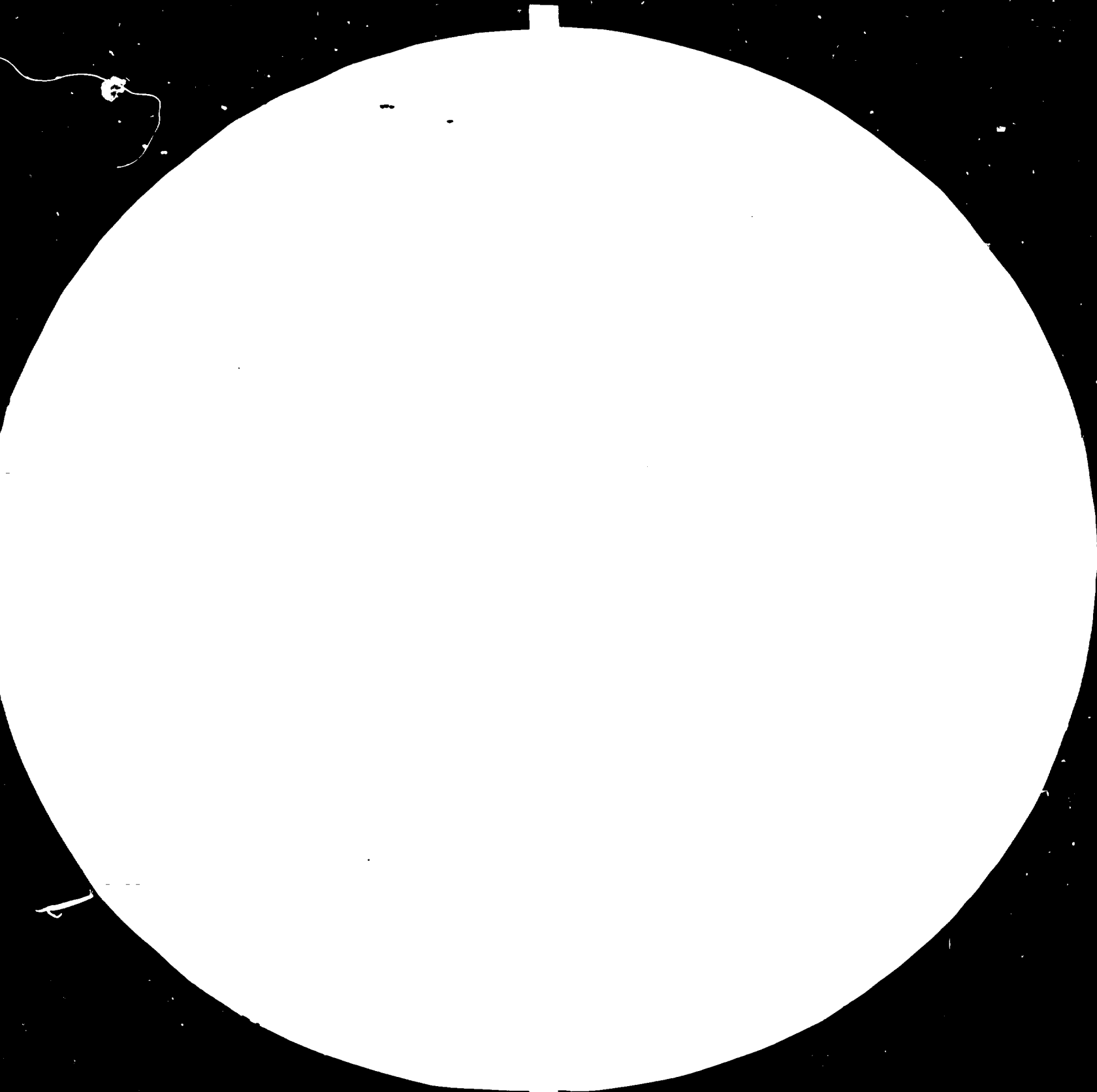

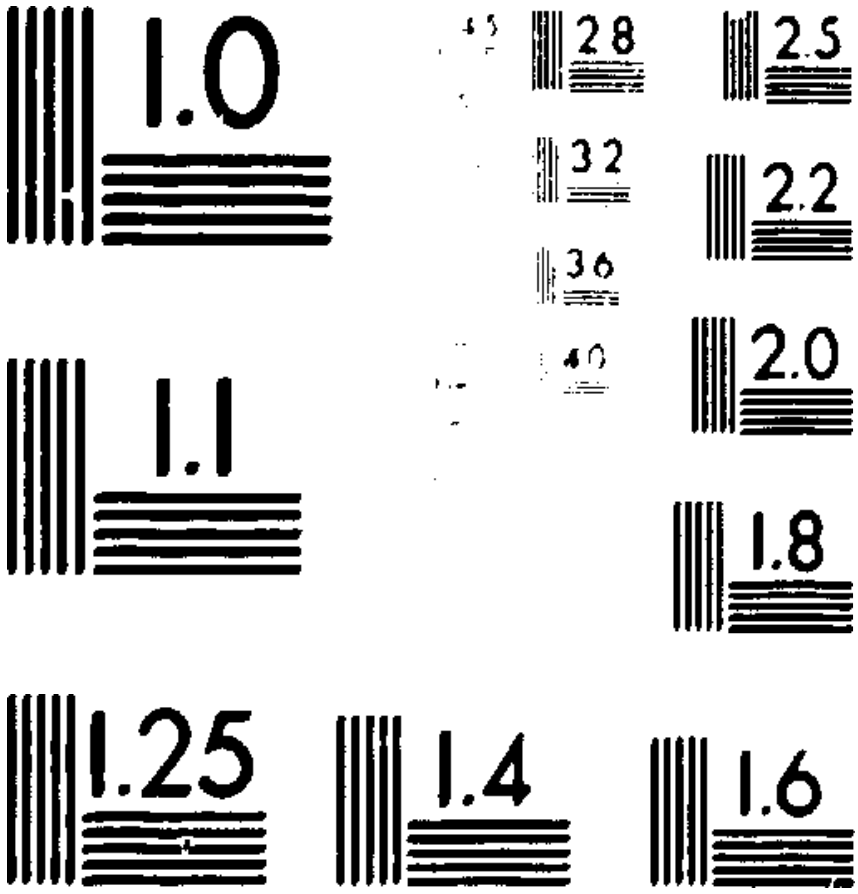

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Budapest, Hungary, 21-25 November 1983

ITEMS WHICH COULD BE INCLUDED IN LICENSING ARRANGEMENTS FOR THE TRANSFER OF TECHNOLOGY FOR THE FORMULATION OF PHARMACEUTICAL DOSAGE FORMS**

Prepared by
the UNIDO secretariat

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FOREWORD

This document is the final version recommended as a result of a review by the Ad-hoc Panel of Experts */ in their advice to the UNIDO Secretariat in accordance with the recommendations of the Second Consultation on the Pharmaceutical Industry (21-25 November 1983, Budapest, Hungary). This Third Meeting of the Ad-hoc Panel was held in Vienna, 22-24 April 1985, and following experts participated in it:

Mr. Alberto Mansur (Brazil), Mr. Ahmed Ali Aboul-Enein (Egypt), Mr. Daniel Biret (France), Dr. Karl F. Gross (Federal Republic of Germany), Prof. Dr. György Fekete (Hungary), Mr. S. Ramanathan (India), Mrs. Catalina Sanchez (Philippines), Mr. Antonio F. Cano-Martin (Spain), Mr. Ernst Vischer (Switzerland), Mr. Ali-ben Mohamed Stambouli (Tunisia), Mr. Joseph M. Bernik (United States of America), Mr. Richard B. Arnold (IFPMA).

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*/ The Second Meeting of the Ad-hoc Panel was convened in Vienna 25-29 April 1983 and discussed the draft of this document before it was presented to the Second Consultation meeting. The Ad-hoc Panel consisted of the following experts:

Mr. Luis Gustavo Florez (Andean Group), Mr. Sebastian Bagó (Argentina), Mrs. Geneviève Abondo (Cameroon), Mr. Ahmed Ali Aboul-Enein (Egypt), Mr. Daniel Biret (France), Dr. Karl F. Gross (Federal Republic of Germany), Mr. Gyorgy Jancsó (Hungary), Mr. S. Ramanathan (India), Mrs. Isabel Roque de Oliveira (Portugal), Mr. Ernst Vischer (Switzerland), Mr. Ali-ben Mohamed Stambouli (Tunisia), Dr. Arnold Worlock (United Kingdom), Mr. Paul A. Belford (United States of America), Mr. S.M. Peretz (IFPMA).

CONTENTS

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 into account the already large experience of developing countries in the matter. */

In line with such recommendations, this paper provides general guidelines and drafting proposals for the negotiation and conclusion of licensing arrangements related to the formulation of pharmaceutical forms. These guidelines have general application to all those drugs contained in WHO's model list of essential drugs, including those on UNIDO's illustrative list. This document is intended to cover two main situations, on the assumption that the Licensee wishes to set up a new formulations unit, and requires the Licensor to provide the process know-how and basic engineering, and a situation where the Licensee already operates a plant for formulations and requires the Licensor to supply process know-how for new products.

In the context of this document a contract means an agreement freely entered into by parties in accordance with national laws and regulations and the specific circumstances of each case.

2. Purpose, scope and content of this document

This document includes items which could be incorporated in contractual arrangements, while negotiating the transfer of technology for the formulation of pharmaceutical forms.

The document is primarily addressed to parties negotiating such arrangements, 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,

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

**/ See "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.

with an aim at substantially improving the availability of essential drugs in developing countries at reasonable costs and quality conforming to official specifications for quality.

(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 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, 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) 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 may include :

- 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 dosage forms (injectables, tablets, capsules, etc.);
- iv) recommendations as to how to deal with the particular issues;
- v) possible clauses and variations thereof.

It should be noted here that the illustrative clauses provided in this document are included as examples that could be used to achieve transfer of technology. These clauses should not be construed as being exhaustive or covering all possible situations that can arise in transfer of technology.

Since the general guidelines contained in the document as well as the clauses and variations proposed, cannot cover all the possible alternatives available for dealing with each particular item, the document only includes those factors which could be deemed more important or appropriate in view of the principles and objectives that are involved in its preparation. The importance and appropriateness of possible alternatives have been assessed on the basis of four main criteria:

i) the potential 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, in developed and developing countries;

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

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

(**) This document is under revision

2. Main features in the production and sale of formulations:

(a) Types of formulations:

Formulations are finished pharmaceutical products in dosage form. They are manufactured from pharmaceutical raw materials. Dosage forms may be, for example:

1. Tablets (coated and uncoated), granules, capsules, powders, liquids, etc. for oral use;
2. They may be for parenteral use such as ampoules, vials (containing liquids, granules or powders).
3. They may be for topical or local application in the form of ointments, creams, paints, eye-, ear- and nasal-drops etc.
4. Other systemic forms such as suppositories and vaginal tablets are also included under this definition.

Pharmaceutical formulations require careful packaging both to provide protection and to ensure their stability as described in Annex IV.

(b) Manufacturing practices and standards

As pharmaceutical formulations are mainly used for human consumption, they must be manufactured under hygienic conditions, and with the greatest care. Parenteral products, eye ointment, etc. must be prepared under sterile conditions. In all cases the manufacturing operations should be in accordance with WHO specifications for pharmaceutical preparations described in the "Good Practices in the Manufacture and Quality Control of Drugs". */

(c) Quality and Process Control

Formulations being important health and life- saving products, most countries have framed their own rules, regulations and acts, regarding preparations, use, and marketing as well as standards and specifications of drugs. Information regarding standards, specifications, testing, etc. are normally compiled in the form of a Pharmacopoeia, which lays down monographs on most drugs, detailing their description, specification, solubility, etc. as well as analytical procedures, standards regarding reagents used for testing these drugs. Many countries and WHO have

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*/ WHO Technical Report No. 567, 1975, see Annex II.

their own pharmacopoeias. to ensure the quality of drugs. Some countries have national formularies, giving part or all of this information. Pharmacopoeias/National Formularies are prepared by eminent persons in the profession and usually have legal sanction.

The function of process and quality control laboratories is to ensure the quality and to fulfil the statutory obligations. This function which should be exercised independently from productions is of utmost importance for health policies. In the interest of all the parties involved and of the recipient countries, a license agreement for the manufacture of pharmaceutical products should contain specific provisions for the creation or adaptation of an efficient quality control department. Details regarding process and control functions as well as the illustrative clauses that may be considered in the case of a licensing agreement are given in Annex III.

(d) Categories of products on the market

Formulations may be classified in two categories according to the type of marketing methods applied

i "generic products"
ii "brand name products"

Generic products are named after the pharmacopoeial or common chemical names. Some generics which are known as "branded generic" are sold with a trade mark.

The "brand name products" are those products which bear a trade mark.

Generic and brand name products may either be prescription only products or OTC (over the counter) products which are sold or advertized and sold directly to the public.

4. Licensing for formulations

As already indicated */, the technology for the formulation of final pharmaceutical products, in contrast to the technology for the manufacture of bulk drugs is in most cases well-known and well diffused and non-patented. For this reason, arrangements for the transfer of technology (other than those involving industrial property rights) for formulations may be limited to the supply of technical assistance for short periods, or alternatively to other type of agreements which do not oblige the recipient to effect continuous payments or observe restrictive conditions.

Nevertheless, in exceptional cases, arrangements extended over a reasonable period might be required. This would apply if galenic technique for new dosage forms contain patented specifities, or where their adaptation to a given case present special difficulties or when this is so desired by the two parties in order to spread over time the payment for the use of a relevant patent.

In practice, however, arrangements for the formulation of pharmaceuticals 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 and the licensing of the relevant industrial property rights.

Following this practice, and in order to assist enterprises in developing countries, particularly in less developed countries to improve the negotiation of such arrangements, this document presents illustrative clauses and variations related to issues typically dealt with in licensing agreements for formulations. **/

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*/ See ID/WG.331/3, op.cit.

**/ For the purpose of collecting information on developing countries' experience in arrangements for formulations, the 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.

It should be noted that currently many developing countries have well established modern formulation units which can offer their own know-how for setting up such units in other developing countries. As stressed by the First Consultation Meeting on the Pharmaceutical Industry, the co-operation among developing countries may constitute an important mechanism to transfer technologies and experiences suited to the particular conditions of the recipient countries.*/

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*/ See UNIDO ID/259 - 1980

II BACKGROUND NOTES AND ILLUSTRATIVE CLAUSES

1. Recitals

The inclusion of "recitals" of 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, references 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.

Illustrative clauses*/

1. Recitals

WHEREAS the Licensor .....

(Alternative a: has manufactured and sold the Products defined below for several years, and is able and has the right to transfer technology for the manufacture of the Products);

(Alternative b: is in the possession of technology for the manufacture of the Products defined below);

AND WHEREAS the Licensee .....

(Alternative a: has facilities for the manufacture, packaging and marketing of pharmaceutical products);

(Alternative b: is willing to set up a plant a ..... for the manufacture and packaging 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 manufacture and sale of the Products;

AND WHEREAS the Licensor and the Licensee intend to conclude and execute this Contract in a manner that is mutually beneficial to both parties and 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:

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*/ See page 5, first paragraph

2. Definitions

While not indispensable, a clause 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 agreement for formulations, terms such as "Technical information", "Medical and scientific information", the "Products" (i.e. the medicines to be formulated) the "Basic Drugs" (i.e. the required ingredients), etc.

Illustrative clauses*/

2. Definitions

In this agreement the following words will have the meaning herein assigned to them.

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

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

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 at .....

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

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 market authorization/registration of the Products with the Health Authority of the Licensee's country. **/

2.8 "Products" will mean .....

2.9 "Basic Drugs" ***/ will mean the following drugs entering into the formulation of the products .....

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*/ See page 5, first paragraph

**/ See points 4.1, 4.2 or page 24

***/ (Pharmaceutical Chemicals)

2.10 "Improvements" will mean any technological advances developed or otherwise acquired by the Licensor or developed by the Licensee related to the manufacture or packaging of the Products. Major changes which essentially alter the technology transferred do not constitute "Improvements" within the meaning of this clause.

2.11 "Effective Date of the Contract" will mean the date on which this Contract will come into force in accordance with provision 19 thereof.

3. 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 competence 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 usually simple, and in such cases may be handled without great difficulty. However, technical assistance and training may be required when the Licensee has a low technical competence.

The expression "know-how" is rather imprecise and ambiguous, both in commercial practice and in legal terms, but is often understood to include non-patented confidential knowledge. It may be advisable, hence, to avoid the use of the expression, and replace it (as suggested in the attached illustrative clauses) by "technical information".

The Licensee will be interested in receiving from the Licensor technical information which has been proved to be commercially feasible. Its description should be sufficiently clear, comprehensible, correct and complete (see also point 14 "Improvements"). The contract should also determine the form in which it is to be transferred (specifications, instructions, etc.), the language in which it should be drawn up and specify those parts of the technical information which should be deemed confidential (see also item 12 "Confidentiality").

Technical information can include formulae, some manuals and other written documents, or explanations, plus some complementary information related to the environment of the production process, such as inputs, maintenance, storage and basic design.

The contract should contain a detailed and exhaustive list of all the components of the technology to be transferred. 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.

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, drawings, charts, computerized documents, tapes, training sessions, demonstration sessions, etc.) which contain said components of the technology.

In the case of setting up a completely new formulation unit, the Licensor should provide the following documents regarding the process and the basic engineering:

1. Detailed process description with all parameters and process conditions for formulations.(*)
2. Specifications of raw materials, excipients, utilities etc. (**)
3. Specifications of finished products.
4. Specifications of packaging materia s.(***)
5. Consumption co-efficients of raw materials, excipients and utilities.
6. Analytical procedures and methods for raw and packaging materials and excipients, in-process and finished products quality control.
7. Operating manuals.
8. Process flow-sheets.
9. Master layout, utilities, services and maintenance - Annex VIII.
10. Layout drawings for equipments and services equipment.
11. Suggestions and recommendations for material handling and storage of materials, including finished products.
12. Suggestions and recommendations for industrial safety, identification of hazardous material and areas.
13. Detailed equipment list with specifications.(****)
14. Effluent treatment (whenever applicable).
15. Recovery of solvents (whenever applicable).
16. Strain specifications (whenever applicable).
17. Requirements of manpower.

(*) For the production schemes applicable to the manufacture of different dosage forms, see Annex V.

(**) See Annex VI.

(***) See Annex IV.

(****) See Annex VII.

As regards to equipment (point 13), the Licensor should provide a comprehensive process and auxiliary equipment machinery list. The specifications should be elaborated enough and indicate material of construction, capacities, dimension, thickness, weight, types of stirrers - in case of mixing and solution preparations, vessels or tanks - as well as in case of motor power, voltage, and r.p.m. It should be noted that some developing countries are at present self-sufficient in the production of various types of equipment and machinery required for the formulation industry for a batchwise production.

Annex VII presents an illustrative list of equipment and machinery required for a formulation unit.

In order to enable the Licensor to fulfil his obligations in connection with the provision of basic design and engineering, the Licensee should be prepared to provide the Licensor with the full range of information needed by the Licensor to fulfil his functions, including the following:

1. Site plan for preparation of master plan and layouts.
2. Meteorological information.
3. Soil conditions and test report.
4. Data regarding climatic and seismological conditions.
5. Information about the availability of utilities including water analysis.
6. Local codes, laws or regulations on drugs, health, toxic explosive, solvents and effluents.
7. Copies of official pharmacopoeia, specifications and norms fixed by the State

The above information is generally submitted to the Licensor prior to the signing of the Agreement (or soon thereafter).

Illustrative clauses*/

3. Technical information

3.1 (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 date on which the Licensee has fulfilled his obligations under 3.7 below.....

(Alternative c: Within ... days from the Effective Date of the Contract) .....

The Licensor will provide the Licensee with Technical Information which has been proved as commercially feasible as defined in 1 above ("Definitions") required for the manufacture, quality control and packaging of the Products, including the following:.....
.....

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

3.3. All documentation referred to in 3.2. will be drawn up in ..... (language) and be presented in a clear manner comprehensible for a normally skilled professional in pharmaceuticals, using ..... (units system).

3.4. The following documentation will be considered as confidential, in accordance with article 12 of this Contract ("Confidentiality").....
.....
.....

3.5. The documentation will be .....
(Alternative a: sent by registered air mail to the following address:.....
The Licensor will confirm by telex or other means to the Licensee the mailing date of each set of documentation).

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

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

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*/ See page 5, first paragraph

3.7. The Licensee will provide the Licensor, within .... months from the signing of this Contract the following information, as required for the preparation by the Licensor of the basic design and engineering of the Licensee's Plant:

.....

....

4. Medical and scientific information. Registration of Products.

(a) Importance and use of the information

The communication of medical and scientific information related to the Products to be licensed is normally one of the main objectives 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 the Licensee's country.

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

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.

Given these two characteristics of the contracts for formulations, in agreements which do not include the supply of basic engineering for a new unit, it is usual that the Licensee does not effect any payment, as in the case when the remuneration is based upon royalties on sales */, until the approval of the Products by the competent health authorities has been obtained. Lacking such approval, the contract remains without object and may therefore be declared without responsibility for any of the parties.

In some cases, and in order to avoid entering into a contract which may become ineffective if the products are not approved, a preliminary agreement is signed for the communication of the medical and scientific information necessary for requesting and obtaining the product's authorization. A licensing agreement is subsequently concluded only if and when that approval has been obtained.

The Products are normally registered under the Licensee's name. Nevertheless, in the case of termination of the Contract by reasons attributable to him, it may be stipulated that the Licensee has an obligation to transfer the respective certificate to the Licensor or to any person designated by him, and to keep secret any confidential information he might have received.

In case the information and documentation required for market authorization/registration is not in possession of the Licensor, the parties should agree on the modalities for the preparation and transfer of the additional information, and on the charging of the respective costs.

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*/ This is one of the main forms of payments suggested in the illustrative clauses attached here. See "Remuneration" page 44.

Scope of the information to be supplied

(i) Registration

In order to enable the Licensee to obtain the registration of the products, the Licensor should provide the Licensee with a complete file comprising full data and reports needed by the Licensee's health authorities for market authorization/ registration of each product, comprising in particular:

(i) Chemical description of the drugs, declaration of the internationally or nationally accepted generic name or the name under which it is proposed to be sold:

a. description of product

b. full chemical composition

c. description of pharmaceutical forms in which it is proposed to be marketed and the route of administration, the proposed doses and the claims to be made for such a product

(ii) Composition of the product giving amount of each ingredient

(iii) Methods of production

(iv) Analytical specifications, methods of analysis in detail

(v) Stability studies in detail

(vi) Bio-availability, safety and efficacy studies in detail, if required by Licensee's health authorities (see Annex III)

(vii) Certificate of approval or free sale certificate issued by the health authority in the country of origin, and the names of the countries where the drug is registered and marketed.

(viii) All contra-indications and precautions necessary during the administration of the product to individual patients including problems such as those that may arise with special items of food and drink.

(ii) Promotional and medical information

Literature for medical profession giving factual data, supported by acceptable scientific evidence, such as

(i) History

(ii) Structural Formula

(iii) Pharmacological aspects

(i) Serum levels; (ii) Kinetics; (iii) Distribution of drug in the body; (iv) Mode of Anti-microbial action; (v) Therapeutic uses of the product.

(iv) Comparison with known drugs and its advantages

(v) Toxicity and side effects

(a) Hypersensitivity; (b) Nephrotoxicity;

(c) Haematological toxicity; etc.

(c) Extent of disclosure

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 the therapeutical uses of the Products have been restricted 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 some countries due to their verified or presumed adverse effects are sold, without appropriate limitations, in other countri s.

Illustrative clauses */

4. Medical and scientific information

4.1. 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.

4.2. 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) .....

within ..... days following the Licensee's request.

4.3 During the lifetime of the Contract the parties will promptly communicate each other any new data known to themselves concerning adverse or side effects of the Products, as well as any changes in the registration status of the Products in the countries where such Products are marketed, where such changes have been determined by the actual or possible adverse or side effects of the Products.

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

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

4.6. 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.

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*/ See p. 5, first paragraph

5. Technical assistance

In cases where the Licensee has limited or no experience in the formulation of pharmaceutical products, he may require the Licensor's advice by means of technical assistance to be 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 assistance, should he deem it necessary, up to a maximum of man-months specified in the Contract.

The determination of the schedule and programme for the technical assistance may be left to an agreement between the parties to be made reasonably in advance from the date when 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, transport costs etc. or a fixed amount (normally payable in local currency) per each day of presence in the Licensee's country.

For example, the following categories of Licensor's experts will be needed at different stages: for periods to be agreed upon in accordance with the specific requirements of the project:

Designation of Expert	Function	Stages/Duration
Engineer	Selection, inspection of machinery and installation	can be called in two spells.
Chemist	Setting up of Laboratory Facilities	3-4 months prior to commissioning
Pharm. Technologist	Testing, commissioning and carrying guarantee trials	Beginning of mechanical and instrumentation trial runs

Illustrative 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 execution of this Contract. 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 experts to the Licensee's Plant, in order to provide technical advice and assistance to the Licensee. 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 suitable 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).

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.

(*) See page 5, first paragraph.

6. Training

In some cases, the Licensee may need to ensure the learning of the transferred 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 comprise the manufacture and control of a certain number of batches, or take place for a determined period.

The Contract should establish the number, categories, experience and qualifications of trainees (see an illustration thereon in the table inserted below) 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 for the periods to be agreed on.

Illustrative Categories, Qualifications and experience of Licensee Personnel to be trained by the Licensor

Category	Qualification	Experience	Nature and Period of Training
Managers	Graduate/Postgraduate in Pharmacy-Technology	5 years in the production/ analytical laboratory of drugs	2 months
Foreman/production maintenance in charge Process/ Quality Control Laboratory	Graduate in respective discipline of engineering/graduate or Post graduate in Chemistry, microbiology, pharmacy etc.	3 years	2-3 months in specific area
Operators/ Chemists (for sensitive area)	Diploma in engineering/ pharmacy, science	1 year	2-3 months in specific area.

Illustrative clauses (*)

6. Training

6.1. The Licensor will provide training to qualified employees of the Licensee nominated by him and agreed upon by the Licensor 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)

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

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

(Alternative a: The costs of the trainees' travel, board and lodging and health insurance whilst in the Licensor's country will be borne by the Licensee.)

(Alternative b: The Licensor will provide at his cost the Licensee's trainees with suitable accommodation, meals and transport during the training period.)

(*) See p.5, first paragraph

7. Patents

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

The manufacture of formulations on the basic of finished basic drugs does not entail the use of process patents, which may refer to the production of the basic drugs, but not to that of the formulations themselves */ except in some specific cases relating to galenic improvements. Therefore depending upon the legislation in force in the Licensee's country, this matter of process patents will not normally arise in regard to the production of pharmaceutical formulations.

Where product patents exist **/ the Licensee will need a license to make use of and sell the patented basic drugs entering into the formulation, even though the Licensee will not manufacture the basic drug itself ***/

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*/ See first paragraph, page 13

**/ A large number of developing countries presently do not recognize product patents in pharmaceuticals; they are:

Argentina	Iran
Benin	Iraq
Bolivia	Kuwait
Brazil (1)	Lebanon
+ Cameroon	Libya
Chad	Morocco
Chile	Mexico (1)
Colombia	Nigeria
Congo	Paraguay
Ivory Coast	Peru
Korea	Central African Republic
Ecuador (1)	Senegal
Egypt	Syria
Gabon	Thailand
Ghana	Togo
Guyana	Tunisia
Honduras	Upper Volta
India	Uruguay
Indonesia	Venezuela
	Yugoslavia

(1) process patents are not recognized either in these countries

***/ A survey is to be undertaken by UNIDO Secretariat in order to examine the status of these patent situations as regards essential drugs, contained in the WHO model list of essential drugs, including the UNIDO illustrative list.

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

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

(b) Licensor's warranties regarding its title to the licensed patents and to grant licenses and as to the absence, to the extent known to him, of factors adversely affecting the validity of the patents;

(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 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.

Illustrative clauses */

7. Patents

7.1. The Licensor hereby grants the Licensee, with effect from the Effective Date of the Contract, a license to make use and to sell 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 in a direct manner 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.

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*/ See page 5, first paragraph

8. Trademarks

Licensing agreements for specialities sometimes cover 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 entrepreneurial 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: when the agreement has expired, the Licensor may either decide to renew it or to exploit the market himself, or to grant a license to a third party. The Licensee, on its side becomes completely dependent upon the Licensor's decision and may be forced, to accept less advantageous terms and conditions if it wishes to continue the use of the trademark.

Furthermore, the license of trademarks may involve additional payments by the Licensee which, in the absence of specific legislation on the matter, may continue as long as the marketed product retains its commercial viability. The acceptance of such a license may also provide an argument for requiring that the basic drugs that enter into the formulation be purchased only from the Licensor or other sources designated by it to safeguard the quality of products (see point 9 below).

In view of these problems, and except where very special circumstances justify it, it would seem advisable that the Licensee should use its own trademark or other trademarks determined by it on the Products formulated under license. If the Licensor requests the right to approve the choice of trademarks by the Licensee, objection may only be made by the Licensor on the basis of legitimate reasons.

However, if the Licensee opts for using a Licensor's trademark, some effects may be obtained from a health policy viewpoint to the extent that it involves the Licensee in stricter and appropriate quality controls. Such use may, on the other side, give rise to the Licensor's product liability in case of injuries or damages caused by the use of the Products.

Illustrative clauses */

8. Trademarks

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

9. Supply of basic drugs (pharmaceutical chemicals):

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 will not be produced locally and hence need to be imported from external sources.

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

However, when the Licensor is a producer of basic drugs, one of his major interests in granting a license for formulation is often the possibility of selling the Licensee the basic drugs he produces entering into the formulation. A reasonable compromise between the parties interests might be, in such a case, to allow the Licensor a preference as a supplier of the basic drugs, provided that the latter offers at least the same price, quality and delivery conditions as the Licensee can secure from the other alternative sources.

It should be noted that in many cases, particularly at the initial steps of the development of a formulation industry in developing countries, the bulk drugs required will be mostly essential drugs largely available from various sources. In such cases, the problems related to patents will not arise, and the purchasing of the required drugs should mainly be based on quality and price competition and the continuity of supply. Therefore, the contract should ensure the Licensee complete freedom in this respect.

There is only one situation where the Licensee may be legally bound to buy the basic drugs from the Licensor. This is the case where the latter holds product patents in force in connection with the basic drugs concerned 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 it is so imposed by the patent in force.

In any such situation, 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 of the same standard as the Licensor.

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 when not required to maintain the quality of the product or service when the supplier's trade or service make or other identifying item is used by the acquiring party, or to fulfil a specific performance obligation which has been guaranteed, provided further that adequate specification of the ingredients is not feasible or would involve the disclosure of additional technology not covered by the arrangements. The Licensor's 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 may be 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.

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

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

Illustrative clauses */

9. Supply of basic drugs (pharmaceutical chemicals):

9.1 (Alternative a: 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 not less favourable than the price usually charged by the Licensor or other suppliers of the same standard for Basic Drugs conforming with the specifications set out by the Licensor under the Contract.

(Alternative b: (i) The Licensee will be free to buy the Basic Drugs (as listed in ...) from any source, 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 comparable offers, the Licensee will communicate to the Licensor the terms of the best offer he has obtained. The Licensor will indicate within ..... days from the receipt of Licensee's communication whether it is able to modify its offer in order to meet the better terms that the Licensee could obtain from that source.

9.2 (**) 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

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*/ See page 5, first para.

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

bearing Licensor's trademarks with respect to which it has been determined that they do not conform to the specifications set out in Annex of the Contract. Any dispute arising from differences in analytical results of samples will be finally decided by .....
..... (*)

9.3 (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 meet the minimum specifications stipulated in that Annex. The Licensor will replace, free of charge, the Basic Drugs which do not meet these specifications.

(ii) 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.

(iii) 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.

(iv) All costs, charges, taxes, occurring 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.

(*) A recognized testing laboratory should be indicated here, preferably the State laboratory for control of drugs in the country.

(**) For the preparation of this Annex to the Contract, see Annex VI.

10. Improvements

The access to improvements made by the Licensor may be of interest for the Licensee, particularly if they imply a reduction of costs of production.

Such a reduction may be obtained by cutting the operation cycle. This may be achieved by adjustments in process parameters or sometimes by the way of use of improved equipment or machinery. In such cases, a cost-benefit analysis on the investment needed as compared to the savings obtainable from such changes should be carried out. The energy-saving could be brought in sterilization and drying operations due to improved techniques. Similarly, the use of new pharmaceutical aids may also improve the quality of the products.

It is convenient that the Contract defines what is meant by "improvements" either in a general clause on definitions (see point 2.10, page 14 above) 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 the transfer of improvements reached by him, the parties should agree upon the terms for such a transfer, including the price. A clause of this type 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, except if the confidentiality requirements of the main contract are jeopardized.

When the improvements have been obtained by the Licensor from a third party on the basis of remuneration, and the Licensor has accepted no restrictions in transfering them to the Licensee, the contract may stipulate that an additional reasonable payment be effected by the Licensee, in accordance with the nature and importance of the improvements concerned.

Illustrative 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 Licensor will inform and, if entitled to do so, furnish to the Licensee any improvements acquired by the Licensor upon terms requiring payment by the Licensor to a third party, subject to a reasonable fee to be agreed.

10.3. 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.

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*/ See page 5, first para.

11. Exclusivity

In general, it is in the mutual interests of the parties that the agreement for the formulation and marketing of pharmaceutical forms be of an exclusive nature, and this should be the first priority. 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 extent of exclusivity should be negotiated in accordance, inter alia, to the type of products involved, the size of the market, the economic feasibility of the project for the Licensee, and the legislation applicable in the Licensee's country.

Further, the exclusivity may include only the country of the Licensee or extend to a larger territory, for instance, the neighbouring countries.

Illustrative clauses(*)

11. Exclusivity

11.1. The Licensor grants the license 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 .....)

(*) See p. 5, first para.

12. Confidentiality

As mentioned before */, technologies for formulations considered in this document are well known and diffused. In most cases they do not comprise of secret information, in contrast to the case of technologies for the manufacture of bulk drugs.

However, the technical information related to formulations may include some confidential information, e.g. information concerning stability - with special regard to tropical condition and some of the process parameters and excipients, the minimal pharmacopoeial standards of which may be inadequate. There are extra specifications and standards adopted by some companies relating to factors like bio-availability and stability of active ingredients.

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 this 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 or for complying with governmental regulations requiring the approval or registration of the agreement or of the Products sold thereunder for subcontracting or procurement. In this latter case, a written undertaking by subcontractors and other third parties against disclosure may be required.

The confidentiality obligation would normally expire on the date of expiration of the Contract stipulated by the parties. However, it may be established that said obligation be extended for an additional and reasonable period after that date, if the novelty of the technology 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 value justifying it remuneration.

It is customary that the Licensee require its own employees to give written undertakings as to the obligation of non-disclosure of confidential information. Such an obligation might even apply for a period after the employee has left his job with the Licensee.

*/ See page 9

Illustrative 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. In these cases, the Licensee will require subcontractors and other third parties a written undertaking against disclosure of confidential information transferred along the lines of this Contract.

(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.

(*) See page 5, first para.

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 the case where the Licensor is also a supplier, separate calculations for payments to suppliers and for royalties may be considered. In some developing countries **/ the price of the basic drugs supplied by the Licensor is deducted from the basis of calculation of royalties.

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

In case of setting up a new formulation unit, the major part of the remuneration corresponds to the process and basic engineering and is generally paid on the basis of certain percentage of the total investment involved, commonly up to 5% thereof. Besides this, the Licensee would normally remunerate separately the technical assistance and eventually - if agreed upon - the deputation of Licensors' experts to assist the Licensee in the selection of equipment, construction, erection, commissioning, etc.

(*) 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

**/ See e.g. Brazil, Venezuela, Yugoslavia

In such a case, the schedule of payments may conform, according to general practice, to the following scheme:

- 10% on the effective date of the agreement against bank guarantee in favour of the Licensee; (*)
- 30% on the receipt of layout plans, process flowsheets, detailed equipment list with specification, utilities specification, and other basic engineering details;
- 30% on the receipt of process documents, list of raw-materials with specifications, analytical procedures, operating construction;
- 10% on the completion of mechanical and water testing trials;
- 10% on the completion of the commissioning;
- 10% on the fulfilment of the guarantees provided for.

The Contract should determine which of the parties will bear the taxes and leviesrelating to the stipulated remuneration, in accordance with the applicable legislation (in some developing countries, taxes - particularly income taxes - must necessarily be borne by the Licensor) **/

(*) This guarantee - which may consist of a first or simple demand bank guarantee - would be normally released of to the satisfactory fulfilment of Licensor's obligations.

**/ See e.g. Colombia (Decree 1234/72, art.2.1): Venezuela (Decree 746/75, art. 1.h)

Illustrative clauses*/

13. Remuneration

13.1 In consideration for the supply of technical, medical and scientific information 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), in instalments scheduled as follows: .....)

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 clause 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.)

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*/ See page 5, first para.

14. Guarantees

a) Suitability for use

The Licensor 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 (see illustrative clause 14 a.).

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 should be correct and complete, in order to permit the full transfer and appropriate application of the technology (see illustrative clause 14 b.).

c) Performance guarantees

The provision of performance guarantees in agreements for formulations may be particularly relevant in case the contract involves the supply by the Licensor of basic design and engineering for the establishment of a formulation unit. If the contract only refers to the transfer of a process to be applied in an existing unit, in current practice no specific performance guarantee is provided for. Moreover, licensors would be reluctant to undertake such obligation as far as they are not involved nor are able to control the application of the technology supplied. On the other side, a performance guarantee would eventually represent additional or higher costs for the Licensee, which the relative simplicity of the technology may not justify.(*)

The main function of a performance guarantee clause in an arrangement for formulations would be to ensure that the products conform in quality to the labelled specifications.

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*/ The concern of the Licensee as regards the results to be obtained with the technology may be eventually satisfied by a demonstration of the process at the Licensor's plant, during the training of the Licensee's personnel.

In particular, in the case of a combination product, if the material does not conform to the specification, there can be a total loss, for only in a few cases can it be reprocessed. Such problems are confronted in the case of vitamins and antibiotics having expiry dates. These quality problems may result from deviations in norms of raw material, utilities, excipients, etc.

The capacity of the plant is directly related to the performance of various machinery and equipment and generally falls beyond the scope of the Licensor's responsibilities. In general, the machinery suppliers have to demonstrate the guarantee of their units. Most pharmaceutical machinery, particularly in packaging, is of high speed and precision requiring packing materials, like gelatine capsules, glass vials, pilfer-proof caps, rubber bungs, etc. of uniform quality

The Contract (or an annex thereto) should specify with precision the guaranteed standards and parameters, the method of analysis and evaluation, the conditions to be met (e.g. use of basic drugs conforming to Licensor's specifications) and duration of the test run. It may also indicate the term within which the latter should be carried out; however, it may be advisable to keep the Contract flexible on this point since the registration or approval of Products depend upon the issuance of an administrative authorization which may be granted with varying delays outside the control of the parties.

If the test run fails and the Licensor is not willing or able to rectify deficiencies, the Licensee may have the right to terminate the Contract and the Licensor may be liable to pay penalties (see illustrative clause 14 c.).

Illustrative clauses*/

14. Guarantees

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 the Products.

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

14.c.1 The Licensor guarantees that the Prodcuts to be obtained by the Licensee will meet the standards specified in Annex ..... provided that (i) the technical information is properly used in accordance with the Licensor's instructions; and (ii) intermediates, basic drugs and other inputs employed meet the specifications agreed upon as indicated in Annex ..... 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 formulation produced meets the guaranteed parameters.

14.c.2 Should the test run fail, the Licensor will assist the Licensee to achieve the agreed parameters within ..... from the end of the first test.

14.c.3 If the Licensor does not provide the assistance referred to in 14.c.2 or after the second test run the guaranteed parameters are not demonstrated, the Licensee will have the right to terminate this Contract.

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*/ See page 5, first para.

15. Warranty against infringement

The Licensee may request the Licensor (especially where the production of new specialities is involved) 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.

Illustrative 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.)

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*/ See page 5, first para.

16. Liability

The manufacture of the Products, or the use thereof by patients, may eventually derive in damages to property or injury to persons.

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

The Licensor 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 conscientiously 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 warnings timely communicated by the Licensor.

Licensors may be reluctant to accept a wide or unlimited liability emerging from the causes referred to. A possible compromise may be reached by limiting the Licensor's liability 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.

Illustrative 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 the Licensee may be held legally liable to pay in respect thereof and for 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: provided that the damage or injury was a consequence of negligence of the Licensor.)

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

*/ See page 5, first paragraph.

17. Duration

The duration of the Contract will depend upon the interest of the parties. If royalty payments are stipulated, the longest duration of the Contract is in direct benefit of the Licensor, since the total value of the Contract increases proportionally to its duration. For this reason, and given that improvements in formulations are not in general very significant, some developing countries have established limitations to the time of duration of agreements of this type.

Illustrative clauses*/

17. Duration

17.1 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.)

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*/ See page 5, first paragraph.

18. 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 supra).

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).

In that case, the Licensor may rightly request the inclusion of a reservation limiting his responsibility to the uses specifically stipulated in the Contract.

It should be noted, however, that in order to comply with the registration as a veterinary product, the Licensee will generally require new information which is generally not included in the medical and scientific information supplied by the Licensor (see point 3 above).

In some complex situations, the negotiation of an extension of the existing Contract may be required.

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

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

If the Contract involves product patents granted for a term that extends beyond the date of termination of the Contract, once the Contract has expired, the Licensor might use its exclusive rights against the Licensee, as it might 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.

In such a case 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 determined in the Contract (e.g. provision of the drugs by the Licensor at competitive prices and payment by the Licensee of a reduced rate of royalty) or to be left for negotiations at the time the Contract comes to an end.

As regards technical information, 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.

In some countries, a licensing contract should not contain by law export restrictions */. Where this is not the case, and complete freedom is not agreed upon, the contract may contain a list of countries where exports should or should not be made. One such example of the latter could be where the Licensor or his exclusive Licensees are formulating and/or selling the products.

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*/ E.g. Spain, Portugal, Japan, Brazil, Bolivia, Colombia, Ecuador, Peru, Venezuela, Mexico, India, Nigeria, Philippines, Yugoslavia

Illustrative clauses*/

18. Use of information and patents

18.1 Nothing in this Contract will be interpreted as directly or indirectly:

(a) limiting the field of use by the Licensee of the Technical, Medical and Scientific information supplied by the Licensor, being understood, however, that the Licensor's responsibilities under this Contract 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 .....)

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

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

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*/ See page 5, first paragraph.

**/ Applicable only in case the Contract includes the license of patents.

19. 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.

Illustrative clauses(*)

19. Effective Date of the Contract

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

19.2. The Effective Date of the Contract will be the date .....

(Alternative a: of signing thereof by Licensor and Licensee)

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

(Alternative c: of payment of the first instalment to the Licensor.)

(*) See page 5, first paragraph.

20. Termination

Clauses on anticipated termination of the Contract will normally vary according to the applicable law, particularly as regards to 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 effect 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 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.

Illustrative clauses (*)

20. Termination

20.1. 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.

20.2. (Alternative a: This Contract may be terminated by either party by written notice to the other 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", "Guarantees"), and the default is not remedied within ..... from receipt of the Licensee's notice thereon.)

20.3. 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").

20.4. 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.

20.5. In any event, the Licensee will not be released from its obligations as regards to confidentiality, as stipulated in article... ("Confidentiality").

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*/ See page 5, first paragraph

21. 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 control) of the parties. Likewise, instead of the extinctive 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.

Illustrative clauses(*)

21. Exoneration (Force Majeure)

21.1. 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.

21.2. 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.

21.3. If the consultations referred to in the preceding clause have not resulted in mutual agreement, or have not taken place because the parties have been unable to communicate with one another....
(Alternative a: either party will have the right to terminate the Contract giving written notice to the other party).
(Alternative b: either party will have the right to resort to arbitration pursuant to article... ("Applicable law and settlement of disputes").

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*/ See page 5, first paragraph

22. Assignment and sublicensing

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 reputation of the counterpart into account.

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.

A flexible alternative would be to provide for in the agreement the participation that the Licensor would have in situations where the Licensee is willing to sublicense the technology to a third party. For instance, the agreement might stipulate that the Licensee may grant sublicenses, subject to approval of the Licensor and the sharing that would correspond to the latter on royalties or other payments to be made by the sublicensee.

A still more elastic approach conditions the Licensee's right to sublicense upon appropriate negotiations with the Licensor and the third party concerned. In some instances, the parties may agree to limit the right of sublicensing to the Licensee's country, or to certain types of firms (e.g. public enterprises) within it. Of course, these restrictions would impair the likelihood of fostering the technological co-operation among developing countries.

The Licensor may be requested to give the new sublicensee facilities of visit and training of its personnel at the latter's expense.

Illustrative clauses (*)

22. Assignment and sublicensing

22.1. (Alternative a: this contract is not assignable .....)

(Alternative b: unless with the prior written consent of the other party). neither party to this Contract will assign any of its rights or obligations thereunder to a third party, except to its legal successor or to any legal person which has acquired all or substantially all the assets and business of one of the parties).

22.2 (Alternative a: The Licensee will not grant sublicenses without the written consent of the Licensor which will, however, not be unreasonably withheld).

(Alternative b: The Licensee may grant sublicenses under this Contract to any third party in (Licensee's country and other specified countries) upon such terms and conditions as may be agreed upon among the Licensor, the Licensee and that third party).

(Alternative c: Subject to the written consent of the Licensor, the Licensee will have the right to grant sublicences under this Contract, provided that:

(i) The Licensor will receive ..... per cent of the total amount charged by the Licensor in concept of the licence and transfer of technical information supplied by the Licensor under this Contract;

(ii) The Sublicensee will assume the same obligations as regards to confidentiality as the Licensee under article ..... ("Confidentiality") of this Contract;

(iii) The Licensor will have no obligations of any type towards the Sublicensee, but will provide facilities for the training of its personnel at the Sublicensee's expense).

(*) See page 5, first paragraph.

23. Applicable law and settlement of disputes

The alternatives chosen for dealing with these important issues will depend on the preferences of the parties and the applicable law.

One possibility - encouraged or imposed in some developing countries */ - is to submit the contract to the law of the Licensee's country, and any disputes between the parties to the judicial courts of that country.

Another usual approach in international trade practice is to stipulate the recourse to arbitration, provided that the law of the parties allows or does not forbid it. In respect of the law governing the contract, the parties may choose a law that has a close and real connection with the contract, or stipulate that arbitrators decide "ex aequo et bono". In any case, the choice of law should not be effective in matters relating to the internal or international public policy (ordre public) or sovereignty of the country where arbitration takes place and of the countries of the parties. With this reservation, the arbitration may conciliate its procedural advantages with the respect due to imperative rules of the States connected with the transaction, and also ensuring its enforcement in the jurisdiction of one of such States.

If arbitration is provided for the contract should specify, at least the following:

(a) The number and method of nomination of arbitrators;

(b) The seat of arbitration;

(c) The procedure and language of arbitration.

The pertinent clauses may also refer to the binding character of the arbitral award. It is generally recognised that. in any case, any of the parties could request the submission of the arbitral award to an examination of legality, for instance before the courts of the country where the arbitration has taken place.

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).

*/ E.g. Phillipines, India, Mexico, Nigeria, Andean Group countries (Bolivia, Colombia, Ecuador, Peru, Venezuela)

Before making use of any of the provisions referred to in this section, it is advisable that the parties endeavour to solve their differences by direct and amicable negotiations. Eventually, the Contract may also stipulate the nomination by mutual consent of an independent expert, whose findings and recommendations may not be binding on the parties, but which may contribute to the clarification and solution of the conflicts at stake.

Illustrative clauses */

23. Applicable law and settlement of disputes

23.1 (Alternative a: This Contract will be construed under and governed by the law of (Licensee's country)).
(Alternative b: This Contract will be construed under and governed by the law of (specified country or jurisdiction thereof), except as to matters relating to public policy (ordre public) of (Licensor's or Licensee's country) which will be decided in accordance with the applicable law of that country).
(Alternative c: The arbitral tribunal will apply the proper law under the conflict of laws rules which it considers applicable, without prejudice to any provisions relating to public policy (ordre public) of (Licensor's or Licensee's country)).

(Alternative d: The arbitral tribunal will decide ex aequo et bono and according to public policy (ordre public) provisions of the countries of the parties).

23.2. (Alternative a: All disputes arising out of or in connection with this Contract will be decided by the competent court of .....).

(Alternative b:

(i) All disputes arising out of or in connection with this Contract, if not resolved amicably by bona fide negotiation between the parties, will be finally settled by three arbitrators, of whom two will be appointed by the parties (one by each) and the third will be appointed by mutual consent of the parties. If the parties do not agree on the third arbitrator, either party may request the Director (name of institution) to appoint the third arbitrator. The arbitration will take place in accordance with (law of arbitration or rules, e.g. Arbitration Rules of the United Nations Commission on International Trade Law);

(ii) If either party hereto defaults under any provision of this Contract and such default continues unremedied for ..... days after written notice has been given by one party to the defaulting party and settlement has not been arrived at by article (i) above, then the former party will have the right to have the matter resolved and settled by arbitration;

*/ See page 5, first paragraph

(iii) The award of the arbitrators will be final and binding on the parties hereto. Judgement upon the award may be entered by the court of (country);

(iv) The Licensor will continue to undertake its obligations under the Contract during any arbitration proceeding unless otherwise agreed by the Licensee in writing. The Licensor and Licensee agree that in the event of arbitration proceedings, the arbitrators will have unrestricted access to the Licensor's and Licensee's respective plants for the purpose of the said - arbitration;

(v) Arbitration will be in (town) and all proceedings will be in ..... (language).

Annex I

Sample Illustrative List of Commonly used Pharmaceutical Formulations in Developing Countries

A. Tablets

(a) Analgesics and antipyretics

1. Acetylsalicylic acid 100-500 mg*
2. Paracetamol 100-500 mg*

(b) Antidiabetic agents

3. Glibenclamide** 5 mg

(c) Antacids and other antiulcer drugs

4. Aluminium hydroxide 500 mg
5. Cimetidine 200 mg

(d) Antiallergics

6. Chlorphenamine maleate** 4 mg

(e) Antileprosy drugs

7. Dapsone 50 mg and 100 mg

(f) Antimalarial drugs

8. Chloroquine** 150 mg (as phosphate or sulphate)
9. Primaquine 7.5 mg and 15 mg (as phosphate)

(g) Anthelmintic drugs

10. Piperazine 500 mg (citrate or adipate)
11. Mebendazole** 100 mg

(h) Antiasthmatic drugs

12. Salbutamol sulfate 4 mg

(i) Antiamoebic drugs

13. Metromidazole** 200-500 mg

(j) Antituberculosis drugs

14. Ethambutol hydrochloride 100-500 mg*
15. Isoniazid 100-300 mg*

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* Suitable strength from given range should be selected on the basis of local need/availability

** Example of a therapeutic group or sub-group

(k) Antibacterial drugs

16. Sulphadimidine** 500 mg
17. Sulphamethoxazole 100 mg * Trimethoprim 20 mg
18. Sulphamethoxazole 400 mg + Trimethoprim 80 mg

(l) Vitamins

19. Ascorbic acid 50 mg

(m) Antihypertensive drugs

20. Methyldopa 250 mg

B. Capsules or Coated Tablets

(a) Antibacterial drugs

1. Ampicillin** 250 mg and 500 mg
2. Chloramphenicol** 250 mg
3. Erythromycin 250 mg (as stearate or ethylsuccinate)
4. Tetracycline** hydrochloride 250 mg

(b) Antituberculosis drugs

5. Rifampicin 150 mg and 300 mg

C. Elixirs

(a) Analgesics

1. Paracetamol 120 mg in 5 ml

(b) Anthelmintic drugs

2. Piperazine hydrate 500 mg (as citrate in 5 ml

D. Oral Suspensions

(a) Antibacterial drugs

1. Sulphamethoxazole 200 mg + Trimethoprim 40 mg in 5 ml

E. Injections

(a) Solvents

1. Water for injection in 2-ml, 5-ml, 10-ml ampoules

(b) Solutions correcting water, electrolyte and acid-base disturbances

2. Glucose, isotonic, 5%
3. Glucose 4% + sodium chloride 0.18% (Na^+ 30 mmol/l, Cl^- 30 mmol/l)

F. Ointments and Creams

(a) Antiinflammatory and antipruritic drugs

1. Hydrocortisone** 1%

ANNEX II

RECOMMENDED GOOD MANUFACTURING PRACTICES - WHO - A short resumé

1. Manufacturing Premises

Drugs should be manufactured, processed, packaged, labelled and tested in premises that are suitable for these purposes. Attention should be paid to the following points in determining suitability of premises.

a) The adequacy of working space.

b) The compatibility of other manufacturing operations that may be carried out in the same or adjacent premises.

c) Buildings should be so designed and constructed so as to prevent the entry of animals and insects; whether interior surfaces (walls, ceilings and floors) should be smooth and free from cracks, should not shed particles, and should permit easy cleaning.

d) Lighting, heating and ventilation/air-conditioning required to maintain satisfactory temperature and relative humidity that will not effect the drug during manufacturing and storage.

e) For special purpose, such as for manufacture of sterile products, separate enclosed areas; specifically designed for the purpose, should be provided. These areas should be entered through an air-lock, and should be dust free and ventilated with an air supply through bacteria - retaining filters. Routine microbe counts of the air in these areas should be carried out before and during manufacturing operations.

2. Storage Areas

The following principles may be observed for the suitability of storage areas:-

a) The storage areas should provide adequate space, suitable lighting.

b) The storage areas should provide for suitable and effective separation of quarantined and other materials.

c) Special and segregated areas should be available for storage of substances presenting risks of fire and explosion; highly toxic, narcotic and other dangerous drugs and rejected and recalled materials/products.

3. Equipment

The manufacturing equipment should be designed, placed and maintained in such a way as to be suitable for its intended case; facilitate through cleaning whenever necessary; eliminate any contamination of drugs and their containers during manufacture, and minimise the risk of confusion or the omission of a processing step such as filtration or sterilisation.

Manufacturing equipment and utensils should be thoroughly cleaned to avoid the carry-over of drug residues from previous operations, and when necessary, sterilized. Maintenance should guarantee equipment and utensils for continuous, trouble free manufacturing at set conditions. Adequate records for such procedures should be maintained. Equipment used for aseptic meanufacturing and filling should be checked at suitable intervals by microbiological methods. Weighing and measuring equipments used in production and quality control should be calibrated and checked at suitable intervals.

4. Sanitation

Manufacturing premises should be maintained in accordance with the highest sanitary standards. A written sanitation programme should be made indicating the areas to be cleaned and cleaning intervals, cleaning procedures to be followed and personnel assigned to and responsible for cleaning operations. Eating, smoking and unhygenic practices should not be permitted in manufacturing premises nor in toilets. Adequate recreation space is recommended. Sufficient clean, well-ventilated toilet facilities including facilities for hand-washing and rooms for changing clothes (cloak rooms) should be available near working areas for the use of manufacturing personnel.

5. Starting Materials (raw and packaging)

An inventory should be made for all starting materials to be used at any steps of manufacture. Records should be kept of the suppliers, the

origin, date of receipt, date of analysis, date of release by the quality control department,validity and their subsequent use in the manufacture. All materials must be identified and their containers examined for damages. These should be properly stored in quarantine, properly sampled by quality control department and tested for compliance with requirements, and released from quarantine by the quality control department with written instructions. Materials that are accepted or approved should be properly labelled as such and then transferred to areas designated for storage. All rejected materials should be identified and destroyed or returned to the supplier soonest possible. Issuance of material should be on first-in, first-out basis.

6. Manufacturing Operations

Manufacturing operations and controls should be carried out under supervision of qualified personnel.

a) Cleanliness: Before any manufacturing operation is started checks should be made that all apparatus and equipment to be used in the operation are clean and functional.

b) Equipment and Containers: The contents of all vessels and containers used in the manufacture and storage between manufacturing stages must be identified with clearly legible labels, bearing the name and/or identification code of the processed materials and necessary batch identification data. Similar labels should also be attached to the mechanical manufacturing equipment during its operation.

c) Precaution against contamination and mishaps: All manufacturing operations should be confined to separate areas ear-marked for such purposes or care should be taken to ensure that neither cross-contamination nor mix-up should occur. In manufacturing areas, clean working garments should be worn instead of personal clothes. Whenever different operations are not physically separated and there is a possibility that the sterilised and unsterilised products might be confused, all containers of batches of products for sterilization should bear clear indication of whether or not their contents have been sterilized. Products that undergo sterile operations should be protected from contamination by using methods such as laminar-flow techniques. All dust-producing operations involving highly potent substances, particularly antibiotics, should be conducted in areas that are provided with adequate exhaust systems

or maintained under appropriate pressure so as to prevent cross-contamination. Adequate precaution should be taken to prevent the recirculation of contaminated air.

d) Batch Manufacturing Records: Manufacturing records must provide a complete account of the manufacturing history of each batch of a drug, showing that it has been manufactured, tested and analysed in accordance with the manufacturing procedures and within instructions. A separate batch manufacturing record should be prepared for each batch and it should include:

- name and dosage form;
- date of manufacture;
- batch identification;
- complete formulation of batch;
- the batch number;
- the actual yield obtained at different stages of manufacture of the batch as compared with theoretical yield;
- duly signed record of each step followed, precautions taken and special observations made throughout the manufacturing of batch;
- record of all in-process controls followed and the results obtained;
- identity, quantity and quality of each starting material;
- identification of packaging materials, containers and closures used;
- the theoretical yields to be expected from the formulation at different stages of manufacture and the permissible yield limits;
- detailed instruction for, and precautions to be taken in, manufacturing and storage of the drug and of half-finished products; and
- description of all necessary quality control tests and analysis to be carried out during each stage of manufacture;
- signature of official responsible for the manufacturing of operations and date of his signature;
- analytical report showing whether the batch complies with prescribed specifications, dated and duly signed by the official responsible;
- record of the decision regarding the release or rejection of the batch by the quality control department;
- validity, and
- record of disposal or utilization of the rejected batch.

7. Labelling and packaging: Labelling and packaging materials should be stored and handled in such a way as to ensure that labels, packaging materials relating to different products do not get mixed up. Access to such materials should be restricted to authorised personnel only.

Prior to packaging and labelling, it should be checked from the records that the batch has been duly approved and released by the QC* Department. To eliminate errors, a known number of labelling and packaging units should be issued. Upon completion of the packaging and labelling operations, a comparison should be made between the number of labelling and packaging units issued and the number of items labelled and packed plus the number of units not used.

All finished drugs should be identified by labelling that should bear, and clearly indicate the following information:-

- the name of the drug
- list of active ingredients showing amount of each present and a statement of net contents, e.g. number of dosage units, weight or volume
- batch number
- the dates of manufacture and expiry (as required)
- any special storage conditions or handling precautions that may be necessary
- directions for use, and warnings and precautions that may be necessary
- name and address of manufacturer.

8. The Quality Control System: It should carry out the following functions:
   - prepare detailed instructions for carrying out each test and analysis
   - release or reject each batch of starting material, semifinished product, packaging and labelling materials, and finished drugs
   - evaluate quality and stability of starting, semifinished, and finished material and establish expiry date and shelf life specifications
   - examine returned drugs to determine whether such drugs should be released, processed or destroyed in accordance with the laid down procedures,

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*Quality Control

- keep and maintain all records regarding observations, analytical results including calculations along with the signature of persons concerned
- periodical shelf inspection should be carried out
- maintain distribution record
- complaints and reports of adverse reaction should be promptly attended and corrective measures taken.

Annex III

Illustrative clauses relating to 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.

4. The information to be transmitted and the verifications to be operated by the licensor shall concern, but not be limited to:

4.1. Internal 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 reaction agents as well as their respective maintenance.

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

4.6. Records of control 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 licensor 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 raw materials 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 license agreement the relations between their respective Quality Control Departments.

(N.B. Services of independent laboratories could be obtained if need arises.

Arrangements should be considered for clearing of batches by the licensor at the beginning of the cooperation and then random approval of batches after initial years of successful cooperation.)

ANNEX IV

PACKAGING MATERIALS

SOLIDS

(i) Powders:
- Sachets of moisture protecting plastic foil or aluminium foil, inner side plastic lined
- Aluminium containers, inner side occasionally plastic lined
- Carton container
- Glass bottles (depending on product amber glass)
- Plastic bottles (appropriate quality material)
- Glass vials.

(ii) Efffervescent and other granules:
- Sachets of moisture protecting plastic or aluminium foil, inner side occasionally plastic lined
- Aluminium container, inner side occasionally plastic lined
- Glass bottles.

(iii) Tablets:
- Blister packs of 1 to 10 to 30 units, blister side of thermo foil, cover side of aluminium. For tropical zones and coated tablets: blister side of ACLAR, Tristar or similar foil, or use normal foil material and pack the blister in an aluminium sachet. If unit dosages are required, use perforated fault grooves.
- Strips of plastic or aluminium foil.
- Amber glass bottles for 20 up to 500 units
- Tins for hospital use (1000 - 5000 units)
- Drums for large quantities of coated tablets.

(iv) Capsules:
- Hard gelatine:
  - Blister packs identical to those for tablets
  - Amber glass bottles
  - Tins, inner side coated, for hospital use
- Soft-elastic gelatine:
  - Special blister packs similar to those for tablets
  - Amber glass bottles.

(v) Suppositories and vaginal tablets:
- Aluminium strips with thermo- or mechanically formed cavities
- Blister packs with aluminium foils on both sides

Storage of finished packs at temperature not exceeding 20°C.

SEMI SOLIDS*

- Collapsible metal tubes, normally preprinted with orientation code, inner side lacquered, inner tail end plastic lined for better closure. Closure = 3,4 or 5 folds.
- Plastic tubes
- Bulk is stored and transported in plastic lined containers (drums)
- Glass- or tin jars as exception.

LIQUIDS

(a) Aqueous oral preprations (emulsions**), suspensions, syrups, tinctures, etc.):

- Glass bottles, amber or clear
- Plastic bottles, as alternative where compatible with the products.
- Glass, metal or plastic containers for bulk.

(b) Aqueous non-oral preparations (eye lotions, eye-drops*):

- Glass bottles, amber or clear
- Plastic bottles with nozzle
- One shot type plastic or rubber tube

(c) Injectables*:

- Glass ampouls, transparent or amber (neutral/soda glass, etc.)
- Glass vials
- Glass bottles or disposable plastic bags for infusions/transfusions.

(d) Non aqueous liquids:

- Oils, oleovitamins: Glass, metal or plastic containers.
- Collodions, elixirs, glycerits, liniments, spirits: Glass bottles.
- Inhalers: Metal-, glass- or plastic-spray containers with generally chlorofluor compounds as propellant. The valve is normally of dichlorodifluoromethane or trichloromonofluoromethane (special plastic-like material).

STORAGE AND TRANSPORTATION OF CONTAINERS FOR PHARMACEUTICALS

According to the prevailing situation and requirements, the containers may be cartoned, cellophaned and packed into fibre board boxes or wooden cases and strapped.

The quality of packaging materials should ensure the stability of the products to be licensed.

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* Where ophthalmological sterile or parenteral preparations are packed, the containers (ampoules, vials, tubes, etc.) must be properly sterilized before use.

** It is a two phase base with an emulsifying agent. One or both phases could be also non-aqueous.

ANNEX V

PROCESS TECHNOLOGY

Tablets

Tablets represent the most used dosage form. Besides plain tablets, sugar coated, enteric coated, film coated, press or dry coated, layered or prolongated action tablets offer a wide range of application of medicinal need.

The commonly used shapes are: flat with bevelled edges, convex, oval, oblong, ovular shaped, triangular, square.

For better distinction colours, grooves, cross grooves, letters and other symbols are used. For dosage variation breakline is used.

The flow diagram in Figure I describes the various steps in the manufacture of tablets, as further described below.

(a) Milling and sifting

The ingredients are pulversied and sieved.

(b) Mixing

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

(c) Preparations of paste/granulation liquid

The paste is prepared in a separate jacketed vessel.

(d) Wet mixing

The paste is added to the mass and mixed thoroughly until it has the consistency of damp snow or brown sugar.

(e) Wet granulation

The wet mass is granulated in an oscillating or rotating granulator to required mesh size.

(f) Drying

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

(g) Granulation

The dried granules are again passed through an oscillating or rotating granulator to required mesh size.

(h) Blending

The granules are blended with the lubricating and disintegrating agents.

(i) Tabletting

The lubricated granules are fed to the tabletting machine where tablets are formed by compression. During the tabletting in process control tests for disintegration, hardness, friability, uniformity of weight etc. are carried out.

(j) Inspection

Tablets are passed on inspection belts for checking of specks, chips, uniformity, coating etc.

(k) Packing

Depending on the requirements, tablets are packed either in blister packs, glass bottles, tin containers or strips. Counting is done either manually or by machine.

(l) Labelling or printing

The packed containers are labelled; batch number, manufacturing and expiry dates are indicated on the label/carton. The pack should indicate the contents of active ingredients and average doses. In case of blister packs and strips the relevant information is printed onto the foil.

COATED TABLETS

There can be sugarcoating, enteric coating, film coating, press or dry coating. The tabletting and packaging process is the same as described in case of tablets (see Figure I).

(a) Sugar coating

The coating is applied in successive layers to the tablets, subdivided into sealing solutions, subcoating powders and adhesives, rounding and smoothing solutions, colour and finishing solutions and polishing solutions or suspensions. Arsenic free shellac dissolved in alcohol is commonly used to seal tablets to prevent moisture penetrating the tablets. Other materials are beeswax, silicone, resins or water resistant polymeres, in conjunction with purified talc. Coating powders consist of sugar, acacia flour, starch, calcium carbonate, etc. For polishing carnauba wax, paraffin or beeswax is used.

(b) Dry coating

The granules of different pharmaceutical substances are prepared separately. One or more substances are fed to a rotary tabletting machine to form the core. This core is transferred to another rotary tabletting machine and further compressed with the granules of the remaining pharmaceutical substance. This process allows more stable conditions amongst the different substances or against atmosphere.

(c) Enteric coating

Enteric coating may be defined as a film which does not permit release of a significant quantity of drug in the stomach but rapidly and completely releases the pharmaceutical substance when the dosage form passes into the testine.

(d) Film coating

The advantages over sugar coating are: Coating less than 3% by weight of the finished tablets, better resistance to chipping of the coating, increased tablet strength, decreased product cost and the visibility of identification marks through the film coat, e.g.: letter codes, score marks and tablet colour. As disadvantage the less elegant appearance may be mentioned. As film substances are used polymers - water soluble or dispersible cellulose derivatives such as hydroxypropyl methylcellulose and carboxymethylcellulose.

CAPSULES

Capsules are solid dosage forms in which the pharmaceutical substances are enclosed in either a hard or soft soluble container or shell of a suitable form of gelatin.

- Hard gelatin capsules: single or a combination of pharmaceutical substances in powder form may be administered at an exact dosage level, giving an advantage over tablets. The capsule sizes available vary from No. 5 (approx. 30 mg capacity) to No. 000 (approx. 600 mg capacity). The water content of hard gelatin is 12-16%. The storage of the empty capsules should be in a cool, humidity controlled room (about 15°C, 40-50% rel. humidity).

- Soft elastic gelatin capsules: the pharmaceutical substance may be a liquid, paste or powder. The shape may be elliptical, oblong or round. The gelatin is plasticized by the addition of glycerin, sorbitol and may contain a preservative to prevent the growth of fungi. For the manufacture of capsules see Fig. II.

(a) Milling and sieving

Basic ingredients are powdered and sieved through a suitable mesh.

(b) Mixing

The required ingredients are weighed and mixed thoroughly in a high speed mass mixer or planetary mixer.

(c) Preparation of solution or paste

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

(d) Wet mixing

The solution or paste is added to the mass and mixed thoroughly in the above mentioned high speed mass- or planetary mixer.

(e) Wet or dry granulation

The wet or dry mass is granulated to required mesh size.

(f) Drying

The wet granules are dried in a thermostatically controlled dryer. Wet granulation and step (f) are not commonly followed unless otherwise required for special type of preparations.

(g) Blending

The granules are blended with the lubricants.

(h) Sorting and cleaning of capsules

The empty hard gelatine capsules, stored in humidity-controlled air-conditioned areas, are sorted out and cleaned before filling, if need be.

(i) Filling of capsules

The empty gelatine capsules are taken into the hopper of an automatic capsule filling and closing machine. The top of the capsule is removed, a given weight of the pharmaceutical substance filled and the same top again inserted onto the lower capsule part. Hand-operated machines are also used for filling the capsules. The operations require a humidity-controlled air-conditioned area (30%+ 5% rel. humidity). Weight variations are to be eliminated by frequent controls and properly adjusting the machine.

(j) Polishing and inspection

The filled and sealed capsules are handled in polishing pans to clean them. The capsules are subjected to inspection and quality control before packing.

(k) Sealing

Due to variations in tolerances and adhesive features of gelatine often the sealing of capsules is required.

(l) Printing

For identification purposes the capsules may be printed. As alternative different colours of gelatine are used.

(m) Packing

Depending on the requirements, the capsules are filled in glass, blister packs or tin containers. Counting is done either manually or by machine.

(n) Labelling

The containers are labelled, the label indicating batch number, manufacturing and expiry dates as per requirement. The labels also indicate the composition of active components and average doeses. Steps (h) to (m) and storing require an adequately humidity-controlled air-conditioned area.

ORAL LIQUIDS

The active ingredient(s) is (are) dissolved in an aqueous or non-aqueous solvent or, if it is insoluble in pharmaceutically or therapeutically acceptable solvents, dispersed in emulsions, suspensions, etc. Figure III shows the flow diagram for the manufacture of oral liquids. The subsequent operations, in principle, are followed in the manufacture of liquids.*/

(a) Preparation of demineralized water

Most of the preparations require demineralized water of specific quality with respect to ionic concentration, pH, conductivity and purity. Potable water passes through a carbon filter, a series of ion-exchange columns and finally a filter. A reversed osmosis, UV-radiation or ozonisation may be added to the plant for reasons of economy and securing a high standard of purified water.

(b) The active ingredients and base material are weighed precisely into a tank with a propeller- or high speed-stirrer. Demineralized water, if required, is added. The mass is mixed thoroughly to a uniform solution preparation. In case of suspensions, the product is passed through a homogenizer. Depending on the process-permitted preservatives, stabilizers, colouring and flavouring agents 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 a plate filter. Suspension does not require filtration.

(e) Transferring the mass

The final mass is transferred to the storage tanks for filling.

(f) Washing and cleaning of bottles

The containers are cleaned and washed thoroughly in machines or by hand with demineralized water and dried in ovens or continous driers.

(g) Washing and cleaning caps

The caps are cleaned, washed and dried in batches.

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*/ For the sake of clarity the following distinction is made:

- Aqueous solutions: e.g. water, aromatic waters, aqueous acids, juices, sprays, syrups (tinctures), etc.
- Nonaqueous solutions: e.g. elixirs, oleovitamins, spirits, etc.
- Two phase bases: emulsions, suspensions

(h) Filling

The liquid preparations are filled into bottles to uniform volume by a filling machine. The dosing principle may be vacuum or piston stroke.

(i) Capping

The filled containers are capped either by hand, semi mechanized device or machine. For safety reasons, several sealing devices are applied. Inert gassing is required for products not compatible with oxygen.

(j) Labelling

The containers are labelled with labels where during the same operation the batch number, manufacturing and expiry dates are printed on. The label should indicate the composition, average dose, storage conditions, etc.

(k) Packing

For transportation, each bottle is inserted into a folding carton or carton box or, a suitable number of containers are packed into a shipping carton of 6, 8, 10 or 25, exceptionally 50 units and transferred to commercial stores.

NON-ORAL LIQUIDS

Non-oral prepations are manufactured in the same manner as oral liquids, only under aseptic conditions.

PARENTERALS (Injectables)

The administration of pharmaceutical substances is carried out by intracisternal, intradermal, intramuscular, intraspinal, intrathecal, intravenous or subcutaneous injection. Injections may be classified in five categories: solutions ready for injections; dry, soluble products ready to be combined with a solvent just prior to use; suspensions ready for injection; dry, insoluble products ready to be combined with a vehicle just prior to use and emulsions.

The flow diagram in Figure IV describes the operations involved in the manufacture of injectables. Air-conditioning is mainly required for the comfort of the operators who are requested to operate in completely enclosed cloths and masks. The whole section must work under clean, aseptic

conditions. Filtration and filling of the injectable preparation, drying and sterilizing of the ampoules and vials, their transport to the filling station and closing must take place under absolute sterile room conditions to ensure a non-contaminated product.

Sterile room conditions are reached, when fresh- and for economic reasons recirculated-air is passed through three sets of filters, namely a mechanical or electrostatic standard filter, then through a fine filter made of plastic fibres and finally through a sterile filter, normally consisting of glass fibres. To achieve the required sterility the air must pass the rooms at least 10-15 times per hour. Should extreme sterile conditions be maintained, laminar flow is applied which assures a complete flushing with turbulence free air.

Operations in the manufacture of ampoules and vials are as follows:

(a) Preparation of pyrogen-free distilled water

Suitable equipment is used for preparation of pyrogen-free distilled water. It must be circulated in the stainless steel pipes and pass a sterile filter/sterilized through autoclaving before being used.

(b) Preparation of solution

Precisely weighed quantity of the active ingredient(s) is filled into the solution preparation tank, stirred well in the solvent to ensure a homogenous solution.

(c) Filtration

The solution of thermolabile substances is sterilized with deep or plate filtration under aseptic conditions, while ordinary solutions are filtered and are then subject to thermal sterilization. The solution is ready for filling after quality control and sterility tests and is stored in pressure tanks. The room must be sterile.

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

The ampoules or vials are cleaned, washed thoroughly with pyrogen-free distilled water and flushed with compressed filtered air. These containers are then sterilized by indirectly heated sterilizers. Stoppers are also washed and sterilized in autoclaves. An alternative to ampoule washing is the use of closed stem ampoules which are automatically opened on the filling machine just before filling. The exit of the autoclave or washing/sterilizing machine must lie in the sterile zone.

(e) Filling

The ampoules or vials are filled with the solution in suitable filling machines and sealed. The filling room must be sterile and under positive air pressure. U.V. lamps and laminar flow hoods are used to maintain aseptic conditions in the filling area.

(f) Sterilization by autoclaving

The sealed containers are heat sterilized by autoclaving with direct steam at particular steam pressure and for a given period of time. The thermolabile substances, under certain conditions, may be sterilized by radiation.

(g) Leak testing and quality control

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

(h) Labelling and packing

The containers are labelled (if not preprinted), batch number, dates of manufacture and expiry are printed during the same operation. Folding cartons and shipping containers must take care of the fragility of ampoules.

(i) Manufacturing of penicillin products

This group of products must be manufactured and filled in completely isolated areas to avoid contamination with all other products.

INFUSIONS - TRANSFUSIONS

Large volume parenterals are meant for intravenous use. The flow diagram in Figure V describes the manufacturing steps. All procedures are similar to those for injectables. Here too, strictly maintained sterile conditions are required in the filling and sealing area.

Instead of glass bottles, plastic bags may be used. The "BOTTLE PACK" system e.g. produces the bag just before filling, starting with granules forming a hose and blowing it up to the required container.

OINTMENTS

Ointments are semisolid preparations intended for external (topical) application to the skin or mucous membranes. The manufacture is carried

out under clean conditions. An exception are ophthalmic preparations which are manufactured in sterile rooms.

The ointment is a water-in-oil or oil-in-water emulsion base, an oleaginous base or a so called water soluble base. If large amounts of solids are contained, the product is called paste. The base materials are: white petrolatum, hydrophilic petrolatum, (Paraffins) etc.

The flow diagram for the manufacture of ointments is shown in Figure VI. In broad, the following steps are involved in the manufacture of topical ointments:

(a) Preparation of base

The ointment base is prepared in a jacketted vessel with a system of mixers including a high speed stirrer and the provision of heating and cooling.

(b) Incorporation of ingredients

Precisely weighed quantities of active ingredients are added slowly into the base under continuous stirring and mixed thoroughly. For sterile preparations, the base is sterilized either in a dry heat sterilizer in suitable containers or in the jacketted vessel itself. The ingredients are also added under aseptic conditions as described in the parenteral section.

(c) Smoothing

The mixture is passed through a further homogenizer/emulsifier should the action in the vessel not be sufficient.

(d) Filling

The ointment is then filled into the collabsible or plastic tubes by automatic filling and crimping machine. For sterile preparations tubes are sterilized before filling using ethylene oxide, formalin etc.

(e) Labelling

Tubes are printed with the necessary information which include contents, warning etc. Batch number, date of manufacture and expiry is either press-printed in code form on the crimped tube tail or printed on the folding carton together with the code number, which is also press-printed on the crimped tube tail.

N.B.: Creams are ointments on water-in-oil base.


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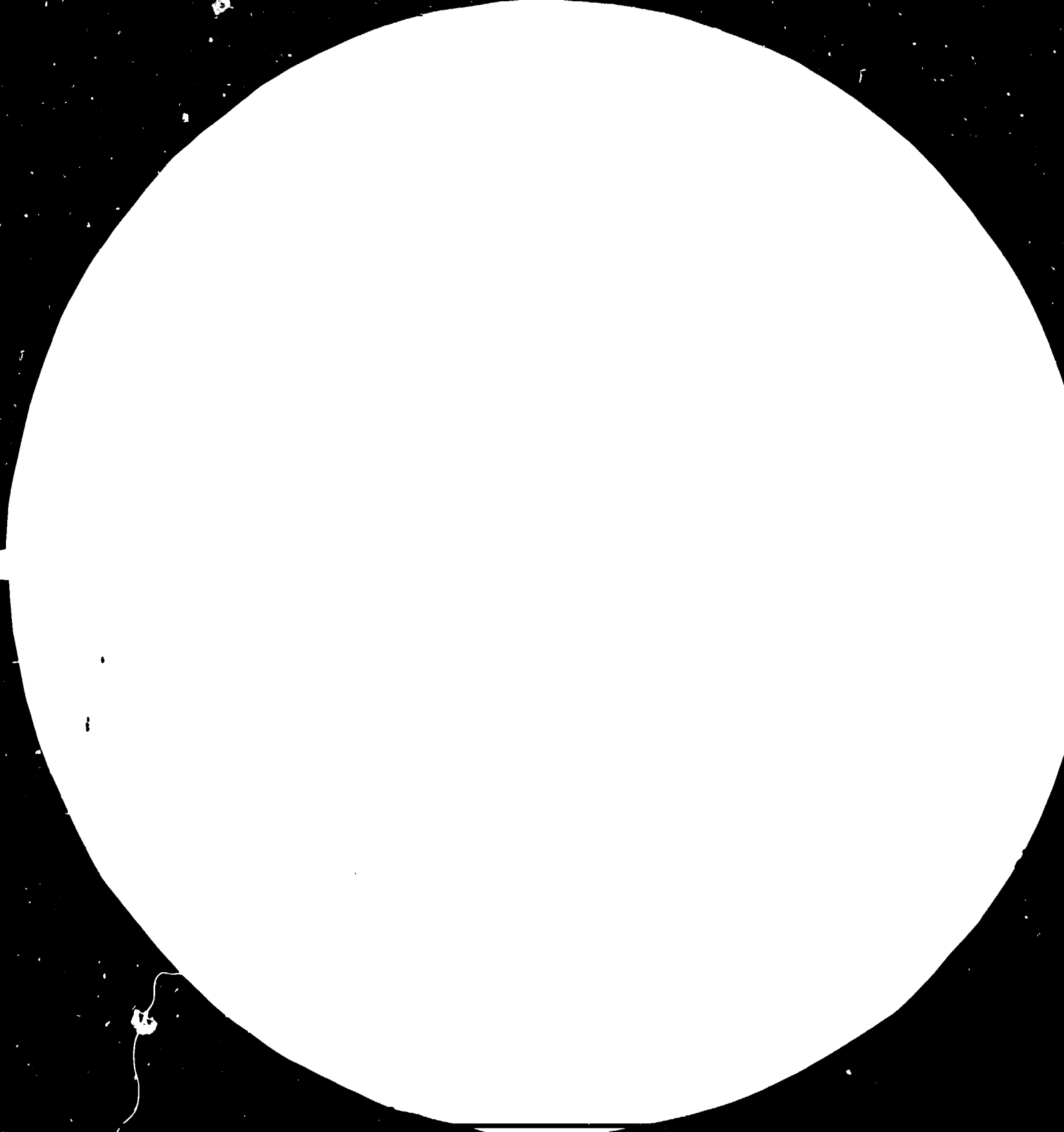

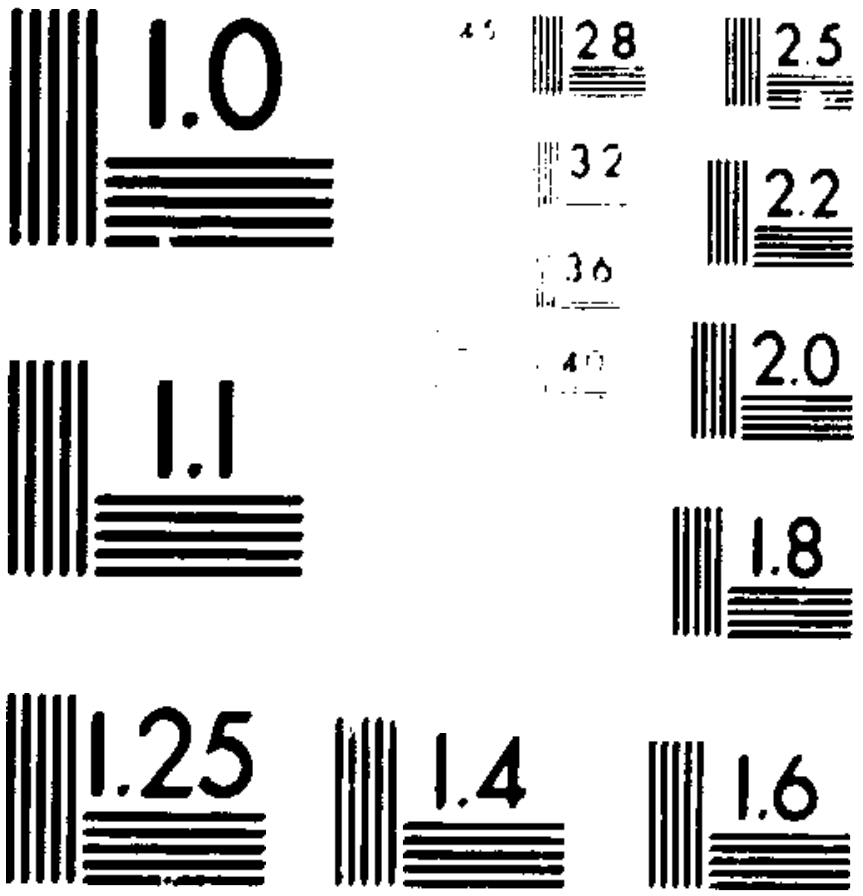

POWDERS AND GRANULES

Powders and granules are used for oral, topical or parenteral administration. The flow diagram for the manufacture and filling is shown in Figure VII. The major operations are similar to those described under tablet manufacture. After milling, sieving, granulation, drying, blending, quality control tests are conducted. The granules are then filled into bottles or sachets by an automatic filling and capping or sealing machine. Sampling is done for weight variations. The bottles are labelled (sachets printed) and packed. Depending on the nature of product and final use, sterile and air-conditioned dry areas are required for manufacturing and filling operations.

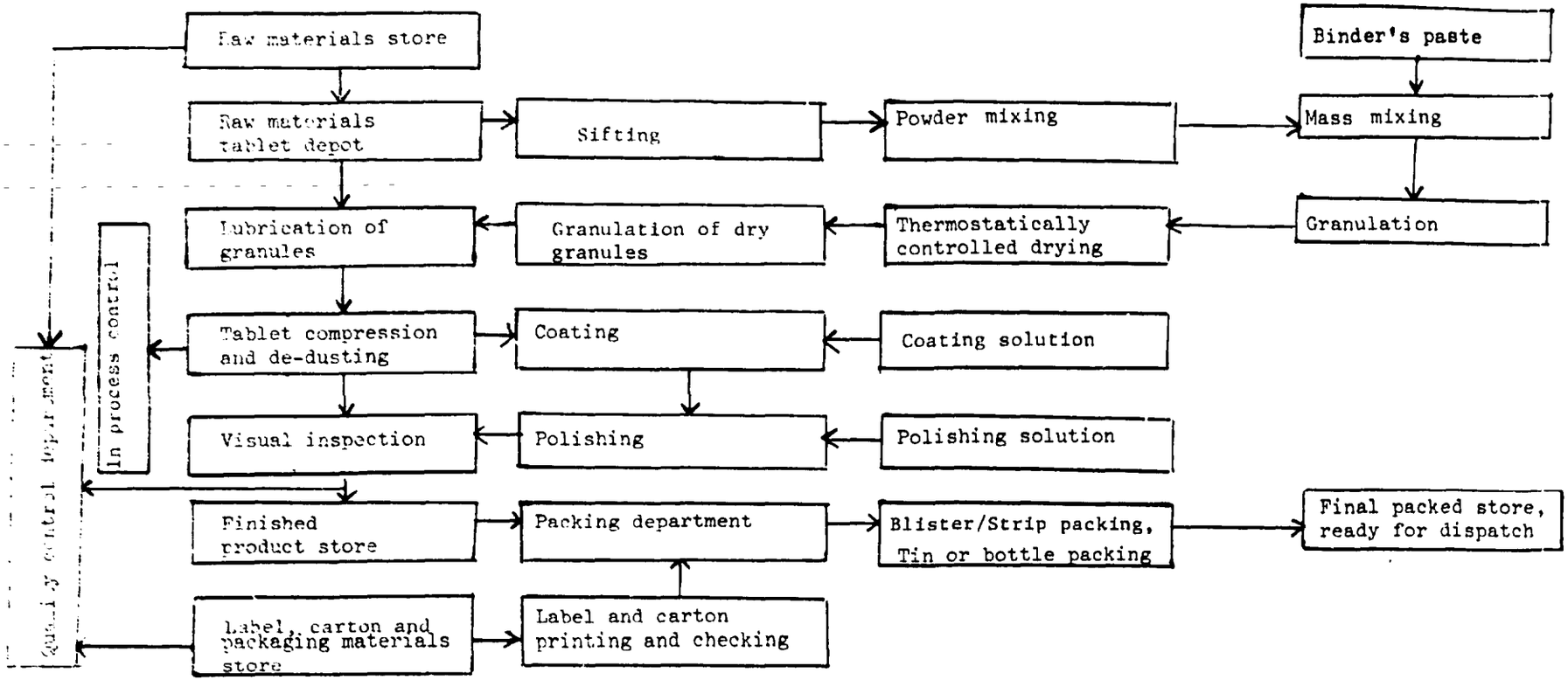

Figure I Flow diagram for manufacture of tablets

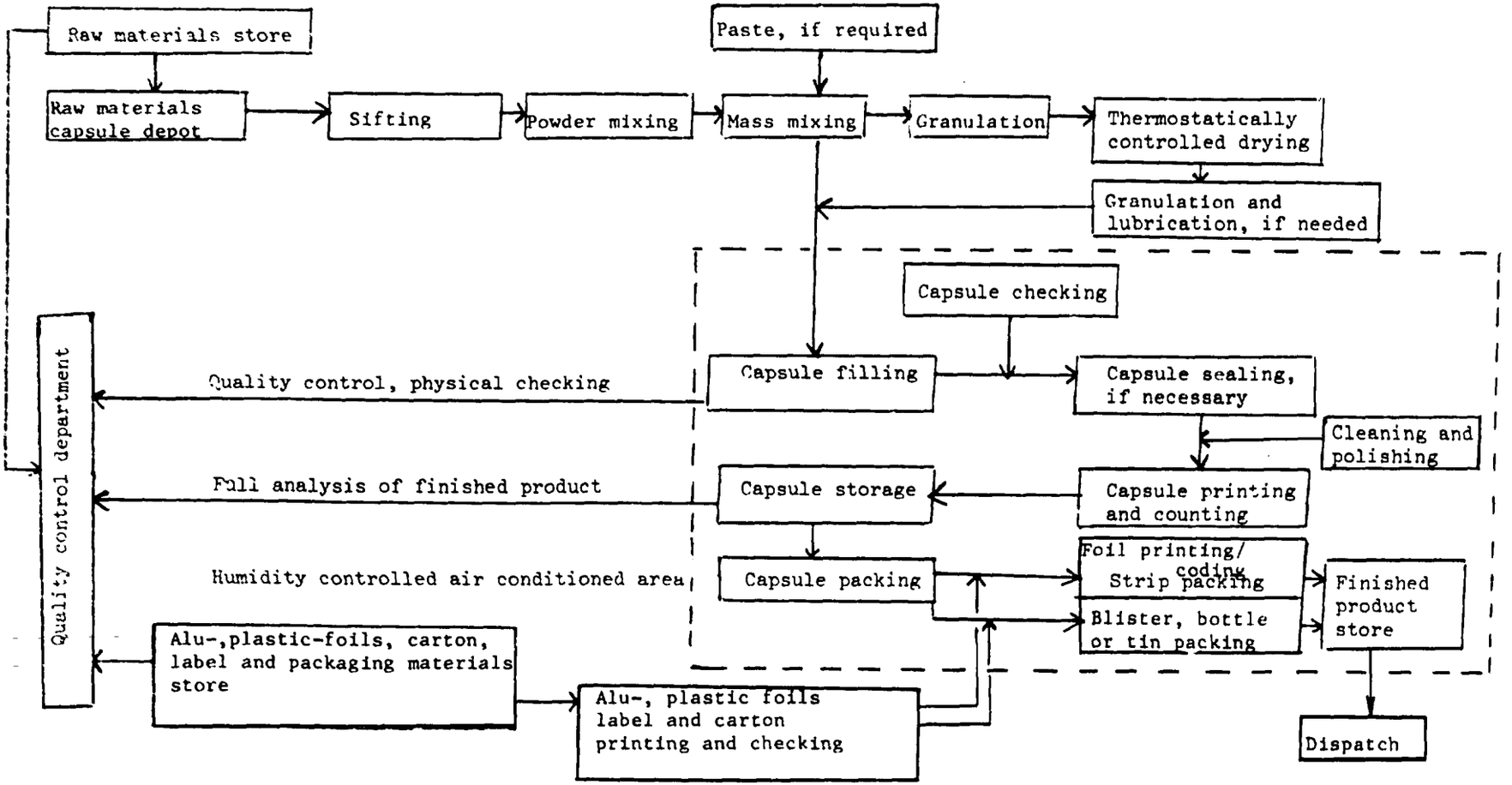

Figure II Flow diagram for the manufacture of capsules

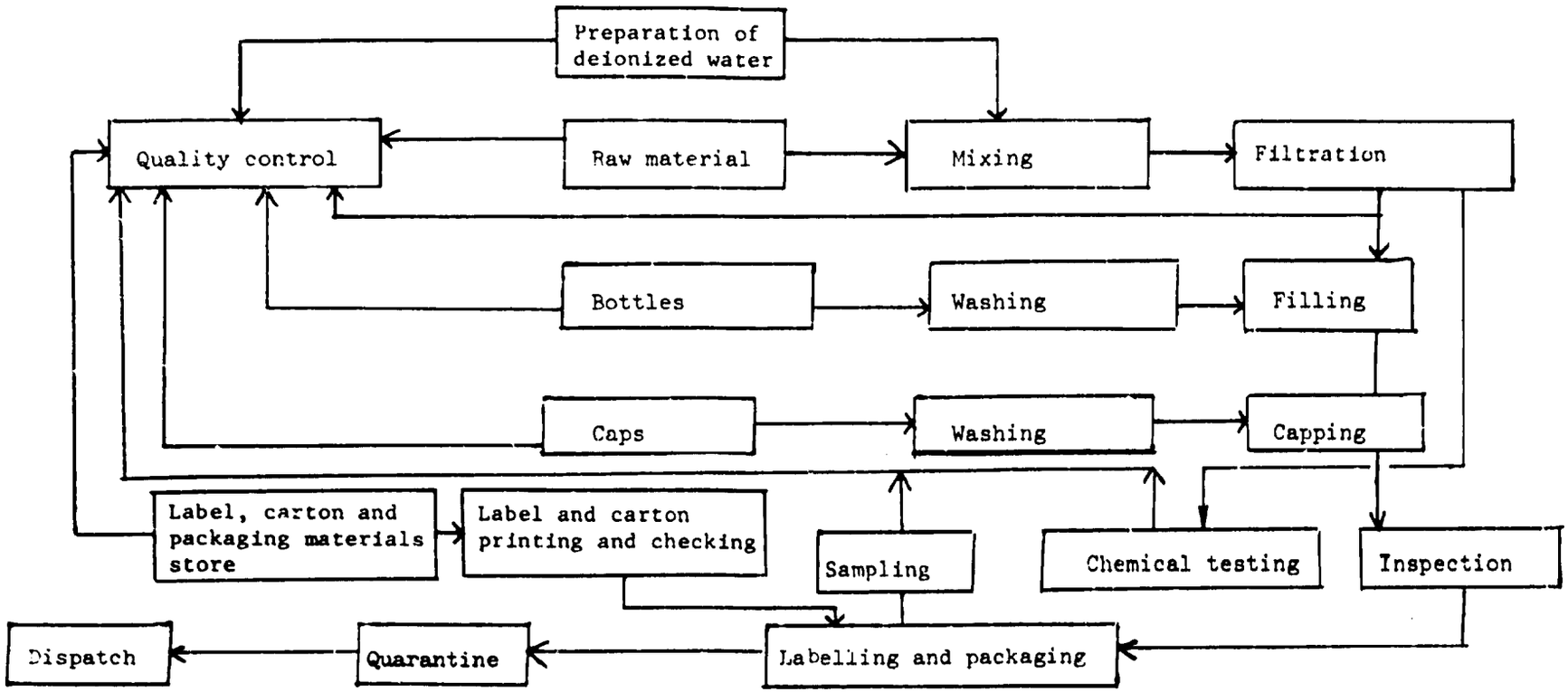

Figure III Flow diagram for the manufacture of syrups, elixirs and solutions

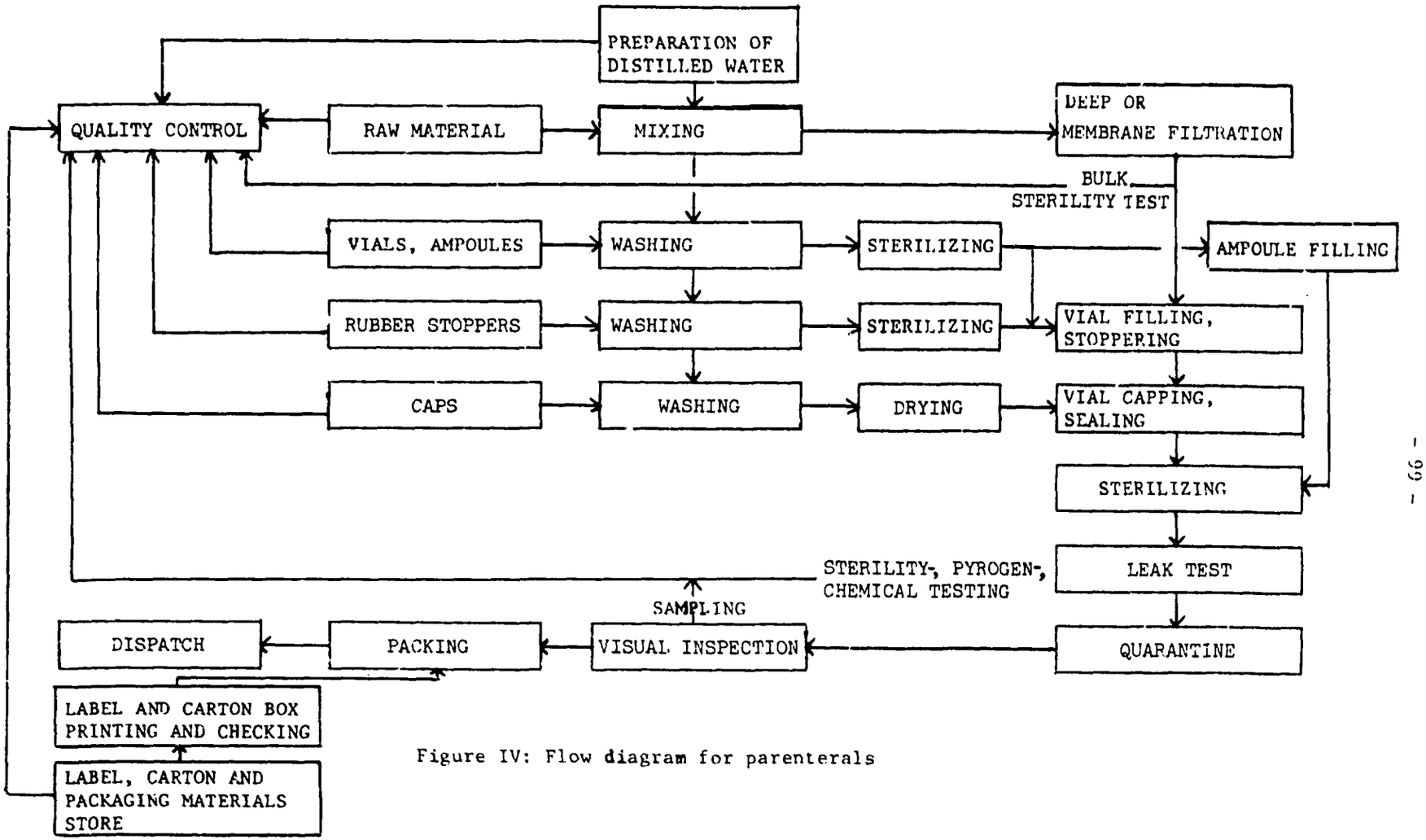

Figure IV: Flow diagram for parenterals

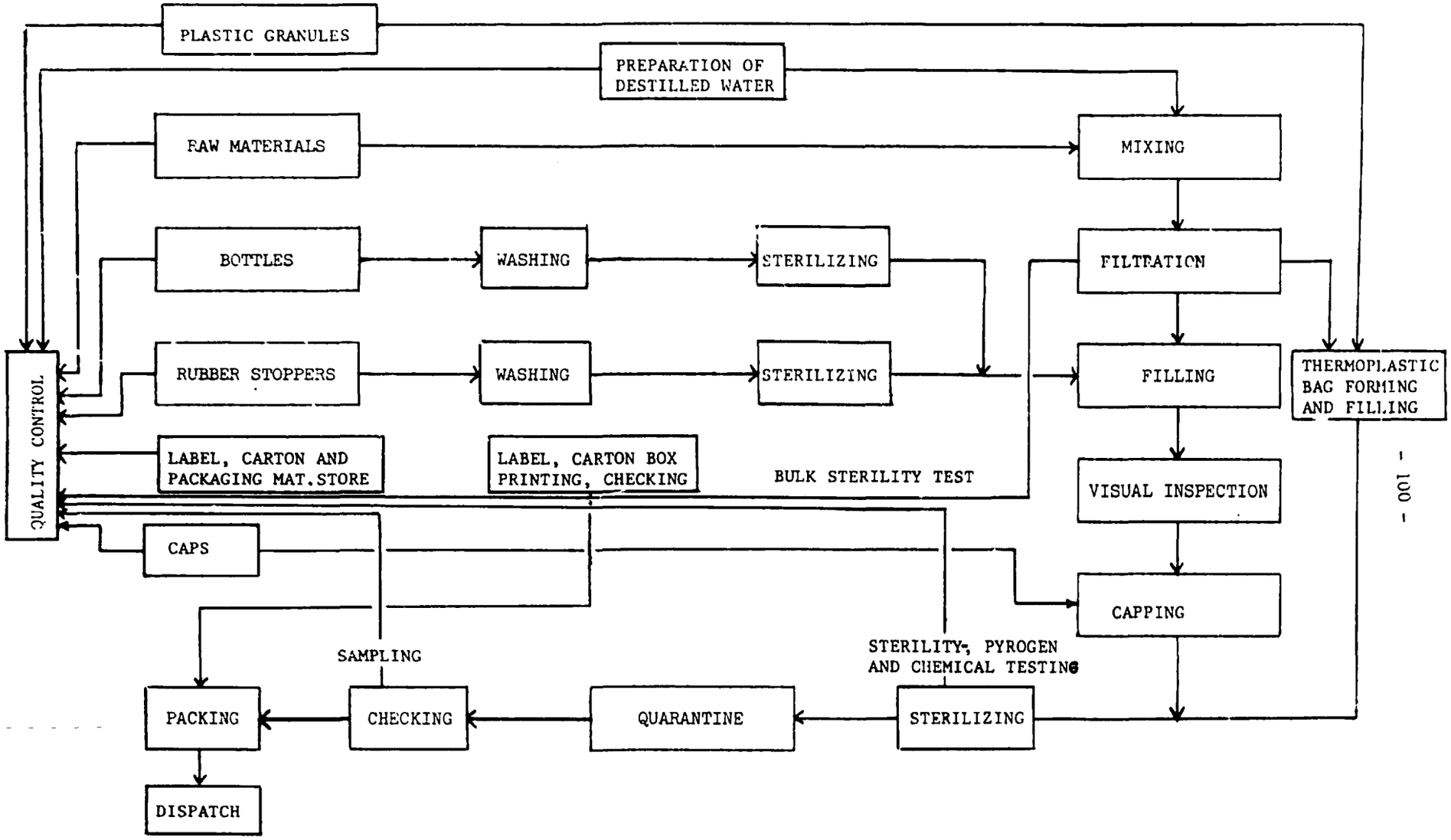

Figure V: Flow diagram for transfusion fluids

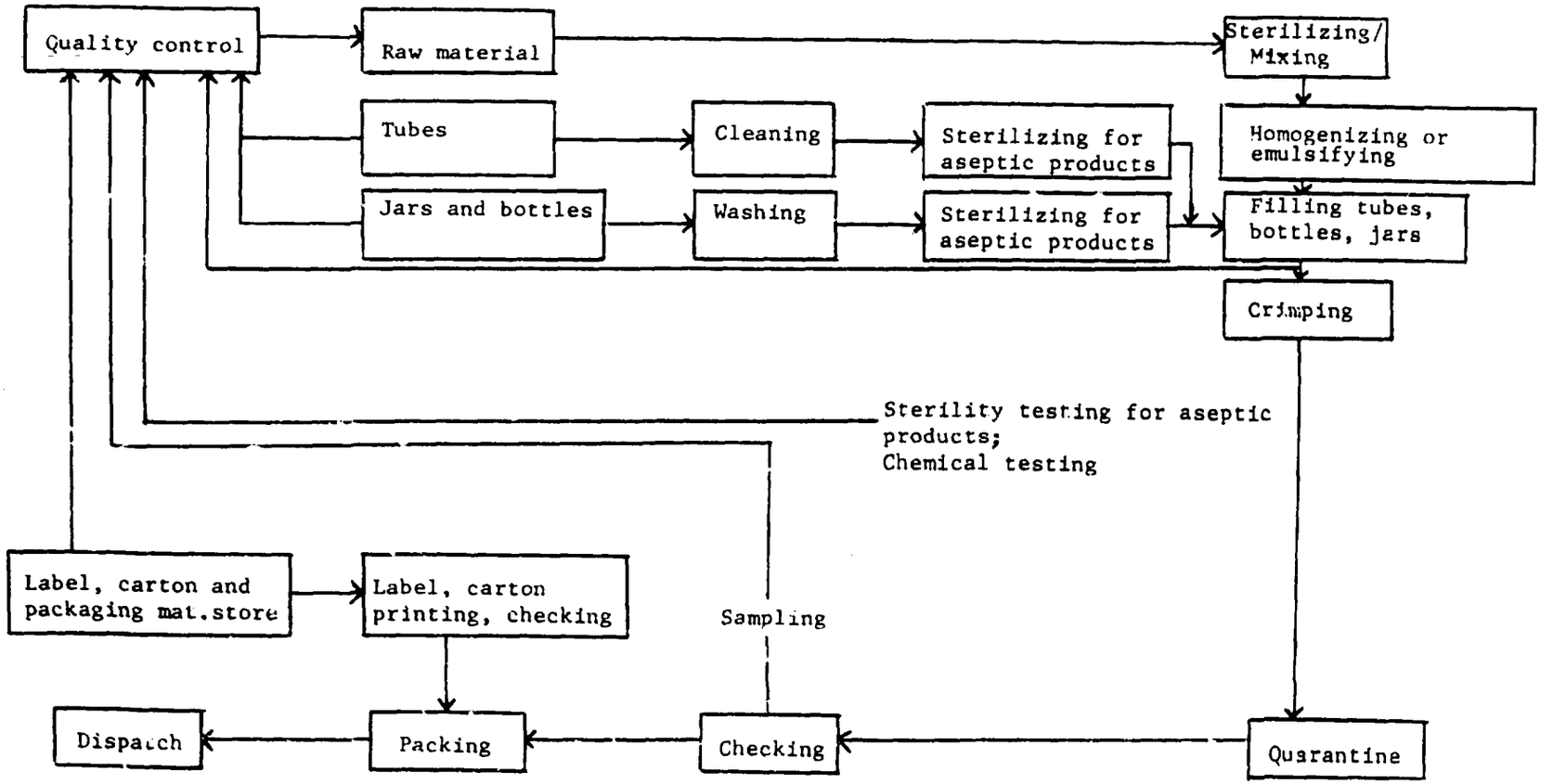

Figure VI: Flow diagram for the manufacture of creams, ointments, emulsions, lotions and suspensions

(Tubes are delivered with caps already screwed on!)

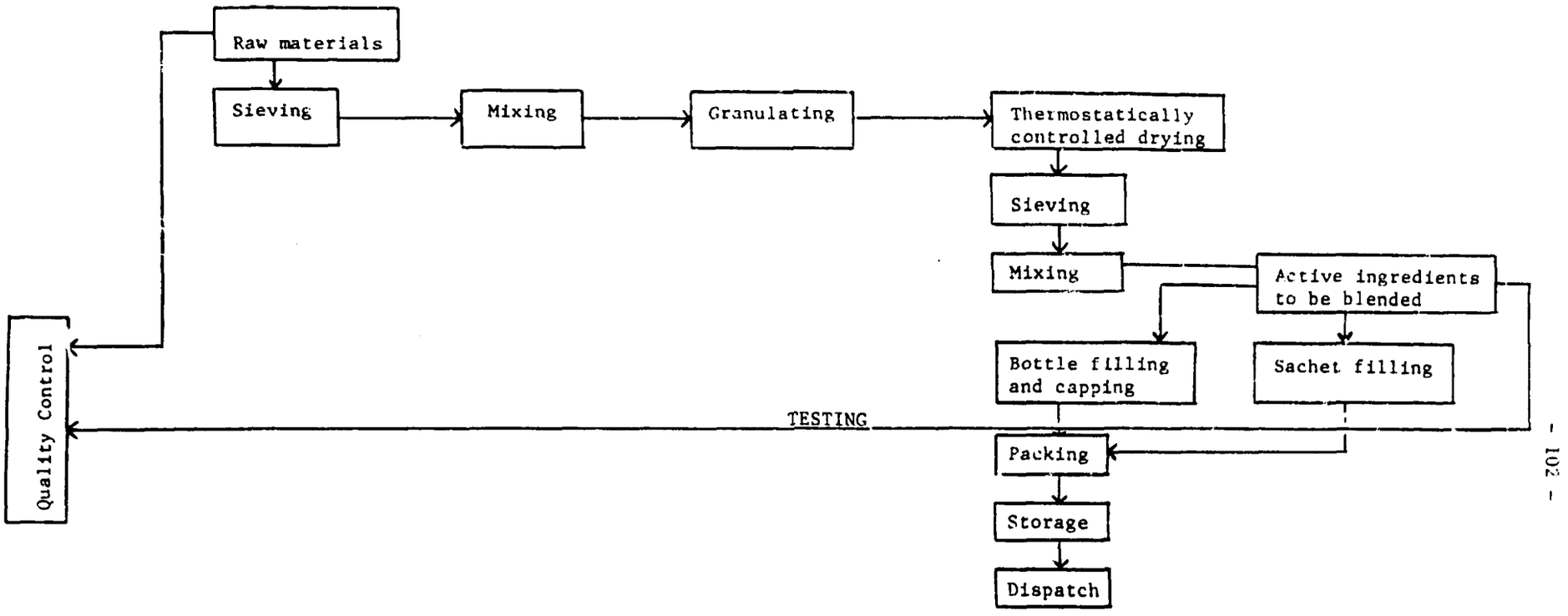

Figure VII: Flow diagram for powder filling

ANNEX VI

SOME ESSENTIAL PHARMACEUTICAL CHEMICALS AND AUXILLIARY MATERIALS FOR PHARMACEUTICAL FORMULATIONS

Pharmaceutical Chemicals

Acetylsalicylic acid, Paracetamol, Mebendazole, Ampicillin, Penicillin-benzyl, Erythromycin, Streptomycin, Sulphadimidine, Tetracycline, Diethyl-carbamazine, Dapsone, Chloroquine phosphate, Primaquine, Ethambutol, Isoniazid, Propranolol, Reserpine, Furosemide, Insulin, Ethinylestradiol/ Norgestrel (Levo), Retinol, Hydroxycobalamine, Ascorbic acid.

Diluents for solid dosage forms

Calcium sulphate, Dextrosemonohydrate, Dicalcium phosphate, Lactose, Mannitol, Microcrystalline cellulose, Starch, Sucrose.

Diluents for liquid dosage forms

Acacia syrup/mucilage, Corn oil, Cotton seed oil, Iso-alcoholic elixir, Lemon tincture, Orange flower water/spirit, Peppermint spirit/water, purified water, Sesame oil.

Diluents or base for ointments, etc.

Cotton or olive seed oil, hydro-wool-fat, white soft paraffin, Liquid paraffin, Polyethylene glycols, Silicon base, Stearic acid, Wool-fat, white or hydrophilic petrolatum.

Binders

Alcohol, Ethylcellulose, Gelatin (solution), Gum tragacanth, Liquid glucose, Methylcellulose, Mucilage of acacia gum or guar gum or starch, Polivinyl pyrolidene, Purified water, Sodium alginate, Sodium carboxy-methylcellulose.

Lubricants

Aerosil, Calcium stearate, Liquid paraffin, Magnesium stearate, Stearic acid, Talcum.

Sugar coatings

Sucrose together with purified talc, starch or other suitable innocuous substances.

Enteric coatings

Endragit derivatives.

Colouring agents

Any approved, certified food and drug dyes and mixtures of same, furthermore caramel sugar.

Flavouring agents

Any approved agents like Anethole, Anise oil, Camphor water, Cherry syrup, Cinnamon, Cocoa, Eucaluptus, Honey, Lavender oil, Lemon oil, Orange oil, Peppermint spirit/water, Pine needle oil, Rose oil, Saccharin, Sugar, Vanilla, etc.

Disintegrating agents

Alginic acid, Cellulose derivates (microcrystalline), Starch, etc.

Emulsifying agents

Agar, Benzalkonium-chloride, Glyceryl-monostearate, Gum acacia, Span-20, Tween-80.

Suspending agents

Gum acacia, Gum tragacanth, Polyacrylic acid, Sodium-alginate, Sodium carboxymethylcellulose, Sorbitol.

Sweeting agents

Dextrose, Glucose, Saccharin, Sodium saccharin, Sugar.

Anti oxidants

Butylated hydroxy anisole, Butylated hydroxy toluene, Propyl-gallate, Sodium sulphite, Sulphoxylates.

Preservatives

Alcohol (phenylethyl), Hydroxy benzoates, Methyl- or propyl ester, Methylparaben, Parahydroxy benzoic acid, Potassium sorbate, Sorbic acid.

Base for suppositories

Cocoa butter, Polyethylene glycol polymers or Glycolsurfactant combinations.

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 VII - General data for production and tentative equipment/machine list

Units/quantities per dosage form	per year	min. units per pack	max.	packaging units per year
a) Tablets (0.3g/T and 50% coated T)	300 mio	30 T		10 mio
b) Capsules (C)	30 mio	15 C		2 mio
c) Liquid orals	100 000 l	50 ml -	100 ml	2-1mio
d) Injectables (ampoules, average=3ml) (A)	4,5 mio	3A -	5 A	1.5-0.9 mio
e) Ointments	4,400 kg	5g -	15g	0.9-0.3 mio
Assumed total packs				16.4-14.2 Millions

- 240 working days per year
- Manufacturing shift = 2 x 7 hours/day
- General shift incl. packaging = 8 hours/day

Ref.No.	Description of equipment and machines	Parts in contact with product *)	Capacity	Requ.energy	Quantity
1	2	3	4	5	6
A.	TABLETS				
1	Mechanical sifter, movable, single desk, variable mesh sizes 12-120	CrNi	300-1000kg/h	0.4-1.5 kW	1
2	Paste preparation kettle, jacketed, with stirrer	CrNi	30-601	0.5 kW	1
3	High speed granulation mixer with chopper, mechanical discharge to wet granulating machine	CrNi/CrNiMo	300-4001	18-35 kW	1
3.1	Planetary mixer with spare bowl	CrNi	3001	8-9 kW	(1)

*) Stainless steel with: Cr = chromium
Mc = molybdenum
Ni = nickel
Ti = titanium

1	2	3	4	5	6
4	Wet granulating machine	CrNi/CrNiMo	200-500 kg/h	1-4 kW	1
5	Fluid bed drier, steam heated, product container + spare, flame proof ventilation motor	CrNi	50-100 kg/ batch	15 kW compr.air= 6 bar	1
6	Tray dier, steam heated	CrNi	18-36 trays	1-3 kW	1
6.1	Vacuum drier for products which should not contact oxygen	CrNi	0.5 cu.m	5 kW	(1)
7.	Dry granulating machine with knifeedged, rotating blades and sieve of different screen sizes, variable speed	CrNi	1500 kg/h	5-6 kW	1
8	Oscillating granulator	CrNi	500-1000 kg/h	0.6-1.1 kW	1
9	Drum blender	CrNi	30-60 l	0.5 kW	1
10	Rotary tabletting machine, 15-25 stations for 13-25 mm T Ø	Special treated punch and dye surface	up to 100000 T/h	1.1-5.5 kW	1
11	Rotary tabletting machine, 12-20 stations for 3-28 mm T Ø	- " -	up to 15000 T/h	1-3 kW	2
12	Syrup-lacquer preparation tanks, jacketed with stirrer	CrNi CrNi	1 = 60 l 1 - 160 l	0.5-2.5 kW 0.5-5.5 kW	1 1
13	Coating pan, standard with hot air blower	CrNi or copper	50 kg end weight	0.6-3 kW	2-3
14	Coating pan for large quantities, hot air blower	CrNi or copper	300 kg end weight	2.2-4.5 kW	1
15	Film coating pan with complete airconditioning system	CrNi	100-200 kg end weight	9.5-12.5 kW	1-2
16	Polishing pan with variable speed drive	CrNi	50 kg	0.6-0.8 kW	2
17	Coated tablet drying in drums	CrNi	2oo l/drum	1 kW	6 drums
18	Tablet inspection belt	rubber/plastic	60-100 kg/h	0.5-0.7	1

1	2
19	Blister pack machine with foil printing and perforating
19.1	Alternative: with integrated cartoning machine
20	Strip packing machine, 2-4 tracks, batch printing
21	Bottle filling and capsule capping machine
22	Pilfer proof swaging machine (sealing)
23	Tin filling apparatus
24	Tin sealing device
25	Cartoning machine
26	Check weigher
27	Conveyor belt working table for 10 workers, 5 m long
B. CAPSULES	
1	Milling apparatus - ball mill
1.1	Alternative: tumbler mixer
2	Sifter
3	Wetting agents preparation kettle
4	Mixer: use either A/3 or A/3.1 or planetary mixer
5	Wet granulation: use A/4
6	Fluid bed drier: use A/5

3	4	5	6
alu/PVC or ACLAR or similar	18,000 blister/h	15 kW	1
	18,000 blister/h	19 kW	(1)
alu or PVC or ACLAR or similar	60,000-100,000 T/h	2.1-2.6 kW	(1)
CrNi	up to 6000 bott./h	0.5-0.6 kW	(1)
CrNi	up to 6000 caps/h	0.2 kW	1
CrNi	up to 240,000 T/h	0.2 kW	1
	up to 1000 tins/h	0.2 kW	1
	1500-4500 P/h	1-4 kW	1
	2000-30,000 P/h	0.2-0.6 kW	3
		1 kW	1-2
porcelain	50-100 l	0.2 kW	1
drum or porcelain	50-100 l	0.4-2.2 kW	(1)
CrNi	300-1000 kg/h	0.4-1.5 kW	1
CrNi	60 l	0.4 kW	1
CrNi	150 l	6.2 kW	(1)

1	2
6.1	Vacuum drier: use A/6.1
7	Dry granulation: use A/7
8	Blending: use A/9 or B/1.1
9	Capsule filling and closing
10	Capsule polishing in coating pans with salt: use A/13
11	Blister packing machine with foil printing and perforating
11.1	Alternative: with integrated cartoning machine
12	Strip packing machine, 2-4 tracks, batch printing
13	Cartoning machine
14	Check weigher: same as A/26
15	Conveyor belt working table for 10 workers, 5 m long

C. LIQUID ORALS

1	Preparation vessel, jacketed, with cover; surface
2	inside ground, outside brushed; movable; stirrer
3	Storage tank, with cover; surface inside ground, out-
4	side brushed; movable; detached, movable stirrer: (suppliers same as above)
5	Centrifugal or rotary piston pump, movable
6	Plate filter; filter material of cellulose
7	Bottle washing machine with recycled and fresh deionized wat and clean, compressed air

3	4	5	6
CrNi	4,000-24,000 C/h	2.5 kW	1
alu/PVC or ACLAR or similar	18,000 blister/h	15 kW	1
alu/PVC or ACLAR or similar	60,000-75,000 C/h	2.1-2.6 kW	1
	1500-4500 P/h	1-4 kW	(1)
	2000-30000 P/h	0.2-0.6 kW	1
		1 kW	1
CrNi or CrNiMo(Ti)	1 = 60 l	0.5-3.5 kW	1
	1 = 250-300 l	0.5-3.5 kW	1
CrNi or CrNiMo(Ti)	1 = 60 l	(0.5-3.5 kW)	2
	1 = 250-300 l	(0.5-3.5 kW)	2
CrNi or CrNiMo	0.25-5 cu.m/h	0.25-5 kW	1
MS coated or CriNi	up to 500 l/h	-	1
er CrNi or CrNiMo	up to 1250 bott./h	9 kW comp.air=2 bar	1

1	2
8	Bottle drying machine
9	Piston or vaccum filling machine for different bottle sizes manual or mechanical filling
10	Screw cap capping machine (if not already included in pos.C/9)
11	Pilfer proof swaging machine
12	Conveyer belt working table for 10 workers, 5 m long
13	Demineralized water, pH = 7.0, conductivity = 14 micro-ohms.cm, CO_2 free, with circulation pipe system
14	Portable stirrer
15	Kettle, movable, for general purpose
16	Percolator, if required

D. INJECTABLES

1	Distilled water preparation, dH= 7^{o}, 1 micro-ohms.cm
2	Storage tank for distilled water with circulation in pipe system
3	Centrifugal or rotary piston pump, movable
4	Preparation vessel for solutions; jacketed, closed or with fixed cover; surface inside - outside ground; movable; stirrer

3	4	5	6
CrNi	170-450 $\frac{\text{kg glass}}{\text{h}}$	35-75 kW	1
CrNi	up to 3000 bott./h	0.2-1 kW	1
CrNi	up to 3600 bott./h	0.4-0.6 kW	1
	up to 6000 bott./h	0.5-0.6 kW	1
		1 kW	1
CrNi or CrNiMo	up to 1 cu.m/h		1
CrNi	up to 300 l	0.8-5.5 kW	1
CrNi	60 l		1-2
CrNiMo	100-200 l/h	1-10 kW steam: 2-8 bar 5-8 kg/h	1
CrNiMo	250-300 l		2
CrNiMo	0.25-5 cu.m/h	0.25-5 kW	2
CrNiMo(Ti)	60 l		2
		0.8-1.6 kW	

1	2
5	Storage tank; closed or with fixed cover; surface inside and outside ground; movable; stirrer
6	Deep- or membrane-filter
7	Double door dry heat sterilizer
8	Autoclave, steam heated
7.1/8.1	Alternative: ampoule washing, drying and sterilizing machine unit
7.2/8.2	Alternative: closed stem ampoules
9	Ampoule filling and closing machine (with code ring marking)
7.3/8.3/ 9.1	Alternative: ampoule washing, drying, sterilizing, filling unit
10	Autoclave, steam heated, incl. blue bath control
11	Ampoule labelling machine (alternative=printed ampoule)
12	Conveyor belt working table for 10 workers, 5 m long

E. OINTMENTS

1	Phase kettle, jacketed, movable *)
2	Preparation kettle with stirrer and emulsifier

*) Used also for sterilizing the pharmaceutical substances and bases, alternatively carried out in drying ovens.

3	4	5	6
CrNiMo(Ti)	60 l	0.8-1.6 kW	3
CrNiMo	Depending on type and supplier		1-2
CrNi	500 l (18cu.ft.)	1.5 kW	1
CrNi	400-500 l (14-18cu.ft.)	2.5-37 kW steam: 2.5 bar 50-180 kg/h	1
CrNi	1500-2500 A/h	18-25 kW	(1)
CrNiMo	2500 A/h	0.2-2 kW	1
CrNi	4000 A/h	25-35 kW	(1)
CrNiMo			
CrNi	400-1300 l	2.5-37 kW steam: 2.5 bar 50-180 kg/h	1
CrNi	1000-10000A/h	0.1-4 kW	1
		1 kW	1
CrNi	30-60 l		1
CrNi	100 l	10-16 kW	1

Sterilizing may be

1	2
3	Homogenizing machines (type depending on product and application)
3.1	Alternative: 3 roll mill
4	Tube cleaning and sterilizing unit with ethylene oxide
5	Tube filling machine for 2, 3 or 4 tale folds (with or without saddle fold, tube cleaning, hopper heating, agitator, tale crimping, code embossing, code reader)
6	Tube labelling (which should be avoided whenever possible!)
7	Conveyor belt working table for 10 workers, 5 m long.

3	4	5	6
CrNi	50-500 kg/h	1.5-11 kW	1
		0.5kW	(1)
CrNi	55-115 l	1-9.4 kW	1
CrNi	2000-4000 tub./h	1-2 kW	1
	500-600 tub./ h	0.6 kW	(1)
		1 kW	1

ANNEX XIII

UTILITIES, SERVICES AND MAINTENANCE

1. Electricity (Voltage, frequency and electrical equipment as per specifications of the particular country)

   - Power sub-station: (20 kV to 380 V: 2 x 750 kVA transformers)
   - Distribution system for 380 V and 220 V supply
   - Stand-by generator: 60-400 kVA (depending on reliability of grid)
   - Voltage stabilizer system (where required)
   - Explosion proof fittings (where required)
   - Safety devices.

2. Water

   - Main supply: 50-100 cu.m/day (depending on water reservoir)
   - Storage tanks, underground and overhead: 300-400 cu.m, devided into 2 parts
   - Pressurised water circulation system: 3-4 bar
   - Water deionisation plant: up to 1 cu.m/h, with 4-5 cu.m storage tank
   - Water distillation plant (Pyrogen free for parenteral preparations): 100-200 l/h. Pipes in stainless steel.

3. Steam

   - Boiler - steam generator and insulated supply lines: 5-6 t/h at 6 bar
   - At least 85% of steam condensate should be recovered.

4. Gas

   - Public supply from national main or generator or steel cylinders.
   - Oxygen and Nitrogen

5. Central compressed air supply, oil free, dry: 30-70 N cu.m/h at 7-8 bar. Pipes in copper or stainless steel.

6. Central vaccum supply (normally not used).

7. Air conditioning system (tailor made to requirement of factory)

   - Central air conditioning

     Medium/large scale: package unit preferably air cooled system to save water usage

Alternative:

- Split system - several units connected to a central compressor/ condensor
- Window type units at isolated small areas
- Refrigeration unit for cold storage
- Dehumidified air unit - (at required location e.g. capsule filling)
- Sterile air handling/conditioning system for sterile area operations
- Centralised/isolated dust collection/removal unit
- Laminar flow - clean (sterile) air benches.

8. Maintenance and repair workshop

- Fully equipped for general maintenance, minor repair/parts replacement and reconditioning of equipment and laboratory instruments.

9. Waste disposal system

- Disposal of plant waste, garbage by incinerator, etc.
- Effluent treatment and disposal system with degreasing, separate sewer feed systems, biological process, sludge treatment.

10. Transport facilities

- Hand trolleys
- Fork lift truck
- Shipping conveyor

11. Quality control facilities

- In process control
- Analytical control
- Biological control
- Chemical control
- Physical control

ANNEX IX

Illustrative UNIDO List of 26 Essential Drugs

A. ANALGESICS

1. Acetylsalicylic acid
2. Paracetamol

B. ANTI-INFECTIVE DRUGS

Anthelmintic drugs

3. Mebendazole
4. Piperazine

Antibacterial drugs

5. Ampicillin
6. Benzylpenicillin
7. Erythromycin
8. Sulfadimidine
9. Tetracycline

Antifilarial drugs

10. Diethylcarbamazine

Antileprosy drugs

11. Dapsone

Antimalarial drugs

12. Chloroquine
13. Primaquine

Antituberculosis drugs

14. Ethambutol
15. Isoniazid
16. Streptomycin

C. BLOOD PRODUCTS

17. Plasma fractions

D. CARDIOVASCULAR DRUGS

Antihypertensive drugs

18. Hydralazine
19. Propranolol
20. Reserpine

E. DIURETICS

21. Furosemide

F. DRUGS AFFECTING THE BLOOD

22. Hydroxocobalamine

G. HORMONES

Antidiabetic agents

23. Insulin

Oral contraceptives

24. Ethinylestradiol/Levonorgestrel

H. VITAMINS

25. Ascorbic acid
26. Retinol

Note: This list was prepared by UNIDO in consultation with WHO. The classification and nomenclature was updated according to WHO's "The Use of Essential Drugs", Technical Report Series No. 685.

ANNEX X

To augment our efforts to improve the usefulness of the document, we would appreciate your cooperation in completing the questionnaire given below and returning it to UNIDO, Head of Negotiations Branch, P.O.Box 300, A-1400 Vienna, Austria.

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