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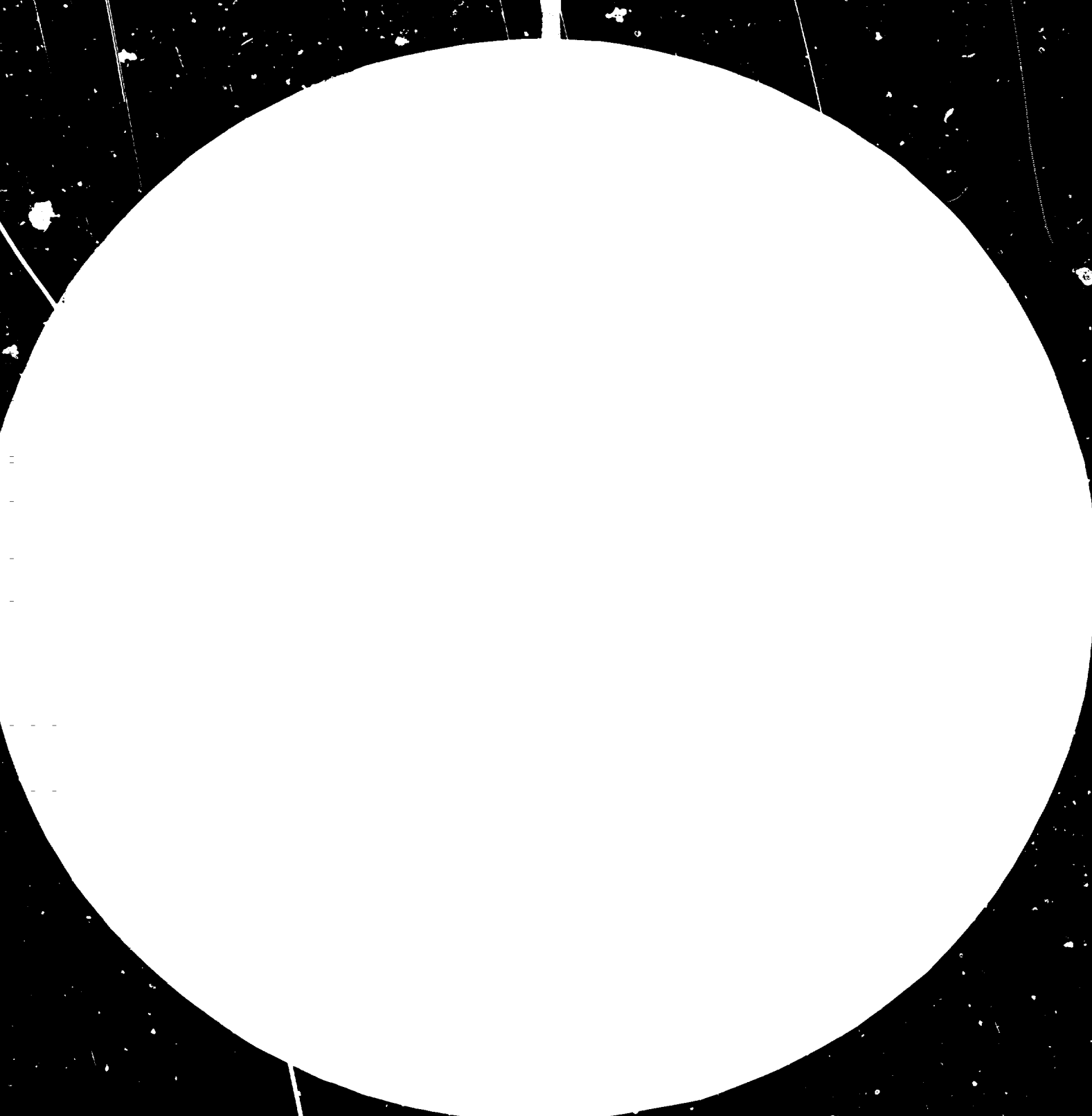

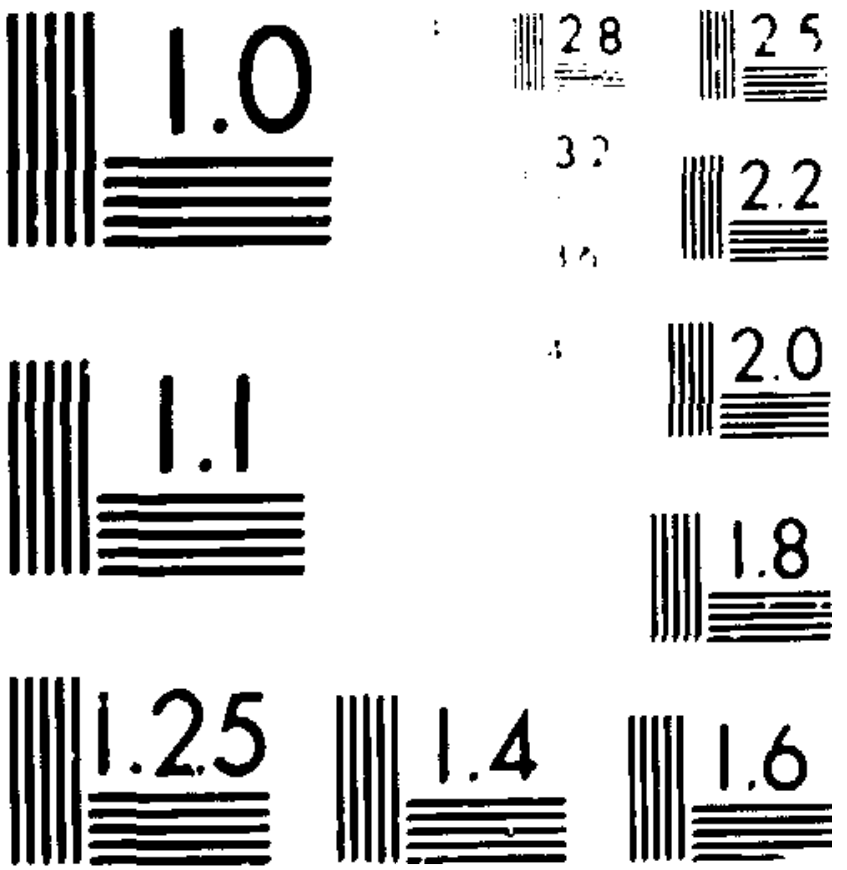
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Meeting of the Ad Hoc Panel of Experts on
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Pharmaceutical Industry

Vienna, Austria, 15 - 17 December 1982

ARRANGEMENTS FOR THE TRANSFER OF TECHNOLOGY FOR THE MANUFACTURE OF BULK DRUGS AND INTERMEDIATES *

prepared by

the secretariat of UNIDO

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CONTENTS

Appendix

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 a document 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) recommended to concentrate, in the first stage of work, on licensing agreements for the manufacture of bulk drugs and intermediates.

This document has been prepared in line with the recommendations referred to. It is intended to provide guidance for the negotiation and drafting of agreements for the transfer of technology for the manufacture of bulk drugs or intermediates, for new entrepreneurs or those who have already a plant in operation and would like to add new products or adopt a new technology.

Separate documents will consider the cases where the contract also involves the creation of new manufacturing facilities.

It should be noted that, for this latter purpose, generally the licensor provides process know-how and basic engineering data whereas detailed engineering, construction and erection is done by the licensee himself or through a contracting engineering firm. Some of the developing countries, in the initial stages have also adopted a turn-key approach for setting up the plants. In this case either the licensor of process know-how or an engineering contracting firm assumes full responsibilities for detailed engineering, construction, erection and commissioning of the plant to the rated guaranteed capacities.

In either case co-ordination assumes utmost importance in fulfilling the objective as per agreed schedule, which in a business enterprise is most important. Any delay will add to the capital cost of the unit resulting in rise in cost due to depreciation and interests. Delayed commissioning of the project also adds to the burden of additional foreign exchange to the country, which has envisaged saving of the same due to the production of such bulk drugs and intermediates.

Purposes, scope and content of this document

This document is primarily addressed to parties negotiating agreements for the manufacture of bulk drugs (and intermediates), and in particular to enterprises in developing countries which are able and willing to increase the range of bulk drugs (or intermediates) locally produced.

In the preparation of this document a number of general principles have been taken into account, as described in previous UNIDO documents, 1/ and recommended at the Morocco meeting:

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

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

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

(d) The agreement should, in particular:

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

(ii) Allow the use, as far as possible, of locally available materials and services;

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

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

1/ See in particular "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.

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

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

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

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

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

(iii) Concrete examples, wherever possible, relating to fermentation, synthesis and extraction processes;

(iv) Recommendations as to how to deal with the particular issue;

(v) Possible clauses and variations thereof.

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

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

(ii) The comparability of proposed solutions with existing regulations and positions on the matter, as described - for a number of issues - in an earlier UNIDO document; 2/

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

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

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

Since the recommendations made in this document are addressed to parties located in any country, the formulations proposed here are not referred to any particular national legislation. This does not mean, however, to support the idea of a contract "without law", i.e. which is self-sufficient for solving all aspects of the relationship between the parties. As indicated expressly with respect to some items dealt with (see e.g., section 9, a and 12). The validity and extent of the parties' rights and obligations will be finally determined by that law.

Obviously, national approaches and solutions to a number of aspects considered vary considerably between the common law and the continental law systems, or even from country to country. To the extent possible, the document attempts to suggest formulations which conform to the general principles referred to above, and at the same time, are compatible with the main current regulatory trends at the international and national level, particularly in developing countries.

It is worth while to note, from a technical point of view, that the licensing of process know-how in the case of the drug and pharmaceutical industry assumes a special feature as compared to other process industries. In the case of drugs, process licensing is normally being done by manufacturing units, which in order to transfer the technology to the licensee need to scale it up or down based upon the latter's requirements. Instead, in the case of fertilizers, for example, the units have been standardized (having rated capacities of 1,300 t or 1,700 t production per day) and the process know-how represents more or less engineering features developed and transferred by firms which may not necessarily be manufacturing units.

Moreover, in the case of basic drugs, the process for the production of the same product may differ. For example, 6-Amino Penicillinic Acid (6APA) can be produced either by enzymatic process by splitting Potassium Benzyl Penicillin with the help of enzyme into 6APA and Phenyl Acetic Acid or it can be produced by synthetic route by interaction of Potassium Benzyl Penicillin with Dimethyldichlorosilan, Dimethylaniline and Phosphorous Pentachloride.

In case of synthetic drugs large number of steps are involved. In between products are sometimes called intermediates. These may be either specific to the scheme of production of the particular drug or may be common for the production of other drugs and industrial chemicals. Therefore the question arises whether one should start with the production from the basic

stage or using penultimate or sometimes intermediate. For example, in the case of ampicilline trihydrate, 6APA is an intermediate and Penicillin G is a basic raw material. Under the present circumstances, the minimum economic size of Penicillin G Potassium may cost more than US$20 million whereas a similar unit for ampicillin trihydrate from Penicillin, for 30-40 t per annum, can be installed within US$ 5-6 million. Therefore, investment becomes the guiding factor for deciding about going basic or not. Moreover, in the initial stage, when a sufficient number of trained technical personnel are not available one has to start with penultimate or intermediate stages.

Besides the above, it may be observed that for the production of 1 kg of bulk drug, one may require 10-50 kg of various chemicals. If most of these are not manufactured in the country, these have to be imported. Under these circumstances also, it is advisable to start with penultimate.

Obsolescence is quite frequent and fast in drug and pharmaceutical industry and explains the high expenditure on research and development as compared to other industries. Research and development also results in improvements in the existing product mix. In the case of antibiotics, strain developments have been quite revolutionary. Just a few years back, Penicillin strain had activity less than thousand whereas today it is almost 50,000 µ/ml; thereby the yields have gone up by 25-30 times. This situation requires changing of capacity of equipment, vessels and machinery at different stages of filtration, extraction, purification etc. to match the enhanced capacity due to better yielding strain mentioned above. It is, therefore, desirable to have access to the benefits of improvements and to such information regarding obsolescence. In one developing country, Chloramphenicol and Citric Acid plants failed to produce the desired results. In the case of Chloramphenicol, the technology was not up to the mark and in the case of Citric Acid, the selection of source of raw materials and its quality was wrong. Similarly, a very good technology failed to give results due to lack of trained staff, management and discipline. This shows the importance of training of personnel of licensees.

1. Recitals

The inclusion of recitals or a preamble in transfer of technology agreements has become a quite common practice, even in cases where the applicable law does not confer such statements a particular juridical effect.

Recitals usually contain references to the business background of the parties, their desire in connection with the agreement and the Licensor's statement as to his titles on the technology to be transferred. In case of divergency between the recitals and the substantive provisions of the contract, the latter prevail.

Recitals may be of particular importance when the technology is being offered by a consortium or is sublicensed with the authorization of its holder.

Specimen clauses

1. Recitals

LICENCE AGREEMENT FOR THE MANUFACTURE OF .....

This contract, made and entered into this day of ..... by and between: ..... a corporation organized and existing under the laws of ...., having its head office at ..... (hereinafter referred to as "the Licensor"), and ...., a corporation organized and existing under the laws of ....., having its head office at ..... (hereinafter referred to as "the Licensee"),

WITNESSETH:

WHEREAS the Licensor has manufactured ..... (hereinafter referred to as "the Drug") for a considerable number of years at his plant of .....,

WHEREAS the Licensee currently operates a plant for the production of bulk drugs and intermediates;

(Alternative a: WHEREAS the Licensor owns patents and has developed know-how for the production of the Drug);

(Alternative b: WHEREAS the Licensor owns a strain producing the drug, patents and know-how relating to its fermentation and recovery);

(Alternative c: WHEREAS ..... has a special agreement with ..... under which the latter has exclusively granted to .... the right to dispose the strain and know-how of .... for the production of ..... by fermentation, recovery and purification).

WHEREAS the Licensee desires to obtain, and the Licensor is willing to grant, a licence for the production of the drug in the plant of the Licensee,

NOW, THEREFORE, the Parties hereto agree as follows:

2. Definitions

For purposes of clarity and avoidance of repetition, the agreement may contain a provision defining some of the main terms and expressions employed in various clauses, such as "Licensor", "Licensee", "Licensee's plant", "know-how", etc.

Specimen clauses

2. Definitions

In this contract, the following expressions will have the meaning herein assigned to them:

1. "The Licensor" will mean the party named as such in this Contract or his successor or permitted assignees.

2. "The Licensee" will mean the party named as such in this Contract or his successor or permitted assignees.

3. "The Contract" will mean this agreement (together with the Annexes) entered into between the Licensee and the Licensor, including any subsequent amendment made thereto in accordance with the provisions of this Contract.

4. "Licensee's plant" will mean the plant of the Licensee established at ....., which will be completed and adapted for the manufacture of the Drug, from the stage of ..... and having an initial capacity of ..... per annum.

5. "Licensor's plant" will mean the plant of the Licensee established at ....., basing upon which the Technical Information has been set up.

6. "The Drug" will mean ....., of the quality set out in Annex ..... thereto.

7. "Technical information" will mean all technical data, information, drawings and designs and instructions relevant to the Process.

8. "The Patents" will mean the patents licensed under this Contract.

9. "The Process" will mean the latest commercially proven process developed or acquired by the Licensor at the Effective Date of the Contract, for the manufacture of the Drug by means of .....

10. "Basic design and engineering" will mean the information as defined in .....

11. "Effective Date" will mean the date on which this Contract will come into force and effect.

3. Obligations of the Licensor

3.a. Transfer of know-how

The transfer of secret know-how normally is a key component in agreements for the manufacture of bulk drugs. An appropriate treatment of the different aspects involved is hence of primary importance in the negotiation of such agreements. This section considers the following items: terminology; definition; content; legal qualification; time and form of delivery of know-how.

Sections 3.g., 5.c. and 9.c.2. separately deal with important issues related to know-how which should be borne in mind when considering the aspects discussed here.

3.a.1. Terminology

In general, "know-how" is understood as a set of techniques and information of unpatented nature applicable in production or commercial activities.

However, there is no universally accepted concept of know-how. The ambiguity of this expression is as great in commercial practice as it is in academic circles. Whenever this expression is used, therefore, the contract should contain an appropriate determination of what exactly the parties intend to mean.

In order to avoid confusion, the expression referred to may be replaced by "technical information", [3/] "unpatented knowledge", or similar terms.

3.a.2. Definition

As valuable know-how is of secret character, and it is not registered (like patents) it is difficult to define in the agreement which is the know-how the licensor is bound to transfer. The determination of know-how should cover as a minimum the following aspects:

(a) The technical description of know-how, including of the means and results to be obtained through its application, e.g., "manufacture of tetracycline by submerged fermentation process, precipitation of crude base, dissolution in methanolic calcium chloride treated with m. h acid and concentration under vacuum, etc.". (See appendix I)

3/ This is the expression used in the attached "specimen clauses".

(b) Since different or the same enterprise may possess more than one "know-how" for the manufacture of a drug, a further determination should establish whether the know-how to be transferred:

(i) Is the latest available to the Licensor, or whether it is an older version. Normally, the interest of the Licensee will be - at least in the specific field dealt with here - to receive the most updated knowledge available;

(ii) Has been commercially proven. As a rule, the Licensee will wish to avoid the transfer of experimental knowledge, which will put on him the risk of proving the appropriateness and efficiency of the know-how furnished.

3.a.3. Legal qualification

It is frequent to find in transfer of technology agreements statements on the Licensor's "property" over know-how or indicating that the knowledge to be transferred is "owned" by him. The proprietary nature of know-how is often argued in order to impose restrictions on its use after the contract's expiration or to restrict sublicensing.

The conception on the proprietary nature of know-how seems to be generally admitted at least in some common law countries. This notion is premised on the identification of "know-how" and trade-secrets, and on a concept of "property" that is wider and more flexible than the notion thereof in continental law countries. 4/ In these countries, the qualification of know-how as an object of property is generally questioned (except eventually for patentable but not patented secret inventions), since absolute property rights can only be instituted there by law, and that is not the case with know-how. 5/ In Latin American countries, the conception of the proprietary nature of know-how has been mostly rejected as well. 6/ This also seems to be the position of international organizations concerned with the matter. 7/

4/ See F. Dessemontet, Le savoir-faire industriel. Définition et protection du know-how en droit américain. Impriméries Réunies S.A. Lausanne, 1974, p.274.

5/ See F. Magnin, Know-how et propriété industrielle, Librairies Techniques, 1974, p. 246.

6/ See M. Laquis, "Révision del Convenio de París en el marco latinamericano. La propiedad industrial y el abuso del derecho. Problemas de la transferencia de tecnología (know-how) a los países en desarrollo. La declaración de México", Revista del Derecho Comercial y de las Obligaciones, Vol. 9, No. 52, 1976, p. 447.

7/ A WIPO study indicates that "so far as the unpatented know-how element is concerned, no proprietary rights exist in respect of which a "licence" in its true sense could be granted", WIPO, Legal aspects of licence agreements in the field of patents, trademarks and know-how, Geneva, PJ/92, 1972, para. 7; see also P. Mathély, Summary Report, AIPPI/1972/I, p. 34.

3.a.4. Content

Know-how should normally include information on the manufacturing process and equipmen'. The exact scope of know-how to be communicated should be precisely stated, including the specification of the pieces of the information which are to be deemed confidential (see section 5 (c) below).

It would be desirable that the description of know-how does not only contain the operative information, but also the scientific and technical explanations as to why certain solutions have been adopted (this information is often called the "know-why"). For instance, the documentation might include the methodology employed for the development of the relevant know-how. This may permit a more serious and fruitful learning of the technology, ensure its efficient application and increase the likelihood of further adaptations and improvements thereon.

The know-how will usually include, in agreements for the manufacture of bulk drugs the following items:

- Strain, in case of fermentation industry (see appendix II);
- Raw materials consumption per kg of the product;
- Process flow diagram and material balance;
- List of facilities (analytical and laboratory services);
- Operation manual including suggestions for the recording of the main operating data;
- Characteristics of the finished product (see appendix III);
- Characteristics of raw materials and intermediates;
- Analytical procedure, methods of analysis and specification (see appendix IV);
- Recoveries and recycling of solvents, if any.

Many countries have their own pharmacopoeia and as per the law of the land the product should conform to the official pharmacopoeia. Similarly, there are specifications or norms fixed by the State or industries' standards organizations. These details should be given to the Licensor prior to finalization of the agreement and should not become the bone of contention in case of failure of fulfilment of guarantees.

In the production of synthetic drugs as well as antibiotics large quantities of solvents are utilized as (a) medium of reaction; (b) for purification including final crystalization; (c) recovery of product from mother liquor.

Licensor should provide complete details and specifications of the nature of the solvent and chemicals - the process for recovery, quantity to be recycled, limitations for any recycling of the same solvent, and alternative use for such solvents.

For a typical example regarding acetone recovery see appendix V.

3.a.5. Time of delivery

The time of delivery of know-how may vary from case to case. In certain situations, the Licensee may have received, during the negotiation phase, some elements of the know-how subject to an obligation of confidentiality and of non-use as long as a final agreement has not been reached. The agreement may provide that the information supplied prior to its signature be deemed as furnished thereunder.

Know-how is normally to be delivered within a certain period from the date of signature, most commonly against payment by the licensee of part of the stipulated price (see Section 5.b.).

3.a.6. Form of delivery

(i) Means of transmission

The transmission of know-how may take place through written documents or through in situ Licensor's personnel assistance.

Written documents may include drawings, specifications, instructions, etc.

(ii) Level of description

It is important to ensure that the know-how is communicated to the Licensee in a manner that it is understandable to its personnel, and that permits its correct interpretation and application. A reasonable standard would be to require, for instance, that the description be adequate for the comprehension by a normally qualified personnel in the field. This would be without prejudice, when necessary, to the training of local personnel to the extent required for the absorption of the technology.

(iii) Language

The language in which the documentation and other information is delivered may also affect the speed and quality of the absorption. The contract should specify the language to be used, preferably that of the Licensees's country or a foreign language well-known by its personnel.

Specimen clauses

3.a. Supply of technical information

1. The Licensor will, within ..... days from the Effective Date of the Contract, supply the Licensee with the latest commercially proven Technical Information, as required for the manufacture of the Drug by the Licensee by means of .....

2. The aforesaid Technical Information shall be furnished in the form of complete sets of drawings, blueprints, specifications and other documents relevant to the Process including: .....
.....
.....

3. The documentation referred to in 2. hereinbefore shall be drawn up in ..... language according to the ..... system and shall .....

(Alternative a: Be presented in a manner comprehensible for normally qualified personnel) .....

(Alternative b: Contain the pertinent scientific and technical background, as necessary for enabling a normally qualified personnel in the field to master the technology transferred) .....

4. The following documentation will be deemed to be confidential, in accordance with article ..... of this Contract: "Confidentiality".

5. The aforesaid stipulations will also apply to the Technical Information received by the Licensee from the Licensor before the signing of the Contract.

3.b. Licence of patents

When one or more patents are involved, the contract must contain a number of specific clauses related thereto. Though obvious for experienced people in the licensing field, it is not superfluous to recall that, due to the principle of territoriality that governs industrial property rights, in order to be relevant to the licence agreement the patent must be registered and valid in the country where the manufacture will take place or, eventually, in those countries to which the Licensee may be willing to export the drug covered by the agreement.

It should also be noted that pharmaceutical patents may refer to the process only or cover also the products themselves. In the first case, the patent confers the right to prevent the use, by a third party, of the protected process; in the second one, any act related to the protected product (independently of the process employed for its obtention) may be legally prevented, in principle, by the patent owner. In general, product patents authorizes to exclude imports from non-authorized suppliers.

In cases where the Licensor holds patent rights in several countries, and according to the respective national laws he is entitled to prevent imports of products covered thereunder, the parties should clarify the extent to which, if any, those rights may be used against Licensee's exports to such countries. From the Licensee's point of view, the desideratum would be to include in the contract a clause stipulating that the Licensor will not use such rights as to prevent Licensee's exports.

Between the complete freedom or the restriction, in principle, to export, some intermediary solutions may be found, for instance, by limiting exports to countries where the Licensor has granted an exclusive licence which is actually employed for production of the drug concerned (see Section 4.b. below).

The prospective Licensee should hence carefully examine the patent situation of the drug he intends to manufacture. In the case of essential drugs listed by UNIDO patents may have already expired - though know-how may still be secret - and then the contract will not include patent licences.

The issues considered in connection with patent licences are the warranties offered by the supplier; rules applicable in case of infringement of patent, rights, and costs of maintaining the patents in force.

3.b.1. Warranties

The contract should normally indicate the Licensor's entitlement to grant the respective licence and contain the Licensor's representation that, on the date of the signing of the agreement, there is no limitation, including any pending official procedure or litigation, which adversely concerns the existence or validity of licensed rights.

Warranties may be also required, in certain circumstances, to make clear that the Licensor has not granted a prior licence on the relevant patents, or that he has not commitments to do so.

3.b.2. Infringement

Under this heading two different situations should be considered: (i) infringement by the Licensee of third parties' rights, when using the licensed patents; (ii) infringement by a third party of licensed patents.

(i) Infringement of third parties' rights

When using licensed patents, the Licensee may be subject to third parties' claims based on infringement of these parties' rights. The contract should contemplate the procedure to be followed, the responsibilities for the Licensee's defence and for any damages or sums that may become payable, as well as the readjustments necessary to cope with the obligations or restrictions emerging from such claims if admitted by the competent authority.

The drafting of clauses on this topic admit a number of variations, according to the distribution of charges and liabilities among the parties. One of the possible solutions may be conceived along the following lines: The defence of the licensed patents should be borne by the Licensor, without prejudice to the participation or co-operation of the Licensee. The former should also bear any indemnity or other sums payable by reason of the infringement, and any costs required for procuring the Licensee, if necessary, a third parties' licence to continue in the use of the technology or to introduce the technical changes required for avoiding the infringement. These changes may not imply, however, higher costs for the Licensee nor impair the application of the technology, and particularly they should not relieve the Licensor from compliance with any stipulated guarantees.

(ii) Infringement by a third party

Licensed patents may be infringed by a third party, to the detriment of the use of the protected invention by the Licensee.

As a rule, the Licensee should be bound to inform the Licensor, as soon as any infringement comes to his notice, and the Licensor to take proceedings against the infringer, at its own expense, eventually with the assistance of the Licensee.

Other alternatives might be to establish that action against infringers should be jointly undertaken by both parties, or to authorize the Licensee to proceed himself, directly, if permitted by the applicable law, or on the basis of powers and authorizations provided by the Licensor.

The contract may also contemplate the consequences of an omission by the Licensor to prevent infringers' action which is detrimental to the Licensee's position in the market. Thus, the latter may be entitled to reduce payments provided for thereunder.

As a result of action undertaken, the infringer may be condemned to the payment of judicial costs, losses and damages. The share of Licensor and Licensee in any sum for these concepts should be established in accordance with their respective role in proceedings and the damages or losses effectively suffered.

It is evident that the treatment of the situation at stake may receive a number of different solutions, more or less balanced for both parties. Licensor's obligations and responsibilities should be stricter in the case of exclusive licences, but should also be present when non-exclusive licences are concerned.

Under any possible solution, the co-operation between the parties with regard to prompt information, and assistance during proceedings, may be a fundamental factor for ensuring a successful action against non-authorized use of licensed patents.

3.b.3. Maintenance in force

The main aspect involved here concerns who is bound to bear the renewal fees of patents, where applicable. In principle, they should be borne by the Licensor. If the Licensor fails to renew the licensed patents, the protected invention enters the public domain and there is no further justification for Licensee's payments related to their use.

Specimen clauses

3.b. Licence of patents

1. The Licensor hereby grants the Licensee, with effect from the Effective Date of the Contract, a licence of use under the following Patents as registered in (country of the Licensee): .....
.....

Warranties

2. The Licensor warrants that:

(a) It owns the listed Patents and that it has the right to grant licences for the production and sale of the Drug in (country);

(b) To the actual extent known to him, there is no limitation, including any pending official procedure or litigation, which adversely concerns the existence or validity of the aforesaid Patents;

(c) It is not aware of third parties' patent rights which would be infringed by the use of the aforesaid patents or the technical information to be transferred as specified in the Contract.

Patent immunity

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

(Alternative a: to said country/countries.)

(Alternative b: to such countries where the Licensor or its exclusive Licensee produces and sells the Drug.)

Infringement of third parties' patents

4. The Licensee will promptly advise the Licensor in writing of any notice, 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.

5. The Licensor shall, upon receipt of such notice undertake at its own expense the defence of any such suit or action. The Licensor shall have sole charge and direction of the defence 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 defence of any such suit or action and furnish evidence in its control.

6. The Licensor shall indemnify and hold harmless the Licensee from any sums payable by reason of infringement, and shall reimburse in full to the Licensee any royalties, licence fee or damages paid to a third party as a result of a ruling of a competent court.

7. In the event of any notice or claim of infringement as referred to above, ..., the Licensor shall have the right to eliminate the alleged or adjudicated infringement by, at the Licensor's own expense (a) procuring for the Licensee an appropriate licence or (b) making such changes in the technology as necessary to avoid such infringement; provided, however, that such changes do not prevent the Licensor from meeting the Performance guarantees as stipulated in the Contract.

8. If the infringement has been adjudicated by a final ruling of a competent court which prevents or substantially limits the Licensee's use of the technology subject matter of the infringement, he will have the right to terminate this Contract.

Infringement of licensed patents by third parties

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

10. (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, licence 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 action 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).

11. In the event that as a result of an infringement, the Licensee's income for the sale of the Drug is actually or likely to be substantially reduced, the price of the Contract shall be diminished to an extent commensurate with such reduction.

Maintenance in force

12. The Licensor shall pay any renewal fees necessary for the maintenance of the patents listed above.

3.c. Technical assistance

The Licensee will usually need the assistance of the Licensor's personnel to learn how to apply the process to be transferred and maintain the plant in proper operation. The Contract (or an annex thereto) should specify:

(i) The category and number of personnel to be deputed;

(ii) The time to be spent;

(iii) The detailed programme of experts' work or the way for its determination.

Licensor's experts are required for:

(a) Certification of mechanical completion;

(b) Testing of the plant and trial runs;

(c) Operations.

Licensor should depute an experienced mechanical engineer having long years of experience in maintenance, commissioning of process plants. He may also be accompanied by the process technologist who should supervise water trial and satisfy and acquaint with the new plant.

In case of synthetic drugs depending upon the number of steps, one or two Licensor's process technologists should normally be deputed during commissioning, trial and guarantee period. Their stay varies from 6-12 months depending upon the product as well as competence and confidence of the Licensee. In case of implementation of know-how of a product in an already existing unit, where Licensee personnel are already well versed in the unit operations and processes, Licensor's experts are not required after fulfilment of the guarantee which is performed within 3-6 months of the initial commissioning of the plant including trial runs. Only in a case where a large number of products are to be commissioned, the Licensor should depute laboratory experts; otherwise, analytical work is carried out by Licensee's qualified chemists trained in the Licensor's plant. In the case of antibiotics, two process technologists, one for fermentation and another for extraction and purification are generally deputed. However, deputation of microbiologist for laboratory to supervise the production of culture in the laboratory and implementation of analytical procedure is a must. The period of deputation is longer and varies from 6 to 12 months. The process of extraction of various vegetative product is simpler and the expert's stay is limited to 2-3 months.

Specimen clauses

3.c. Technical assistance

1. The Licensor will supply the Licensee with technical assistance consisting of:

(i) Advice for the addition and adaptation of its plant for the production of the Drug;

(ii) (Alternative a: communication of Licensor's experience and methods for the efficient operation and maintenance of the Licensee's plant);

(Alternative b: the Licensor will advise the Licensee as to the efficient application of the technology transferred in connection with the operation of ..... reactors/fermentators, each with ..... m^3 capacity);

(iii) Certification of the Licensee's plant and direction of the performance test runs at the Licensee's plant.

2. The technical assistance will be furnished on the following terms:

(i) The Licensor will make available the following personnel:

Qualifications	Period of assistance
.....	.....
.....	.....
.....	.....

(ii) The Licensee will bear the costs of economy class air-travel, as well as of hotel accommodation and meal expenses at the rate of ..... (local currency) for each calender day of presence in (country of the Licensee). The payment of these rates will be made in advance beginning from the date of arrival to the date of departure;

(iii) The provision of technical assistance under this clause will be completed within ..... months from the Effective Date of the Contract.

3.d. Training

In many cases, the provision of an adequate training of the Licensee's personnel is a necessary condition for the effective transfer of technology.

Licensor may avoid training the personnel of the Licensee sometimes on the pretext that his plant is of different capacity as compared to the plant to be installed by the Licensee or the process pertains to only pilot plant studies. In such cases, Licensor takes the responsibility to train the Licensee's personnel at the site. Sometimes Licensor does not depute his capable experts as they are engaged in further developments of their own processes, and hence it takes abnormal time to achieve an adequate training.

3.d.1. Place of training

As a rule, there are substantial advantages if training takes place both at the Licensor's and Licensee's premises. In the first case, the contract should ensure that training comprises operational experience at a factory using the same technology to be transferred.

The imparting of training at the Licensor's plant immediately after the signing of the agreement has the following advantages:

(a) There are many experiences which cannot be imparted through documentations, but can be exchanged by personal discussion;

(b) The trained persons may be the best co-ordinators between the Licensor and the (Engineering) Contractors;

(c) By their association, last-minute modifications could be avoided.

Travel and living expenses of the Licensee's personnel are to be borne by him.

3.d.2. Training programme

The Contract (or an Annex thereto) should establish the programme of training, including the category and number of personnel to be involved, the time to be spent, the materials to be used, and the specific area or purposes thereof.

The training programme should aim at providing the Licensee's personnel an adequate knowledge and experience for permitting it to efficiently operate and maintain in production the technology, without the help of external assistance.

3.d.3 Qualification and availability of trainees

The parties should discuss and agree on the qualifications required for personnel to be trained. The Licensee should undertake to supply personnel fully qualified for the proposed programme and to make it available in due time, in accordance with the respective schedule.

The appropriate training of Licensee's personnel is very important for the successful operation of the plant. Therefore, the selection of people to be sent for training should be carefully planned. Besides the technologists, it is necessary to give training to a mechanical engineer who has to maintain the plant trouble-free. This also helps in better supervision and co-ordination during construction and erection and assistance to the designing organization. The laboratory scientists, who are responsible for maintenance of the strain and preparation of culture for industrial fermentation should also receive training at the Licensor's plant and laboratories.

It is not possible for the Licensee to send a large number of personnel to Licensor's plant. Part of the training has to be given at the Licensee's plant for which Licensor should make its experts available according to the programme agreed to between the parties and set forth in a detailed schedule. There may also be a stipulation that the expert service could also be made available as technical assistance to the Licensee after fulfilment of the guarantee on mutually agreed terms.

As regards qualifications, it is desired that all the supervisory personnel should be degree holders in their respective field of chemical engineering, mechanical engineering, electrical engineering, bio-chemical engineering, civil engineering, instrumentation etc., whereas for laboratory personnel, the chemists in charge should be minimum post-graduate in their field of specialities, e.g. organic, inorganic, bio-chemistry, pharmacy etc.

Operating personnel in the plant as well as the laboratory (chemists) should be graduates, whereas operating personnel at lower levels should have school-leaving certificates and have experience of working in chemical plants. Operating personnel should be recruited 4-5 months in advance of commissioning of the plant and should be acquainted about the processes, safety, analytical procedure etc. They should also take part during water trial and commissioning of the plant.

It is a general practice, in the developing countries, to send only supervisory staff for training whereas operators who have to actually operate the plant never see the Licensor plant in operation. It will be desirable that such operating staff who have to look after the sensitive steps of the operation are also given training at the Licensor's plant.

The following table contains an example of the categories, qualifications and experience of Licensee's personnel to be trained:

Categories, qualifications and experience of persons to be trained by the Licensor

Category	Qualification	Experience	Nature and period of training
1. Managers (Departmental Heads)	Graduate in respective discipline of engineering/Post-graduate in chemistry, micro-biology, pharmacy, etc.	10-15 years in the chemical industry or in general management in case such industry units do not exist	1 month
2. Foremen and other supervisory staff	Graduate (engineering)/Post-graduate (science)	4-5 years	2-3 months in specific area
	Diploma (engineering)/ Graduate (science)	7-8 years	
3. Operators/chemists (for sensitive area)	Diploma (engineering)/ Graduate (science)	1-2 years	2-3 months in specific area

Note: In case of antibiotics, the plant and laboratory technical personnel should be micro-biologists and mycologists.

3.d.4. Training and guarantees

The Licensee's objective in asking for and bearing the cost of a training programme is to ensure its personnel's ability to apply the technology transferred in an efficient manner. Obligations under training provisions are normally interpreted as best effort obligations do not involve the guarantee of any concrete results. The Licensee's interest may be, however, to reinforce the content of such obligations in order to secure the obtention of the expected results.

The failure of Licensee's personnel to successfully complete - under the Licensor's direction - the performance guarantee tests (see section 7.c., below) by reasons identified as lack of competence of such personnel, may be an indicator of the Licensor's failure to fulfil its training obligations, provided that the Licensee has made available adequately skilled or experienced trainees.

The formation of local personnel is, for the proper application of the technology, as important as the proof that the plant can - if appropriately operated - attain the guaranteed parameters. Hence, it is suggested that the Licensor may be requested to assume the responsibility to adequately perform the guarantee test with the trained local personnel, and extend the period of training where it is proven that it has been insufficient or incomplete by reasons attributable to the Licensor.

Specimen clauses

3.d. Training

1. The Licensor will provide training to Licensee's personnel in the Licensor's plant of (country). The training will cover but not be limited to plant operation, plant maintenance, material handling and quality control. It will specifically involve the operation during the demonstration of the technology, as stipulated in article ..... ("Performance guarantees"), of the plant sections concerning the production of the Drug and will be sufficient to enable the Licensee's personnel to master the technology transferred.

2. The training will be as follows:

Qualifications of trainees	Number	Time of training
.....	.....	.....
.....	.....	.....
.....	.....	.....

3. Subject to 1 and 2 above, the parties will establish within ..... days from the Effective Date of the Contract the detailed programme of training. It will be carried out in (language).

4. All travel and living costs of the Licensee's personnel will be borne by the Licensee.

5. The Licensee's personnel will be made available in due time and possess a normal skill and experience in their respective fields of work.

6. If in the Licensor's judgement, which must be expressed within ..... working days from the arrival date, the personnel sent by the Licensee lacks the skills required, the Licensor may ask for replacement, which will be provided by the Licensee within ..... working days from the request.

7. Should the performance guarantee tests fail due to reasons directly attributable to deficiencies in training leading to lack of competence of Licensee's trained personnel, the Licensor will provide further training to the pertinent personnel for the period to be agreed upon by the parties. The costs of this additional training will .....

(Alternative a: be borne by the Licensor)

(Alternative b: be distributed as follows: .....)

8. The personnel to be trained in Licensor's plant will be bound to respect all prescriptions in force and to comply with discipline rules whereto the Licensor's personnel is subject.

3.e. Basic design and engineering

In the hypothesis considered here, the Licensee is likely to require the provision of basic design data and engineering for the addition or adaptation of its plant. The pertinent documentation may include, inter alia:

- Flow-sheet of the equipment; indication of piping and instrumentation; utilities flow-diagram; equipment layout;
- List of equipment (including electrical) and specifications (see appendix VI);
- Utility summary with normal and maximum load;
- Indication of effluents and suggestions for treatment (see appendix VII);
- Indication of hazardous areas and suggestions of protective measures (safety instructions);
- Manual for testing and commissioning;
- Personnel requirement;
- Operating manual including operating instructions: (i) production schedule; (ii) testing and preparation for operation; (iii) start-up procedures: (a) initial operations, (b) for conventional start-up, (c) emergency shut-down, (iv) normal operation, (v) normal shut-down, (vi) emergency shut-down, (vii) emergency, (viii) in-process analytical methods;
- Routine maintenance and plant preventive repairs or plant preventive maintenance annual schedules and instructions;
- List of tools for maintenance.

The contract should specify the language in which this documentation is to be provided, and the system of units to be employed.

Even if the detailed engineering is in charge of the Licensee, it may be advisable to request the Licensor's approval thereof, in order to facilitate the attribution of responsibilities in case of failure of the performance tests.

The layout should be as compact as possible. It has been observed that in spread-over layouts the overall investment cost is high, particularly in case of utilities. Moreover there are recurring transmission losses. For example in the case of an antibiotic plant, air compressors were located far away; this was giving more pressure drop and caused a moisture condensation problem resulting in insufficient air supply to fermenters and also created contamination problems.

(1) Process flow diagrams: Indicating material and energy balances. Since material and energy constitute the major cost elements, the consumption norms must be well defined.

(2) Process flow sheet: This should include the pipelines with sizes and materials of construction, type of valves, type of instruments indicating the ranges, type of controls, flow pattern.

(3) Equipment list with specifications: Comprehensive process and auxiliary equipment list should be provided. The equipment specifications need to be elaborated and should cover the following aspects:

(a) Capacities with filling coefficients, dimensions, thickness and weight. In case of mass transfer operation in fermentations, synthetic or extraction industries, the height to diameter ratios greatly affect the process and hence it should be specified clearly. The operation may produce foam or otherwise the capacity is also important. The operating pressure (or vacuum) may necessitate the thickness specifications. The weights of the equipment are required for civil designs.

(b) Materials of construction. Depending upon the reaction conditions, corrosive nature of the chemicals, sensitivity of the process (e.g. fermentation), the material of construction of equipment should be indicated. The alternative material should be indicated as the case may be. For example, handling of hydrochloric acid at high temperature may necessitate histalloy B which is not available in most of the countries. So alternative material, if any, should be suggested.

(c) Internals of the equipment, like cooling or heating coils, baffles, etc. in case of reaction vessels and fermenters, number of passes in case of heat exchangers, type of plates and their spacing in case of distillation/ extraction column etc. should be indicated.

(d) Externals of the equipment like whether jacketed/ordinary, numbers of size of ports, bottom outlet or blow over pipe, insulation with thickness, type of paints, whether on legs or lugs, etc. may be mentioned.

(e) Type of agitators and drives should be specified. Out of several types of stirrers like propeller, anchor, turbine, helical ribbon, etc., only flat blade turbines are suitable for fermenters, where more sheer force is required; anchor is suitable for crystallizers where axial flow is desired. The revolution per minute (rpm), power requirement, variable speed stirring, drive details, etc. are important parameters. These should be included in the specifications.

(f) Duty of the equipment to be mentioned. Pumps, compressors, heat transfer equipment give best performances under specified conditions. The type of pump, capacity, head, type of motor with rating to be mentioned. The details of the material to be handled like density, viscosity, temperature, corrosive nature etc. to be mentioned. In case of heat exchanges, the nature of duties like simple heating or cooling, condensation or evaporation, number of passes, type of exchanger (shell and tube, plate etc.) to be defined. In case of reactors or fermenters the operating pressure, temperature and other important parameters to be defined.

(g) Speciality of fabrication, if any, should be mentioned. Depending on the processes, the fabrication code (like ASME, BRITISH etc.) should be specified. If any extra care has to be taken for any specific equipment it should be indicated thereof.

(h) For specialized items probable sources of repute and confidence may be communicated to the Licensee.

Some examples for the specifications of equipment are given in Appendix VI.

(4) Summary of utilities to be provided. Services like steam, power, inert gas etc. along with the normal and maximum load should be mentioned. The exact requirements like pressure, temperature, degree of superheat in case of steam, peak demand and normal demand, input voltage and cycles per second in case of power, nitrogen content and operating pressure in case of inert gas should be specified.

(5) Safety. The detailed information about the hazardous areas (toxic, inflammable, explosive) should be provided. Identification, remedial and combating measures - along with detailed equipment specifications should be mentioned.

(6) Refrigeration and air-conditioning. After getting requisite information about the proposed location the details about the normal and maximum load, the desired parameters, instruments and controls in the operating areas and in processes regarding refrigeration and air-conditioning should be clearly indicated. The detailed list of machinery and auxiliary equipment along with specifications should be provided.

Specimen clauses

3.e. Basic design and engineering

1. Owing to the fact that the Licensee's plant requires additions and adaptations for commencing the production of the Drug, the Licensor will supply the Licensee, together with the technical information, Basic Design and Engineering for the adjustment of said plant, in accordance with the good engineering practice with respect to the production in ..... reactors/fermentaters, each with ..... m^3 capacity.

2. The Licensor will provide, in particular .....
.....

3. The documentation will be drawn up in ..... (language) and be presented in a manner comprehensible for a normally qualified technician.

4. The Licensor will, within ..... days from receipt, approve the detailed design drawings prepared by the licensee for the purpose of procurement and erection.

3.f. Supply of raw materials or intermediates

The manufacture of bulk drugs involves the use of a number of intermediates, that the Licensee is not able or does not desire to produce himself. Such intermediates may normally be obtained from different sources, eventually including the Licensor.

In some instances, the technology transferred does not cover the whole manufacturing process of a drug and only enables the Licensee to undertake some or the final steps of a synthesis. While the Licensor may be willing to negotiate the supply of the early intermediates required, it should be clear at the outset that the acquisition by the Licensee of such materials should not be imposed as a condition for the transfer of technology. This requirement - or tie-in clause - is considered objectionable in many developing and developed countries, due to its adverse effects on competition, and likely impact on the Licensee's costs of production.

Whenever the provision of intermediates by the Licensor is regarded as mutually desirable by the parties, and in order to avoid unfair restrictions, the agreement should ensure that the Licensor:

(a) Will communicate to the Licensee the specifications of the required intermediates;

(b) Will provide such intermediates on conditions comparable to those of the international market, taking the type, quality and quantity of the product into account.

Alternatively, and especially when comparable supplies are not readily available, a "non-less favourable" clause may be stipulated.

The supply of raw materials by the Licensor may also be the object of a separate agreement.

Proper quality of raw materials and intermediates is a prerequisite for successful guarantee trials and running of the plant. Though the Licensee should be free to purchase the same on competitive offer from various suppliers, for commissioning and trial runs the Licensor, who is already producing or using these, may supply them on request. This may also avoid disputes and facilitate the quick implementation of the trials.

Finally, another alternative is to request the Licensor only to assist the Licensee in procurement of raw materials, by providing information about the supply and international prices thereof.

Specimen clauses

3.f. Supply of raw materials or intermediates

1. The Licensor will provide the Licensee, as part of the Technical Information,

(Alternative a: the specifications of the intermediates required for the production of the Drug);

(Alternative b: ..... ampoules of the strain producing the Drug).

2. Upon request by the Licensee, the Licensor will supply it with the following intermediates: .....
.....
in the quantities to be agreed upon in each case. The price for such supplies will be non-less favourable than the price usually charged by the Licensor or by other reliable sources for the same intermediates, and under comparable circumstances.

3. The Licensor will assist the Licensee about the source of supply of raw materials, intermediates, catalysts and other items required in the production of the Product.

3.g. Transfer of improvements

The technological developments and innovations in the field of drugs and pharmaceuticals are very fast. A most sophisticated and competitive process of today may be obsolete tomorrow. Even a single stage improvement like strain in case of fermentation, equipment design, process parameters, instruments and controls, unit processes and operations etc. may bring forth a radical change in the entire technology.

About a decade back the strains for tetracycline used to give less than 8,000-10,000 u/ml, which is now more than 30,000 u/ml. What was penicillin strain in the 1940s giving only 100 u/ml is now about 50,000 u/ml in 1980. This 30-500-fold increase in yield is really very significant. Besides the strain, the design of fermenter, oxygen demand as well as change of parameters and isolation and recovery techniques are being constantly improved. The synthetic route of 6-APA is losing momentum with the introduction of enzyme and further improved immoblized enzyme process which is substantially economising solvents and energy (refrigeration). Similar improvements have been achieved in the extraction process. In the extraction of disogenin from dioscorea roots the low boiling solvent n-hexane has been replaced by the higher boiling toluene suited to tropical countries resulting in reduced solvent loss. In the field of synthetic drugs also, tremendous improvements by changing the routes, process parameters, unit processes and operations, equipment design etc. have taken place.

These phenomenal improvements are resulting in the cheaper and easily available raw materials and solvents, lesser operations, nigher yields, energy savings and above all reduction in the production cost.

The improvements may take place between the period of signing of the Contract and fulfilling performance guarantee which vary from one to three years so depending upon the size of the plant. Since substantial investments are behind these improvements, and full-fledged research and development efforts may be prohibitive on the part of the Licensee to start with, it should be obligatory on the part of the Licensor that such improvements be communicated to the Licensee and modifications made during the construction and erection period, if any.

The obligation to transfer improvements should continue till the expiration of the Contract. Apart from the process improvements other aspects like design and engineering may also fall within this purview. After the smooth running of the plant of the Licensee, there should be periodical review of the plant performances by the Licensor and Licensee and sharing of experiences and exchanges of improvements should take place.

The access to improvements made by the Licensor during the lifetime of the agreement may be, hence, of crucial importance for the Licensee, mainly in order to increase his plant's performance and reduce costs. The Licensor may also desire to be informed and acquire the right to use improvements made by the Licensee. The contract should appropriately cover this reciprocal exchange of innovations on the technology transferred.

The importance of these clauses will be commensurate with the likelihood of improvements being made during the term of the agreement. Thus, they will be more significant with regard to relatively new processes than in connection with relatively old and largely applied processes. Likewise, the Licensee will be most interested in securing an appropriate clause of this type when the Licensor is involved in the actual production of the drug covered by the Contract and in research and development activities related thereto.

3.g.a. Access to Licensor's improvements

The drafting of provisions on this issue should cover at least the following items:

(i) Definition of improvements

It is generally accepted that, for the purpose discussed here, "improvements" constitute any modification of the technology, whether patentable or not, which has been developed or otherwise acquired by the Licensor during the lifetime of the agreement, and the application of which may improve the yield, reduce costs or entail other technical or economic advantages. This concept excludes, in principle, radically substantial changes which essentially alter the characteristics of the technology transferred.

(ii) Stage of development

Various alternatives exist in commercial practice as to the moment in which the Licensor should communicate a new improvement. The Licensor may be required to do it as soon as the information is available, or after

appropriate laboratory tests have been undertaken, or even once the industrial realization and commercial advantages of the improvement have been proven. This last alternative is consistent with the requirement (see section 3.a.2.b. above) that the know-how to be transferred be commercially proven. However, the widest and soonest access by the Licensee to improvements available to the Licensor, may help the former to guide, and eventually correct its own adaptative or research and development activities. In any case, the Licensor should be bound to specifically indicate the stage of development of the new pieces of technology to be transferred.

(iii) Consideration

As a rule, though the economic value of the improvements that may arise during the lifetime of the agreement is uncertain, they are deemed to be remunerated through the royalties or other payments stipulated in the agreement. This means that improvements are transferred without additional payments (which, of course, is not the same as being "free of charge").

An exception is normally accepted when improvements have been obtained by the Licensor from third parties and on the basis of a remuneration. In these cases, the contract may provide that an additional reasonable payment be effected by the Licensee, in accordance with the nature and importance of the innovation concerned.

(iv) Patentable improvements

Improvements may be of a patentable nature according to the law of the Licensee's country. Two basic situations may arise out of this case:

If the Licensor decides to apply for a patent there, the Licensee should be automatically entitled to its use, at least until the expiration of the agreement. The contract should also provide the conditions under which the Licensee may continue in the use of the patent after that date (see section 9.c.1. below).

If the Licensor is not willing to apply for a patent, it is sometimes agreed upon that the Licensee is authorized to do so either in the name of the Licensor or in his own name and at its own expense.

(v) Applicability of other contractual terms and conditions

If the likely flow of improvements is relevant, it might also be desirable to specify in the contract if and the extent to which other terms and conditions thereof are applicable to the use of transferred improvements.

In principle, the same terms and conditions should apply, and no alterations should be allowed with respect, for instance, to exclusivity, guarantees, liability or sublicensing. In some cases it may be advisable, however, to provide for specific solutions, such as in the case of confidentiality obligations.

It has been noted, in this regard, that when the confidentiality obligation ceases at the time of the agreement's expiration date, the Licensor may detain, when nearing that date, the transfer of new improvements, in order to avoid the risk of an early disclosure thereof. To prevent this, the contract may stipulate that the Licensee will keep confidential the transferred information for a reasonable period after the date of its transmission, and that this obligation may extend after the expiration of the remaining contractual obligations (see also section 5.c. below).

3.g.b. Access to Licensee's improvements

Clauses stipulating access by the Licensor to Licensee's improvements or "grant-back" clauses should be drafted with an aim to ensuring a substantial reciprocity with Licensor's obligations. The following aspects should be considered, in particular:

(i) The content of Licensee's obligation.

Depending on the patentability or not of the improvements made, they might be communicated for its use by the Licensor (non-patented or unpatentable improvements) or the transfer may involve the rights to use a patent (licence) or to obtain or become the owner thereof (assignment). Licensee's obligations - as those of the Licensor - should be limited to the communication or licence of innovations, and exclude any form of assignment which would transfer property thereon to the Licensor.

(ii) The exclusivity of grant-back clauses.

Exclusive grant-backs mean that the Licensee is forbidden to communicate, license or assign his improvements to parties other than the Licensor. This restriction may be clearly abusive, particularly when the contract is not of an exclusive nature, and it may hamper the diffusion of the technology in the Licensee's country, or its transfer to other countries where the improvements and adaptations made by the Licensee may suit the local conditions better than the original technology.

(iii) The obligations undertaken by the Licensor

The Contract should secure that the Licensor undertakes, in connection with the transfer of improvements, obligations substantially equivalent to those of the Licensee. Such a situation would not exist, for instance, if the reciprocity offered by the Licensor lacks practical meaning, e.g. if he does not exploit the technology himself or has no possibility of gathering additional experience.

(iv) The terms and conditions for the transfer

Unlike the transfer of improvements by the Licensor, which is essentially covered by the general terms and conditions of the Contract, where Licensee's improvements are transferred there is, in principle, no contractual framework to govern their use and compensation. Hence the parties should have to agree on the terms and conditions, including payments, duration, confidentiality, etc., applicable therefor. The contract may provide for some elements, e.g. that the remuneration for improvements will be stipulated taking into account the remuneration agreed upon in the contract, and that the Licensor's right of use will extend for the time of validity of said contract.

(v) The national regulations

Grant-back clauses, or at least certain forms thereof (e.g. non-reciprocal exclusive clauses), are consdiered objectionable in several developed and developing countries. 8/

The enforcement of clauses obliging to transfer improvements made during the lifetime of the agreement, may be frustrated (and it is often in practice) by the lack of information on the developments reached by the other party. One possible means of overcoming this difficulty may consist of a periodical meeting to be held alternatively at the Licensee's and Licensor's facilities, where the parties' technical representatives discuss and exchange information on improvements realized during the period preceding the meeting. Of course, such a meeting would imply additional costs, that most probably the Licensee would have to bear in full or in its major part.

8/ See UNIDO, ID/WG.331/3 op. cit. p. 37.

Specimen clauses

3.g. Transfer of improvements

1. The Licensor will promptly furnish to the Licensee, without additional payment, all improvements on the technology transferred developed by the Licensor during the lifetime of the Contract.

2. The Licensor will also inform and, subject to a reasonable fee to be agreed upon, furnish to the Licensee any improvements acquired by the Licensor upon terms requiring payment by the Licensor to any third party.

3. For the purposes of 1 and 2 above, "improvements" will constitute any modification of the technology transferred, including operating technologies and process developments, whether patentable or not, which has been developed or otherwise acquired by the Licensor during the lifetime of the agreement and the application of which may improve the yield, reduce costs or entail other technical or economic advantages in the production of the Drug.

4. If the improvements transferred to the Licensee are patentable and the Licensor acquires patent rights thereon in (country of the Licensee), the Licensee will be entitled to use such patent rights without additional payments.

5. In the event that the Licensor decides, with respect to such patentable improvements, not to apply for patents in (country of the Licensee), the Licensee will have the right to apply for a patent in the Licensee's name and at its own expense.

Improvements by the Licensee

6. The Licensee will promptly inform the Licensor about any improvements developed by the Licensee in connection with the technology transferred. Subject to the agreement of the parties on the price and other conditions for their use, the Licensee will communicate such improvements to the Licensor or, if the Licensee has obtained patents on such improvements in (the Licensor's country), will grant the Licensor a licence under such patents.

4. Scope of the agreement

Under this heading three important issues will be considered: (a) the exclusivity or not of the licence; (b) the question of the territorial scope of the contract, and (c) the field of use of the technology transferred.

(a) Exclusivity

The grounds for determining the convenience or not of negotiating an exclusive licence are basically of an economic nature. From the Licensee's point of view, it is necessary to assess whether the higher price that the Licensor is likely to ask for an exclusive licence, is justified in view of the market situation and the Licensee's commercial objectives.

Exclusivity may be stipulated with regard to both the application of the technology and the sale of the resulting products, or only with respect to one of them. Thus, the contract may provide for an exclusive right to produce and sell in the Licensee's country, and limit exclusivity for any other country only to sales.

The negotiation of exclusivity is obviously linked to the determination of the territory to which it would apply. In a standard situation, the Licensee may require exclusivity for its own country, and also for some neighbouring countries. When dealing with the manufacture of bulk drugs, in particular, the access to a wider market may be of great importance for attaining competitive costs.

It is possible to find in some agreements clauses stipulating exclusivity for certain countries and non-exclusivity for a number of other countries. In fact, these types of clauses amount to an implicit export restriction, since they imply that the Licensee should not sell in countries excluded from the territory so defined. This issue is considered in the following point.

(b) Territory

The contractual limitation of eventual exports by the Licensee may have a serious detrimental impact on the development and efficient use of his productive capacities, particularly in developing countries, where export markets may constitute a necessary complement to the local demand.

Between the complete freedom and the full restriction to export, a wide range of intermediary alternatives exists. The outright prohibition and some of such other alternatives are objectionable in a number of countries. 9/ Without prejudice to the applicable law, the solution given to this point will conceivably depend upon the bargaining power of the parties and the economic value of the markets at stake.

Among the possible variations that clauses on this issue admits and wherever a complete freedom to export is not sought for by the Licensee or acceptable for the Licensor, a reasonable solution may be to specifically indicate the countries where the Licensee should not sell the drug produced under the contract. The elaboration of such a list should not, however, be arbitrary. It may include, for instance, such countries where the Licensor is using, or has granted an exclusive licence to use the technology object of the agreement. This list may also be shortened or enlarged, during the lifetime of the agreement, according to changing circumstances.

(c) Field of use

Eventually, the technology to be transferred or the resulting product may have more than one commercial use (e.g. use of a drug for human health and for veterinary). The Licensor may wish to limit the contract to only one of such uses and restrict the Licensee's access to others.

This situation is not likely to appear very frequently in agreements dealt with here. However, if such a restriction is required during negotiations, the parties should aim at obtaining a compromise solution on the basis of the right of the Licensee to undertake such other uses of the technology, subject to a clear delimitation as to the guarantees and liabilities of the Licensor for uses not specifically dealt with in the agreement.

9/ See UNIDO, ID/WG.331/3, op. cit. p. 24 to 27.

Specimen clauses: Scope of the agreement

Exclusivity

4.a. The licence granted under this Contract will be exclusive. The Licensor undertakes not to manufacture or sell the Drug, directly or by means of its subsidiaries, licences or other related parties, in (country of the Licensee) and (other countries for which exclusivity is granted).

Territory

4.b. The Licensee will have the right to export the drug to any country, except .....

(Alternative a: to those countries where the Licensor or its exclusive licensees employs the technology transferred under this Contract to produce and sell the Drug.)

(Alternative b: to the following countries: .....
.....
as long as the technology transferred under this Contract is used there by the Licensor or its exclusive licensees to manufacture the Drug.)

5. Obligations of the Licensee

5.a. Provision of information for the preparation of basic design and engineering by the Licensor

To the extent that the object of the agreement includes the provision of know-how, including basic design and engineering, the Licensee should normally provide the Licensor, in due time, with the information and data required for an appropriate design such as:

1. The proposed location of the plant. (Whether near big city or town or rural area.)

2. Source of power. (High tension line and statutory regulation regarding power.)

3. Source of water and its analysis.

4. Transport and communications. (Facilities regarding (a) road, (b) railway, (c) sea - nearest port facility, (d) nearest airport.)

5. Climatic conditions - maximum and minimum temperature, rainfall, humidity.

6. Facilities for sewerage disposal and its regulations, any nearby municipal or city effluent treatment plant availability.

7. Population.

8. Educational facilities.

9. Health-care facilities.

10. Nature of soil and other geographical conditions including seismological data.

11. Local laws pertaining to taxes. Factory Acts, Labour Acts and environment and pollution regulations, health laws.

12. Standards - both for the final product as well as intermediate and raw materials, if produced in the country and imports banned.

13. Data pertaining to equipment and machinery. Many countries have restrictions for imports of equipment and machinery already being manufactured, specifications of such equipment and machinery should be part of documentation to be supplied by the Licensor.

14. Services or utilities: in case of existing units, facilities available for the production of power, steam, refrigeration including brine and chilled water.

15. Availability of fuel - coal, fuel oil, gas, etc., and their specifications and cost.

It is essential that information supplied be accurate and complete. Any omission or mistake may, firstly, lead to an inadequate design, and consequently to delays or losses. Secondly, whenever guarantees, particularly performance guarantees, have been agreed upon, the Licensor may be eventually relieved from its compliance due to such omission or mistake.

Given the differences in technical capacities between Licensor and Licensee, the former is usually in a better position to identify discrepancies or mistakes in the Licensee's information. He should therefore be bound to inform the latter about them in order to allow their correction and completion.

In case the process know-how is for improving the existing product or production of new product(s) in the existing unit, it may be also desirable that the Licensor's technical personnel visit the plant of the Licensee and collect all the data pertaining to utilities, site plan and existing facilities, store, handling of raw materials, laboratories etc. to enable him to submit the basic design data in time.

Specimen clauses

5.a. Provision of information for the preparation of basic design and engineering by the Licensor

1. The Licensee will provide the Licensor, within ..... days from the Effective Date of the Contract, complete and accurate information as required for the preparation, by the Licensor, of basic design and engineering in conformity with article ...

2. The Licensor will diligently examine the information furnished in accordance with 1, above, and promptly inform the Licensee in writing about any omission, inaccuracy or discrepancies thereof. The Licensee will promptly amend or complete the information, as necessary.

5.b. Remuneration

5.b.1. Itemization

Payment conditions in agreements for the manufacture of bulk drugs may vary significantly from case to case, particularly as regards to the form of remuneration for know-how and patent licences.

In cases - like the one described in section 2 above - where the object of the contract includes a multiplicity of supplies, a breakdown of the remuneration according to the nature and scope of such supplies should be examined and negotiated wherever possible.

An appropriate itemization of the price to be paid by the Licensee would permit, among other things: (1) to establish a relationship between price required and costs incurred by the Licensor; (2) to assess the required price vis-à-vis its likely benefits for the Licensee and the price eventually obtainable from other sources; (3) to adequately solve situations that may arise during the lifetime of the agreement and that would lead to a reduction in remuneration, for instance, if the licensed patents are invalidated or the transferred know-how loses its secret character.

5.b.2. Forms of remuneration

Remuneration corresponding to items comprised in section 2.a, b, c, d, e, and f may be categorized in two groups:

(a) Items the price of which cannot or is not normally assessed on the basis of costs incurred by the Licensor for its obtention and transfer, and which are usually remunerated by a firm price or running royalties. This category includes, in particular:

(i) patent licences;

(ii) transfer of know-how;

(iii) transfer of improvements;

(b) Items the price of which may be assessed on the basis of a fee according to the category and duration of personal services supplied by the Licensor, like:

(iv) technical assistance;

(c) Items which may fall either within (a) or (b) above, including:

(v) training;

(vi) supply of design data and engineering.

The price stipulated for patent licences (and eventually, patented improvements) remunerates the granting of a right to use the protected invention. The price applicable to the transfer of secret know-how (and eventually, improvements thereto) remunerates the disclosure of secret knowledge to the Licensee. As the life of both items runs independently, a separate remuneration for each of them may be provided for. Occasionally, it has been observed that, when required to discriminate the percentages of the price corresponding to patents and know-how, Licensors have tended to charge a very low percentage on patents and a very high one on know-how, presumably due to the fear of invalidation of the former and the consequent reduction in price that it may lead to.

Royalties or lump sum (ordinarily paid in instalments over a certain period) present a number of relative advantages and disadvantages that should be carefully evaluated at the time of the negotiation. 10/ A combination of both forms of remuneration is also possible. Running royalties may be advisable when the licence involves a new process and there is reasonable likelihood that a flow of improvements will arise during the lifetime of the agreement.

Lump-sum arrangements are better preferred by parties who are coming in contact for the first time or who need or like to have their dues immediately settled as well as consortium or companies supplying know-how on behalf of producers of product (or process or know-how). Other reasons for preferring lump sums are also procedural delays and sometimes political instability in the Licensee's country. Those companies desiring long term association particularly to assist in the supply of intermediates, improvements, etc., may be willing to accept royalties, which is beneficial to the Licensee as it reduces the capital investment to some extent. This procedure is also adopted by parent companies with their subsidiaries in developing countries.

10/ For a more detailed consideration of this point, see UNIDO, Guidelines for evaluation of transfer of technology agreements, Development and Transfer of Technology Series No. 12, New York, 1979, p. 47.

The compensation for technical assistance should be based on the costs incurred by the Licensor for the provision of expatriate personnel, including for conducting performance tests at the Licensee's premises. Such a compensation will generally include a daily fee in accordance with the category of the deputed personnel, a subsistence allowance payable in local currency and travel facilities.

The contract should determine the number of technicians to be nominated, and specify (or estimate the maximum) period of the assistance to be supplied.

The provision of training and of design data and engineering may be also remunerated through fee, calculated in accordance with the personnel and time necessary for their execution. This latter form may be more appropriate than a global price in the context of agreements where both obligations are likely to be limited in scope and only require a marginal effort from the Licensor's side.

5.b.3. Level and calculation

The evaluation of the price to be paid for patent licences and know-how constitutes one of the most difficult tasks in the negotiating process. The technical and economic aspects, as well as the legal considerations involved have been dealt with elsewhere with some detail. 11/

The parties should, when negotiating these aspects, aim at defining a fair and reasonable price, in view of the nature of the technology involved and the scope of obligations undertaken by the Licensor. As a principle, the price charged to a Licensee in a developing country should be no less favourable than the one required by the supplier or other reliable sources for the same technology under similar circumstances.

The translation of this principle into reality requires good faith from the supplier and the availability of information on other similar transactions, which is normally very difficult to obtain. The governmental action through transfer of technology registries, and the exchange of information at the international level, may contribute significantly to gather data and permit a comparative analysis of prices under negotiation.

In the framework of the agreement considered here, it should be noted that, whenever royalties are provided for, the basis for its calculation should exclude the price of intermediates supplied by the Licensor or other enterprises belonging to the same concern, in order to avoid a duplicative payment on items remunerated separately.

11/ See UNIDO, Guidelines for evaluation of transfer of technology, op. cit. Chapter VII; WIPO, Licensing guide for developing countries, Geneva, 1977, paras. 390 to 527.

5.b.4. Schedule of payments

The opportunity of payments should be linked, as far as possible, to the fulfilment by the Licensor of his respective obligations. Thus, supplies like technical assistance will be payable against presentation to the Licensee of invoices supported by logs of each of the Licensor's personnel at the Licensee's disposal.

Payments regarding patents and know-how - when consisting of a firm price - may be tied to a number of events, mainly the delivery of know-how and the satisfactory completion of performance guarantee tests.

For instance, payments could be made as follows:

- 20 per cent, at the effective date of the contract;
- 30 per cent, on the date of delivery by the Licensor of know-how and basic design and engineering;
- 20 per cent on the date of process demonstration at the Licensor's plant;
- 10 per cent on the date of commissioning of the Licensee's plant (but not later than x months from the effective date of the contract);
- 20 per cent on the date at which the performance guarantee tests are satisfactorily fulfilled at the Licensee's plant.

In the case of the transfer of technology for the production of antibiotics, where strain is an important part of the Licensor's supplies, the following terms may be provided for:

- 20 per cent of the lump sum on the effective date of the contract;
- 40 per cent on the date of delivery of know-how and strain;
- 20 per cent on the date of demonstration of the process at the Licensor's plant;
- 20 per cent on the date at which performance guarantee tests are satisfactorily fulfilled at the Licensee's plant.

5.b.5 Taxes and levies

It is generally understood that the Licensor will bear any taxes, rates, charges and assessments of any kind applicable outside the Licensee's country and pertinent to the supplies under the contract.

In general, it is advisable to stipulate that the amounts paid to the Licensor shall be after deduction of any taxes or levies applicable in the Licensee's country. The Licensee should, if requested by the Licensor, provide the latter with the receipts of payment of such taxes or levies.

Specimen clauses

5.b. Remuneration

1. The Licensee will pay the Licensor as consideration for the execution of the Licensor's obligations under this Contract, together with payments due for technical assistance, as stipulated in article ....., below .....

(Alternative a: a lump sum of ..... (currency)).

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

..... per cent for the supply of technical information and improvements thereto;

..... per cent for the licence of patents and improvements thereto;

..... per cent for training of personnel;

..... per cent for the supply of basic design and engineering.)

2. The lump sum will be paid in instalments as follows:

(i) ..... per cent on the effective date of the contract, against bank guarantee;

(ii) ..... per cent on the date of delivery of all technical information and design and engineering data;

(iii) ..... per cent on the date of successful demonstration of guaranteed parameters, at the Licensor's plant;

(iv) ..... per cent on the date of commissioning of the Licensee's plant, but in any case not later than ..... months from the effective date of the contract;

(v) ..... per cent on the date of successful completion of performance guarantee tests at the Licensee's plant, against statement signed by both parties.

3. The Licensee will open, within ..... days from the effective date of the agreement, an irrevocable letter of credit for the full amount referred to in clause 1 above.

4. In addition to the sums due in accordance with article ..... ("Technical assistance") , the Licensee will pay the Licensor for each Licensor's expert deputed for the provision of technical assistance, the sum of ..... (currency) per day of absence from the Licensor's plant.

5. (Alternative a: The total amount of point 5 will be paid by the Licensee agairst invoice of the Licensor at first presentation.)

(Alternative b: The total cost of technical assistance is estimated as being the sum of ..... (currency). The Licensor will, one month before the commencement of services, establish an irrevocable divisible Letter of Credit in favour of the Licensor. Payments of the sum resulting from clause 5 above, shall be effected out of the said Letter upon presentation to the Licensee of Licensor's invoice duly countersigned by the Licensee.)

Taxes and levies

6. All taxes and/or levies under any existing or future law of (Licensee's country) applicable to the amounts payable in accordance with this Contract will be borne by .....

(Alternative a: The Licensor. Upon request, the Licensee shall provide the Licensor with the receipts of payment of such taxes or levies.)

(Alternative b: The Licensee.)

5.c. Confidentiality

Technology transferred under this type of agreement usually includes information of a different nature, from which only some specific parts may be deemed as of secret character. The Licensee is not normally in a position to appraise which pieces of information are to be deemed confidential. He only has access to it during the execution of the agreement, and particularly when he belongs to a developing country, he has not the capacity needed for evaluating and discriminating among the different types of information transferred. Further, the Licensee cannot be expected to discern whether the technology transferred has or has not been previously disclosed and, henceforth should not be bound, in the absence of a specific provision and indication by the supplier, to take measures that the latter has not asked for.

It is generally very problematic to ascertain when a given know-how is actually secret, particularly if the transaction involves different countries. In addition to factual difficulties, the concept of secrecy admits different interpretations. For the purpose of the agreement it should be understood (and eventually indicated in a clause on "definitions") that the obligation of confidentiality should only apply with respect to information which has not become publicly known by publication or otherwise in any country. This implies that the contract cannot "create" secrecy, but only declare the existence thereof, and that the recipient will be freed from that obligation as soon as it is established that the information was not secret or that it became a part of the public domain.

The agreement should therefore specify which pieces of information are to be treated as confidential, and should expressly contemplate the scope and duration of the obligation, as well as the effects of the disclosure of the know-how during the lifetime of the agreement.

5.c.1. Scope

The obligation of confidentiality should not prevent the Licensee from disclosing information as far as necessary for subcontracting, procurement or other legitimate purposes. In this case, a written undertaking by subcontractors and other third parties against disclosure may be advisable. The same should apply with regard to sublicensees, whenever sublicensing is permitted under the agreement.

The compliance with information requirements imposed by national health authorities may (although this would not probably be the rule) entail the necessity to disclose some information indicated as confidential. A specific provision might also be included to cover this point.

5.c.2. Duration

The set of rights and obligations originated in the agreement shall normally expire at the date of termination specified therein. In principle, the obligation of confidentiality should follow the same pattern.

However, that particular obligation may expire before that date, when the know-how becomes publicly known during the lifetime of the agreement. Conversely, it may be extended by mutual agreement of the parties and eventually survive the expiration of the remaining contractual obligations. In this case, it is advisable that the parties specify the additional period for which that obligation will be in force, and avoid clauses that do not establish a definite duration (e.g. "... until the know-how becomes part of the public domain").

Legislation on transfer of technology existing in some developing countries tend to limit such a duration to the term of the agreement or to a reasonable period thereafter. 12/

Whenever a continuous flow of new technology or improvements is expected to take place over the agreed term of the agreement, the expiration of the confidentiality obligation at the same time than the agreement may disincentivate the communication of developments obtained when the contract is about to expire. For this situation, a determined period of confidentiality after the last delivery of information may be provided for.

5.c.3. Anticipated termination

In the event of anticipated termination of the agreement, conflicting views may arise as to the continuation of the confidentiality obligation and the term therefor. It would be advisable to specifically provide for the solution applicable in this situation, in order to prevent likely disputes between the parties.

These issues are dealt with in section 11 "Rescission".

12/ See UNIDO, Preparation of guidelines. Background paper, ID/WG.331/3, August 1980, chapter 11.2.

Specimen clauses

5.c. Confidentiality

1. The Licensee will, upon the terms set out below, keep confidential all technical information 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, shall require his employees to give written undertakings not to disclose the information referred to in this clause.

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, provided that an undertaking preventing disclosure of the relevant information is obtained from such third parties;

(ii) to governmental authorities to the extent required for approval or registration of the contract or products.

3. The obligation of confidentiality set forth in article 1 above will extend .....

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

(Alternative b: for ..... from the date of the last delivery of secret information.)

(Alternative c: for a period of ..... after the expiration of the contract.)

4. The obligation provided for in this article will cease at any time before the date specified in 3 above when the relevant information has become publicly known independently of the Licensee.

6. Time schedule

Under the contract considered here, the main dates to be dealt with are the following:

(a) Date for the provision by the Licensee of basic information for preparation of design data, by the Licensor;

(b) Date of delivery of design data and engineering by the Licensor;

(c) Date of delivery of documentation on know-how;

(d) Date of demonstration at the Licensor's plant;

(e) Date of certification and of performance guarantee tests;

(f) Date of issuance of performance bank guarantees;

(g) Date of opening of letter of credit by the Licensee;

(h) Date of instalments or other payments.

Of course, the dates indicated above are in some cases interlinked, for instance, when the issuance of a performance bank guarantee is to be made against an advance payment, or instalments against fulfilment of (b), (c) or (d).

Further, the contract may provide penalties for delays in appropriate compliance with the main obligations of the parties. The usual form of doing so is to stipulate liquidated damages, e.g. the Licensor may be bound to pay a certain amount per day or week of delay as regards to obligations indicated in (c) or (e) above.

Specimen clauses

6. Time schedule

1. The parties will timely perform their obligations under this contract in accordance with the terms specifically provided for therein.

2. In case of delay by the Licensor to (i) deliver the technical information, design and engineering, or (ii) undertake the performance tests run, by reasons attributable to the Licensor, it will pay the Licensee the following liquidated damages:

(a) Up to a maximum delay of ..... weeks, nihil;

(b) For delays exceeding ..... weeks, ... (currency) per full week.

3. The Licensee will, at its option, deduct the amount of the liquidated damages stipulated above from any payments due to the Licensor, or obtain its payment against the bank guarantee issued in conformity with article ..... (" bank guarantee").

7. Guarantees

7.a. Suitability for use

Guarantees described in this section and in section 8 below are of particular importance when no, or very weak performance, guarantees have been provided for. When appropriate provisions on the latter exist, they practically cover any consequence that may be dealt with under the former.

Under the guarantee considered here, the Licensor should secure that the technology transferred, if used in accordance with his instructions, is suitable for manufacturing the drug as agreed upon by the parties. A narrower variation of this clause may state that the guarantee only applies, for instance, if the technology is used as specifically indicated by the transferor, under the same conditions, with the same intermediates and other materials used by the Licensor at a specified time.

Specimen clauses

7.a. Suitability for use

The Licensor guarantees that the patents, technical information and other data transferred under this contract are suitable for manufacturing of the drug as stipulated herein, if used .....

(Alternative a: In accordance with the Licensor's specific instructions given pursuant to the contract.)

(Alternative b: under the same conditions, and with the same intermediaries and other materials as used by the Licensor at Licensor's plant at the time of signing of this contract.)

7.b. Correctness and completeness of documentation

An essential obligation of the Licensor is to fully and correctly communicate to the Licensee the information necessary for an actual transfer of the technology, as required for the fulfilment of the contract's objectives. While this guarantee may also be deemed as implicit in many instances, the drafting of an express provision thereon may help for an appropriate interpretation and execution of the contract.

Specimen clauses

7.b. Correctness and completeness of documentation

1. All the documentation to be supplied by the Licensor under the terms of this contract, will be correct and complete. In the event that documents supplied are incomplete or inaccurate, or have to be completed or modified, the date of delivery of the documents will be deemed the date on which such completion of modifications are supplied by the Licensor.

7.c. Performance guarantees

7.c.1. General

The negotiation of performance guarantees in licensing agreements faces one major difficulty: the Licensor is not generally responsible for the construction or adaptation of the Licensee's plant and, hence, does not guarantee the mechanical or electrical performances thereof. Moreover, differences in raw materials and utilities, and in other conditions under which the technology is to be applied, may result in deviations from the yields obtained by the Licensor at his own facilities.

7.c.2. Demonstration at Licensor's plant

The negotiation of such guarantees in agreements for the manufacture of bulk drugs may include a performance demonstration at the Licensor's own plant, at a pilot scale. The satisfactory completion of these tests will be important for the training of the Licensee's deputed personnel and to prove the suitability of the Licensor's technology for achieving the specified parameters.

7.c.3. Certification

In the case considered in this document, the Licensor supplies design and basic engineering which, duly applied by the Licensee, should permit a satisfactory process performance. As a rule, the Licensor will not assume, however, any performance guarantee without ensuring that the conditions required for the proper use of his know-how have been met. It is advisable to require the Licensor to certify, in appropriate time, the fulfilment of such conditions.

The guarantee by the Licensor can be performed once the plant is mechanically completed. The completion certificate is signed by the Licensee and the representative of the Licensor, and eventually by the (engineering) contractor. The construction and erection takes 1-3 years depending upon the size of the plant. During this period, both training of the Licensee personnel as well as submission of technological documents (operational manuals) are prepared and submitted by the Licensor. During mechanical check-up, the final water trials are taken to check that there are no leakages and the equipment including piping can stand the desired

pressure and achieve desired temperature required by the operation. Sometimes, defects pertaining to welding and some of steel joints left inside the pipe or equipment by mistake comes out during the water trial and rectified. Similarly, the instruments are tested to give the desired performance during operation.

7.c.4. Specification of guaranteed parameters

The Licensee should carefully assess and determine which parameters are critical to him and their priority. They should include raw materials consumption rated production capacity per annum, utilities consumption and quality of the products. The failure to meet the selected parameters may have very different consequences, in terms of losses of profit. 13/

7.c.5. Extent of guarantees

The effects of failure to meet guaranteed parameters will usually depend upon the extent of such a failure. As a general principle, the main Licensor's obligation in that case is to make, at his own cost, the rectifications necessary for attaining the predetermined results. If the deviation is important, and the Licensor is not able or willing to do it, the Licensee should be authorized to undertake the rectification at the Licensor's expense. If, however, the deviation does not exceed a certain tolerable percentage (e.g. up to 5 per cent loss of production), the contract may provide for liquidated damages.

7.c.6. Demonstration

The fulfilment or not of Licensor's obligations is to be determined through a demonstration carried out at the specified plant. The contract (or the annexes thereto, where pertinent) should specify:

(a) The term within which the performance tests should be undertaken. If by reasons not attributable to the Licensor the tests are excessively delayed, he may be released from his obligations on this point;

(b) The duration of tests run or the number of operations to be undertaken, e.g. ten consecutive batches;

(c) The conditions of tests run as regards to the supply of raw materials and utilities, which should be in the quantities and qualities specified by the Licensor;

13/ Thus, the Licensee may request absolute guarantees with respect to raw materials consumption and quality of the product - and be more flexible with regard to other parameters.

(d) The disposal of the Licensee's trained personnel, who should operate the plant under the direction of the Licensor;

(e) The recording of operating data and results by authorized representatives of the parties;

(f) The methods of analysis and the procedures to be followed for determining the results. In the case of contracts considered here the average results may be calculated by excluding the two best and the two worst batches. Besides, the average should exclude those batches showing abnormality due to mechanical troubles, utilities breakdown or other deviations which are not under the control nor are guaranteed by the Licensor;

(g) The preparation and signature of the performance test report and the issuance of the acceptance certificate by the Licensee.

Though the rated capacity is based upon annual production, it is neither desirable nor practically possible to keep the Licensor's expert for one year to have this guarantee. There is general practice to run the plant for the first three months, known as trial runs, during which the raw materials behaviour, analytical procedure and training of the Licensee's operating and maintenance staff is carried out. The performance guarantees are taken under the stabilized conditions. In case of plants having continuous nature of product, it is customary that plant performance after stabilization is carried out for one week and rated capacity per annum is determined as follows:

$$\frac{\text{Production during 7 days}}{7} \times 330$$

In a year, 330 days are considered as working days whereas the rest of the period is meant for maintenance. There is also prevailing practice to take 300 days instead of 330 working days per annum as far as rated capacity is concerned. This has to be defined and agreed initially.

In the case of batchwise operation, the performance is based upon results of ten consecutive batches. In the case of utility or raw material trouble beyond the Licensor's or Licensee's power, one could take up the results of 20 batches in which ten successful batches should be counted for performance trials. In the case both in continuous run of seven batches or ten batches either continuously or the result of ten batches in 20 batches is not successful, both the parties should try to find the reason for performance guarantee failures and take the measures to set the plant right to enable to carry out performance guarantee once again.

In the case of synthetic drugs, the process of production involves a large number of steps and it may take days to one or two months by the time the final product is obtained. In such cases, the over-all performance guarantee for batch has to be determined, but, in some cases, it could also be possible to take individual guarantees stepwise, as far as the quality and consumption coefficient of raw materials and utilities are concerned, but for the capacity determination of the plant, it is desirable that five batches should give continuously trouble-free operation. Regarding antibiotics plants, the fermentation step is very sensitive and due to contamination, the initial stabilization period is prolonged. The fermentation time, per batch varies from five to ten days depending upon the product. The performance at each stage has to be satisfied. However, the production capacity per annum is determined as follows:

11 x filling coefficient of the fermenter x yield in BU/m^3 broth/month

Keeping aside one month for maintenance in the year, 11 months are taken for capacity. In the case of photo-chemicals, the active ingredient of the vegetative drug may vary sometimes from batch to batch and hence average guarantee of ten batches should be calculated by giving due consideration for the initial content of the active material in the drug.

7.c.7. Rectification

As mentioned before, should the guarantee tests prove unsatisfactory, the Licensor is bound to effect the rectifications necessary in its judgement to correct the defects. The costs of such rectification are to be borne by the Licensor, and they should be completed within a reasonable time from the date of demonstration. The failure to comply with that term (which may be provided for in the contract or established by common consent of the parties after the tests) may give rise to liquidated damages, or entitle the Licensee to undertake the rectification at the Licensor's expense.

If the failure in performance tests is determined to be caused by incompetence of the personnel trained by the Licensor, he should be bound - except if he can prove that he is not responsible for that incompetence - to extend the training for a reasonable period, as necessary for completing the personnel's formation.

In a situation where the failure is attributable to the Licensee, it will bear the costs of rectifications and the Licensor will be normally required to advise and approve the necessary changes.

In any case, a second performance test run should take place, in order to relieve the Licensor from his obligations in this respect, or eventually make it effective its liability for non-compliance with the guarantee clauses.

7.c.8. Liquidated damages

Liquidated damages often serve as a compensation for loss suffered as well as a penalty in order to coerce the Licensor to perform. In general, liquidated damages - as an accessory obligation - will be a substitute for performance, and will not be accumulatively enforced with the latter. Thus, they may constitute all compensation received by the Licensee for default to attain certain expected results.

The payment of liquidated damages for non-performance [14/] may take place through reduction of the fee due to the Licensor, or against the bank guarantee issued in favour of the Licensee.

In the sphere of pharmaceutical industry, mostly the Licensor is himself the manufacturer of the product, and the failure of guarantee performance fulfilment are rare. However, in the case of eventual failures, the liabilities likely to be obtained is forfeiture of the final payment which varies between 10-20 per cent of total know-how charges in the case of lump-sum fees.

7.c.9. Premium

Sometimes, and according to a tradition, a premium is stipulated for the case where a yield higher than guaranteed is achieved. In the case of antibiotics, a certain amount could be agreed for higher B.O.U. per cubic meter per month. In the production of synthetic drugs, the premium could reach, for instance, up to 20 per cent of saving in consumption of raw materials effected as compared to guaranteed figures.

14/ Liquidated damages are also considered in this document, with regard to delays in performance. See section 6 above.

Specimen clauses

7.c. Performance guarantees

Guaranteed parameters

1. Subject to the following provisions, the Licensor guarantees that the process, properly used as stipulated in this contract, is able to reach the following performance parameters:

(a) The production capacity of the plant confirm to ..... kg per batch ..... tonnes per annum;

(b) The quality of the product meets the requirements of pharmacopoeia;

(c) The raw material consumption conforms to Appendix ... (see Appendix VIII);

(d) Utility consumption will be as follows:

(a)	Electric power	:	Kw hours
(b)	Water at 32° C	:	Cubic metre
(c)	Chilled water	:	Cubic metre
(d)	Brine (liquid nitrogen)	:	Cubic metre
(e)	Steam	:	Tonnes, pressure (kg/cm^2)
(f)	Inert gas	:	Nm^3 and pressure (kg/cm^2)
(g)	Air (in case of antibiotics plant)	:	Cubic metre - Nm^3 and operating pressure (kg/cm^2)

The plant capacity will be designed for a minimum of one year less usual holidays including Sundays and a period of one month for maintenance operation, 15/ provided that:

(a) Annual maintenance is carried out in accordance with the Licensor's recommended maintenance schedule;

(b) A sufficient number of qualified and experienced personnel are available to manage, operate and maintain the plant;

(c) All tools, spares, equipment, materials and samples are available in accordance with the Licensor's recommendations;

15/ This period will not apply for antibiotic plants or continuous operations.

(d) Utilities, raw materials and chemicals of specified quality and quantity are continuously available;

(e) The plant is operated in accordance with the operating instructions of the Licensor and under operating conditions no more severe than those contemplated in the Licensor's technical information;

(f) No unscheduled shut-down of the plant occurs due to the existence of force majeure conditions.

Demonstration at Licensor's plant

2. In order to demonstrate the guaranteed parameters the Licensor will undertake test runs at the Licensor's plant, ...

(Alternative a: with a working volume of .....)

(Alternative b: using ..... reactor/fermentaters each of ..... capacity.)

3. The demonstration will .....

(Alternative a: consist of ..... consecutive batches. For purposes of calculating the average in the demonstration, the two best and the two worst out of the ..... aforesaid batches will not be taken into account.)

(Alternative b: take place for a period of ..... working days. The guarantee clause will be deemed fulfilled if at least ..... per cent of the batches produced during that period comply with the guaranteed parameters.)

In the evaluation of results the batches showing abnormality due to mechanical troubles, sterility defects, utilities breakdown and any other manifest deviation from prescribed parameters will be excluded from the total.

4. The demonstration will take place after ..... days but not later than ..... days from the effective date of the contract. The demonstration will be attended by the following personnel of the Licensee ..
.....

5. At the end of the test runs the authorized representatives of the parties will sign a statement on the results obtained.

Performance guarantee tests at Licensee's plant

6. The Licensee will complete the erection and adaptation of the plant for production of the drug within ..... months from the effective date of the contract.

(Alternative a: Upon written notice of the Licensee on the completion of the plant, and within ..... days therefrom, the Licensor will certify whether the conditions required for the proper use of the process have been met. The performance guarantee test will take place not later than ..... days after certification.)

(Alternative b:

(i) The Licensee's plant will be mechanically complete when construction and erection has been completed, other than in any minor respect which does not prevent its mechanical functioning, and a first batch of the product has been successfully produced at the plant.

(ii) The Licensor shall designate its technicians for the purpose of supervising and assisting in the conducting of the test by the Licensee and verifying the mechanical completion of the plant as referred to in (i) above. If on conducting the test referred to therein, the Licensee's plant is not found to be mechanically complete, such Licensor's technicians will submit a report to the Licensee stating therein in detail corrections required in the plant in accordance with the Licensor's technical know-how. Such corrections will be carried out by the Licensee with the advice and assistance of such Licensor's technicians. After such corrections have been carried out, the test referred to in (i) above will be repeated and if successful, the plant will be deemed to be mechanically complete.

(iii) Immediately after mechanical completion, the Licensee's plant will be started up by feeding raw materials by the Licencee's personnel under the supervision and assistance of the Licensor's technicians and will be operated thereafter for a period of ..... months. After this start-up period, the performance test run will be carried out.)

7. If the start up of the Licensee's plant cannot take place within ..... months from the effective date of the contract, and except if the delay is due to the Licensor's fault, the Licensor will be released from its obligations concerning the performance guarantees.

8. The Licensor guarantees that the Licensee's plant will meet the performance guarantees as listed in 1 above provided that:

(a) The plant has been designed and adapted in accordance with the technical information, design and engineering data supplied by the Licensor, as certified by the Licensor in accordance with point 6 above;

(b) There is an adequate supply of raw materials, in conformity with the specifications provided by the Licensor, and of utilities;

(c) The Licensee provides the number of trained personnel for operating the plant under the direction of the Licensor's personnel.

9. The performance guarantee tests will be carried out and evaluated as specified in 3 above.

The detailed methods of analysis and procedure of execution of the performance test runs will be mutually agreed before the commencement of the test runs. Instrument tolerance for the performance of test runs will be as given by the supplier of the equipment. Where instruments are to be used for measurements, they shall be calibrated before commencement of test and if considered to be inadequate, the instrument inaccuracies established. For the purpose of testing the quality of the product, the product produced during performance test runs shall be tested at the plant's analytical laboratory and failing which at such other approved laboratories as may be mutually agreed upon.

10. During the performance test run the authorized representatives of the parties will jointly ascertain and record the operating data and results. Should such results conform to the guaranteed parameters .....

(Alternative a: The representatives of the parties will sign a statement indicating such results.)

(Alternative b: The Licensee will issue to the Licensor an Acceptance Certificate within ..... days from the end of the test run), and the Licensor's obligation under this section will be held as fulfilled.

Rectifications

11. Should the performance test run fail to conform to the guaranteed parameters by reasons attributable to the Licensor, the Licensor will, at its own expense, proceed to effect the rectifications necessary to achieve such parameters, provided that such changes do not substantially modify the basic layout or schedule of operations.

Should the performance test run fail to conform to the guaranteed parameters by reasons attributable to the Licensee, the Licensee will effect, at its own expense, the required rectifications with the advice and approval of the Licensor.

(Alternative a: The parties will determine a mutually agreeable schedule to incorporate such changes and the date for the second performance test run.)

(Alternative b: The rectifications will be made within ..... from the end of the performance test run. A second performance test run will start the last day of that period.)

Liquidated damages

13. If the Licensor neglects or refuses to take measures in due time to rectify the defects as identified on the basis of the first performance test run, or if the guaranteed parameters are not demonstrated after the second test run by reasons attributable to the Licensor, the Licensee will have the right to carry out, at the Licensor's expense, the required rectifications, except if the results obtained satisfy at least the following:

(a) Production capacity .....
.....

(b) Quality of the drug .....

(c) Raw materials consumption .....
.....

(d) .....

If such minimum parameters are met, the Licensor will pay to the Licensee by way of compensation an amount of:

(a) ..... per cent for every ..... per cent or fraction of ..... per cent of deficiency in production capacity;

(b) ..... per cent for every ..... per cent or fraction of ..... per cent of deficiency in quality;

(c) ..... per cent for every ..... per cent or fraction of ..... per cent of the excess in consumption of .....

(d) .....
.....

14. The Licensee will, at its option, deduct the amount of the liquidated damages stipulated above from any payments due to the Licensor, or obtain its payment against the performance bank guarantee issued in conformity with article ..... ("Bank guarantees").

15. The payment of such liquidated damages will relieve the Licensor only from those specific obligations for which the liquidated damages are provided for.

16. (Alternative a: For every ...../m^3/month over the guaranteed yield as defined in ....., the Licensee will pay to the Licensor a premium of .....)

(Alternative b: The Licensee will pay to the Licensor, as a premium, in case that the raw material consumption is at least ..... per cent lower than the guaranteed figures ..... per ..... per cent of saving below that percentage.)

7.d. Bank guarantees

The Licensee's security requirements as regards the fulfilment of the Licensor's obligations may be satisfied through the stipulation of first or simple demand bank guarantees. They may include:

(a) Guarantees for advance payment, if any;

(b) Performance guarantees.

Under this type of guarantee the guarantor - generally a bank or an insurance company - undertakes to pay the Licensee up to the guarantee's amount upon the simple request of the Licensee, and without being entitled to enquire whether the payment is lawfully asked for or not. In some cases, the Licensee may require that the guarantee be granted by a bank of the Licensee's country with the counter-guarantee of the Licensor's bank.

The amount and term of validity of performance bank guarantees generally are the main issues of discussion and negotiation. The first aspect will be usually determined as a percentage of the contract value, or of the lump sum agreed upon. It may also be determined on the basis of the liability assumed by the Licensor (see section 8 below).

The term of validity of guarantees may be indefinite, or extendable upon the simple request of the beneficiary. Another possibility is to determine a date of expiry, for instance, after x months from the satisfactory fulfilment of performance guarantee tests. The contract may also specify that the guarantee be released at the date on which certain events occur, for instance, as follows:

(i) 20 per cent at the effective date of the contract, against simple receipt;

(ii) 30 per cent on the date on which the delivery of documents will be completed against receipt issued by the Licensee's representative;

(iii) 20 per cent on the date of process demonstration at the plant of the Licensor will meet the guaranteed yield, against a statement signed by both parties;

(iv) 10 per cent on the date of the Licensee's plant commissioning, but not later than ..... months from the effective date of the contract;

(v) 20 per cent on the date at which operating guarantees are fulfilled at the Licensee's plant against the statement signed by both parties.

Specimen clauses

7.d. Bank guarantees

1. The Licensor will provide the Licensee the following first demand bank guarantees issued by (name of the bank) and confirmed in (Licensee's country):

(i) A bank guarantee to secure the advance payment made under this contract, upon receipt of that payment. The amount of this guarantee will be released upon delivery of the documentation on technical information, design and engineering;

(ii) A performance bank guarantee, on receipt of payment for delivery of documentation on technical information, design and engineering, for an amount equal .....

(Alternative a: (to the Licensor's liability in accordance with article ..... ("Liability and insurances")).

(Alternative b: to the ..... per cent of the total lump sum due under article ..... ("Remuneration")).

2. The guarantee stipulated in 1.(ii) above will remain in force .....

(Alternative a: for ..... months from the effective date of the agreement, and will be extendable, upon request by the Licensee, for additional periods of ..... months.)

(Alternative b: until the satisfactory fulfilment of performance guarantees as stipulated in the contract.)

8. Liability - Insurances

8.1. General

The negotiation of Licensor's liabilities faces two clearly differing views from the parties. The Licensee may desire, particularly in contracts involving important investments and relatively new processes, to obtain the maximum coverage as regards eventual losses or damages. The Licensor, on his side, may try to limit his liabilities as far as possible. It has been observed that, in general, the maximum the Licensor can be expected to risk would be his profit on the direct licensing operation. 16/

In considering liability and its eventual limitation or exoneration, due attention should be paid to the ordre public rules that may be imposed by the applicable law.

Among the different solutions available, including the absence of express contractual clauses on the matter, a flexible approach may consist of considering different relevant hypothesis and defining their particular treatment.

8.2. Relevant hypothesis

(a) Injury or damage to persons or property

A negligent act or omission by any of the parties, such as the communication of defective design to the Licensee, may result in damages to property or injury to persons.

At least part of these risks may normally be covered by an insurance policy, the obtention and maintenance of which should be the Licensor's responsibility.

(b) Patent infringement

As indicated above (section 3.b.) the Licensor should indemnify and hold harmless the Licensee from any infringement by the latter of third parties' patent rights when using the technology transferred.

(c) Failure to fulfil guarantees

The first and primary Licensor's obligation when guarantee test runs have failed is to introduce, at its own expense, the rectifications necessary for attaining the guaranteed parameters. In some contracts, liquidated

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16/ See UNIDO, Guidelines for evaluation ..., op. cit. p. 24.

damages for such defaults are provided for. Otherwise a general liability clause may apply if the Licensor is unable or unwilling to undertake, within a reasonable period, the required changes. In this context, some Licensors insist that the overall liability should be limited to a part of the fees.

(d) Delay in performing the main obligations

Remedies for delays in fulfilment of the main contractual obligations may include liquidated damages or other forms of liability, such as the other party's right to recover any loss suffered by reason of that failure.

8.3. Limitation of liability

8.3.1. Indirect damages and loss of profit

Licensor's position is usually to exclude liability as regards to certain damages as well as to limit its total responsibility to a maximum amount or percentage of the price (or part thereof) agreed upon in the contract.

As a rule, the Licensor will be reluctant to admit any liability that does not emerge from direct damages. Thus he may insist in excluding indirect or consequential losses and losses of anticipated profits arising from any cause. It would be possible, however, to make the Licensor liable therefor when such damages are caused by gross misconduct.

8.3.2. Limited amount or percentage

The setting of a maximum liability is common practice in international contracts. It may be established as an overall liability, for all damages or losses attributable to the Licensor eventually arising from the contract's execution. Another possibility is to discriminate such items where the Licensor undertakes unlimited liability from those which might be payable as long as they do not exceed the maximum amount or percentage agreed upon.

Thus, unlimited liability might be established for some of the hypotheses mentioned in 8.2. above, such as items (b) and (c).

In cases of damages or losses covered by insurance policies taken out by the Licensor, he may discharge - partially or totally - his obligation by reimbursing to the Licensee any amount received under such policies.

8.4. Insurance policies

In addition to the insurance policy referred to in 8.2.(a) the parties may be required by contract to take out some other policies and to keep them in force during the lifetime of the agreement or, eventually, until the

satisfactory completion of training, technical assistance, and tests run as provided for in the contract.

The parties should prove, within a reasonable period from the effective date of the agreement - or from the commencement of the relevant task - and thereafter once a year, that said insurances have been taken out and remain in force.

The policies that should be taken out by the Licensor may include risks arising out of errors or omissions in design, as well as those connected with the activities of the Licensor's personnel deputed to the Licensee's plant. On its side, the Licensee should cover injuries or damages occasioned by its personnel being trained at the Licensor's plant.

Specimen clauses

8. Liability and insurances

1. The Licensor and the Licensee will indemnify and hold harmless each other from and against any claims, action, losses, expenses or proceedings made for personal injuries or death, including of the other party's personnel or for damages to property of the other party, or of third parties, arising out or occasioned by the negligent act or omission of the Licensor or of the Licensee (as the case may be), in connection with this Contract.

2. Each of the parties will take out and maintain in force insurance policies to cover the risks referred to above, and will deliver each other, within ..... from the Effective Date of the Contract, and thereafter annually copy of such policies and their renewals.

3. The policies at the Licensee's charge will include coverage against any injury or damage derived to persons or property, including Licensor's personnel and property, through acts or omissions of the Licensee's personnel being trained at the Licensor's plant.

4. The policies at the Licensor's charge will also cover:

(a) Risks arising out of any error, omission or negligence in design or in the information or documentation transferred in accordance with this Contract;

(b) Insurance liability for the Licensor's personnel deputed to the Licensee's plant.

5. Licensor's total liabilities under this Contract will be limited to .....

(Alternative a: ..... per cent of the total lump sum mentioned in article ..... ("Remuneration")).

(Alternative b: an amount of ....., except as regards to the following, where the liability will be unlimited;

(i) Liabilities for patent infringement; and

(ii) Liabilities for rectification or modifications for the fulfilment of minimum guaranteed parameters.).

6. The Licensor will not be liable for loss of anticipated profits or for any consequential loss or damage arising from any cause.

9. Duration

9.a. Effective date of the agreement

The effective date of the agreement is the date defined by the parties as the initial point in time for some or all terms agreed upon in the Contract. That date may coincide with the date of execution (signing) or be determined by the date upon which the last of some other events occur, such as:

(a) The approval of the contract by the authorities of the Licensor's or Licensee's country;

(b) The remittance of an advance payment by the Licensee.

Specimen clause

9.a. Effective date of the Contract

1. The Contract will become valid upon its formal signing by duly authorized representatives of the parties, in accordance with the applicable law.

2. The Effective Date of the Contract will be the date upon which the last of the following requirements, as appropriate, has been met:

(a) Approval of the Contract by the government of (Licensee's country);

(b) Approval of the Contract by the government of (Licensor's country);

(c) Remittance of the advance payment by the Licensee as provided in article .... ("Remuneration") against issuance of the Bank Guarantee provided by the Licensor in article .... ("Bank guarantees").

9.b. Term of the contract

Wherever the Licensor is basically remunerated by means of a lump sum, the term of the contract will mainly depend upon the time necessary for the erection of the plant, the training of Licensee's personnel and the provision of technical assistance. However, if the contract includes patents or technical knowledge subject to confidentiality obligations, the parties may be interested in establishing a longer duration. This would satisfy, on the one side, the Licensee's likely interest in retaining the licence of the patents as long as possible and the Licensor's concern about the disclosure of its secret know-how.

If the Licensor is remunerated by means of royalties the duration of the contract has a direct relationship with the cost, for the Licensee, of the technology transfer. In any case, five years would seem to be a reasonable period for both parties.

Specimen clause

9.b. Term of the contract

The duration of the Contract will be for ..... years from the Effective Date.

9.c. Effects of termination

The effects of the normal termination of the agreement on the use of the technology transferred is often a very hard issue in negotiations.

As a rule, the contract should not restrict the use of technology after the contract's expiration. Instead, it should permit the Licensee to continue the production and sale of drugs, that may be essential for the satisfaction of local therapeutical needs.

As indicated in a former document, [17/] clauses dealing with this matter must, however, differentiate between patented and unpatented technology.

9.c.1. Patented technology

In the first case, the patent holder is generally recognized the right to exclude any unauthorized use of the protected invention, including by the Licensee, once the contract has expired. Two possible alternatives may be envisaged to avoid the interruption of production:

(a) To ensure that the payments made for the patent licences during the lifetime of the agreement will also constitute compensation till the expiry of the patent and that the Licensee will be free to use it after the contract's expiration;

(b) To contemplate the right of the Licensee to continue in the use of the patent after the contract's expiration, against payment of a royalty, preferably at a reduced rate.

Under the first a ternative, the Licensee assumes the risks of an eventual invalidation of the patents, or a loss of its commercial or industrial worth. The second alternative gives the Licensee the right to continue in the use of the patent if he so desires, under the sole condition of paying the applicable royalties. As to the rate and form of payment of the latter, two main alternatives also exist: they may be

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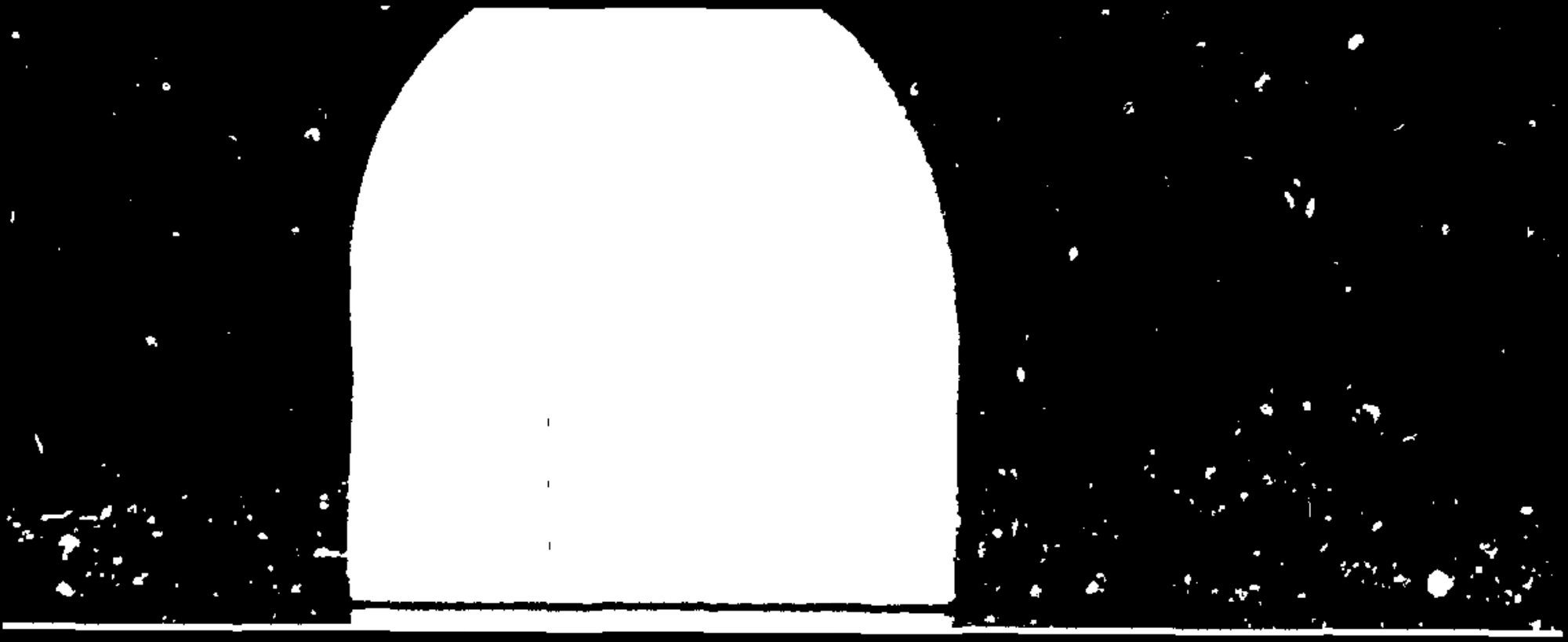
17/ UNIDO, ID/WG.331/3, op. cit. p. 18. This document reviews the different legal solutions given or proposed for the issue at stake in developed and developing countries, and at the international level.



(i) Determined in the original contract;

(ii) Left to the negotiation after the expiration of the original contract, but subject to predetermined conditions, for instance, that the royalties or fee should not be more than 50 per cent of the original royalty rate or fee provided for.

This latter possibility may permit an evaluation, in proper time, of the economic and technical circumstances prevailing at the moment of the contract's expiry. In particular, if several patents have been licensed and some have elapsed, the Licensee may assess the actual value of patents still in force, and negotiate a reasonable readjustment of payment obligations.

9.c.2. Unpatented technology

The Licensor has no exclusive right - unlike the case of patents - to exclude third parties' use of know-how or to prevent the Licensee from continuing in its use after the contract's expiration. Whatever the legal nature of know-how may be deemed to be in accordance with the applicable law, the contract should not contain restrictions or additional payments for the use of unpatented technology once the contract has expired.

If this solution - strictly consistent with the legal position that denies the existence of property rights over know-how - encounters opposition by the potential Licensor, a compromise may eventually be based on the recognition of the Licensee's right to continue in the use of secret know-how after the contract's expiry, but against a payment, at a reduced rate, and for a reasonable period, for instance, not exceeding three years.

The right to use the know-how, as expressed, should be interpreted as including the possibility to pass on the technology to a third party, under the condition that the receiver undertake the obligation to keep secret the information for the remaining duration of Licensee's obligation.

9.c.3. Confidentiality obligations

See on this point, section 5.c. above.

Specimen clause

9.c. Effects of termination

1. The Licensee will have the right to continue in the use of the Process transferred, after the expiration of the Contract in accordance with article ..... ("Duration"), ...

(Alternative a: including the use of all technical information and Patents licensed thereunder).

(Alternative b: provided that, if a substantial part of the Process were still covered by Patents in force after that date, the Licensee will have the right to continue in their use against payment to the Licensor of a reasonable fee or royalty, to be agreed upon by the parties, which will be at least ..... per cent less than the fee or royalty stipulated in this Contract for the license of such Patents).

10. 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 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 should normally include:

(a) Definition of exonerating circumstances;

(b) Enumeration of contingencies that may be comprised in the definition, such as, force of nature (acts of God), acts of war (whether declared or not), strike, lock-out, governmental order or regulation, etc.;

(c) Notification of the occurrence of such circumstances in a given form and delay (and of their termination);

(d) Proof to be supplied;

(e) Effects of the force majeure:

(i) Exclusion of responsibility for non-performance;

(ii) Suspension of execution (eventually extension of contractual terms during the period of prevention);

(iii) Renegotiation, rescission or submission to arbitration.

Specimen clauses

10. Exoneration

1. In this Contract, force majeure will be deemed to be any cause beyond the reasonable control of the Licensor or the Licensee (as the case may be) which prevents, impedes or delays the due performance of the Contract by the obligated party and which, by due diligence, the affected party is unable to control, despite the making of all reasonable efforts to overcome the delay, impediment or cause. Force majeure may include, but will not be limited to any one or other of the following:

- any war or hostilities;
- any riot or civil commotion;
- any earthquake, flood, tempest, lightning, unusual weather or other natural physical disaster. Impossibility in the use of any railway, port, airport, shipping service or other means of transportation or communication (occurring concurrently);
- any accident, fire or explosion;
- any strike, lock-out or concerted acts of workmen (except where it is within the power of the party invoking the force majeure to prevent);
- shortage or unavailability of materials (compounded by the same shortage or unavailability from alternate sources).

2. If either party is prevented or delayed in the performance of any of its obligations under this Contract by circumstances of force majeure, and if the affected party has given written notice thereof to the other party within 15 days of the happening of such event, specifying the details constituting force majeure, with necessary evidence that a contractual obligation is thereby prevented or delayed, and that the estimated period during which such prevention, interruption or delay may continue, then the affected or obligated party shall be excused from the performance or punctual performance of such obligation as from the date of such notice for so long as may be justified. The termination of the force majeure will similarly be notified.

3. The Licensor or the Licensee (as the case may be) will be diligent in endeavouring to prevent or remove the cause of force majeure. Either party upon receipt of the notice of force majeure under 2 above, will confer promptly with the other and agree upon a course of action to remove or alleviate such cause(s), and will seek reasonable alternative methods of achieving the same performance objectives under the Contract.

4. If by virtue of clause 2 above either of the parties is excused from the performance or punctual performance of any obligation for a continuous period of ..... months, then the parties will consult together to seek agreement as to the required action that should be taken in the circumstances and as to the necessary amendments that should be made to the terms of the Contract.

5. 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 ..... ("Settlement of disputes").

11. Rescission

11.1. Grounds for rescission

In the context of the licensing agreement considered in this document, there are some circumstances which may allow the parties to terminate the Contract (patent infringement which substantially impairs the use of the technology; continuation of events constituting force majeure).

There are of course other circumstances which may justify such a decision. Without prejudice to the particular provisions referred to, a general clause may stipulate that either party may, upon appropriate notice and in accordance with the applicable law of the contract, terminate the agreement if the other party has failed to fulfil its obligations under the agreement provided that such default has continued unremedied for a certain period after such notice.

11.2. Effects of rescission

The major issue of consideration connected with the clauses dealt with here is the consequences of termination on the use of patents licensed and transferred know-how, and on confidentiality obligations. Any solution on these points should take into account, firstly, which party is in default, and secondly, the degree to which the parties have performed their respective obligations.

In cases where the termination is based on Licensor's default, the Licensee may be recognized the right to continue in the use of the technology transferred.

It is more difficult to determine the applicable solution when the Licensee is in default, for instance for lack of payments. If he had made a substantial part thereof, it would be unfair to absolutely restrict the further use of the technology transferred. While establishing this principle, divergencies on its application may be left to a decision by arbitration or the competent courts.

Specimen clauses

11. Rescission

1. Without prejudice to any express clause for termination contained in this Contract, this Contract may be terminated by either party by written notice to the other party, for any cause sufficient to terminate the contract under the proper law of the contract, if the party in default has not remedied this fault within ..... from receipt of that notice.

2. In the event that the Licensor, in accordance with 1 above, terminates this Contract for reasons for which the Licensee is responsible, the Licensee will cease in the use of the technology transferred, unless it has substantially performed its payments obligations under this Contract.

3. In the event that the Licensee, in accordance with 1 above, terminates this Contract for reasons for which the Licensor is responsible, the Licensee will have the right to continue in the use of the technology transferred.

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

12. Assignment and sublicensing

12.1. Assignment

Licensing agreements are generally deemed to be of a personal nature (intuitu personae) and hence total or partial assignment by any of the parties is normally excluded, or subject to prior consent by the other party.

12.2. Sublicensing

In the developing countries, where the economic activities are fast growing and more of such production units are installed one after the other, migration of trained and experienced persons is a must. Under these circumstances strict confidentiality is debatable. Moreover, in case of bigger units, no investor would like to go for piecemeal information from individuals, but for composite technology. It will be in the interest of both Licensor and Licensee that Licensee can sublicense the process know-how.

In principle, the contract should establish the Licensee's right to sublicense to other parties the technology transferred. A vast number of variations may exist as to the conditions under which such right may be exercised.

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 (e.g. 20 per cent thereof).

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.

Specimen clauses

12. Assignment and sublicensing

Assignment

1. (Alternative a: This contract is not assignable; .....)
(Alternative b: Unless with the prior 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.

Sublicensing

2. (Alternative a: The Licensee will not grant sublicences without the written consent of the Licensor which will, however, not be unreasonably withheld).
(Alternative b: The Licensee may grant sublicences 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).

13. 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 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 of arbitration.

The pertinent clauses may also refer to the character of the arbitral award, and to the language of the proceedings. 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.

Specimen clauses

13. Applicable law and settlement of disputes

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 of (Licensor's or Licensee's country) which will be decided in accordance with the applicable law of that country).
(Alternative c: [18/] The arbitral tribunal will apply the proper law under the conflict of laws rules which it considers applicable).
(Alternative d: [18/] The arbitral tribunal will decide ex aequo et bono and according to public policy (ordre public) provisions of the countries of the parties).

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;

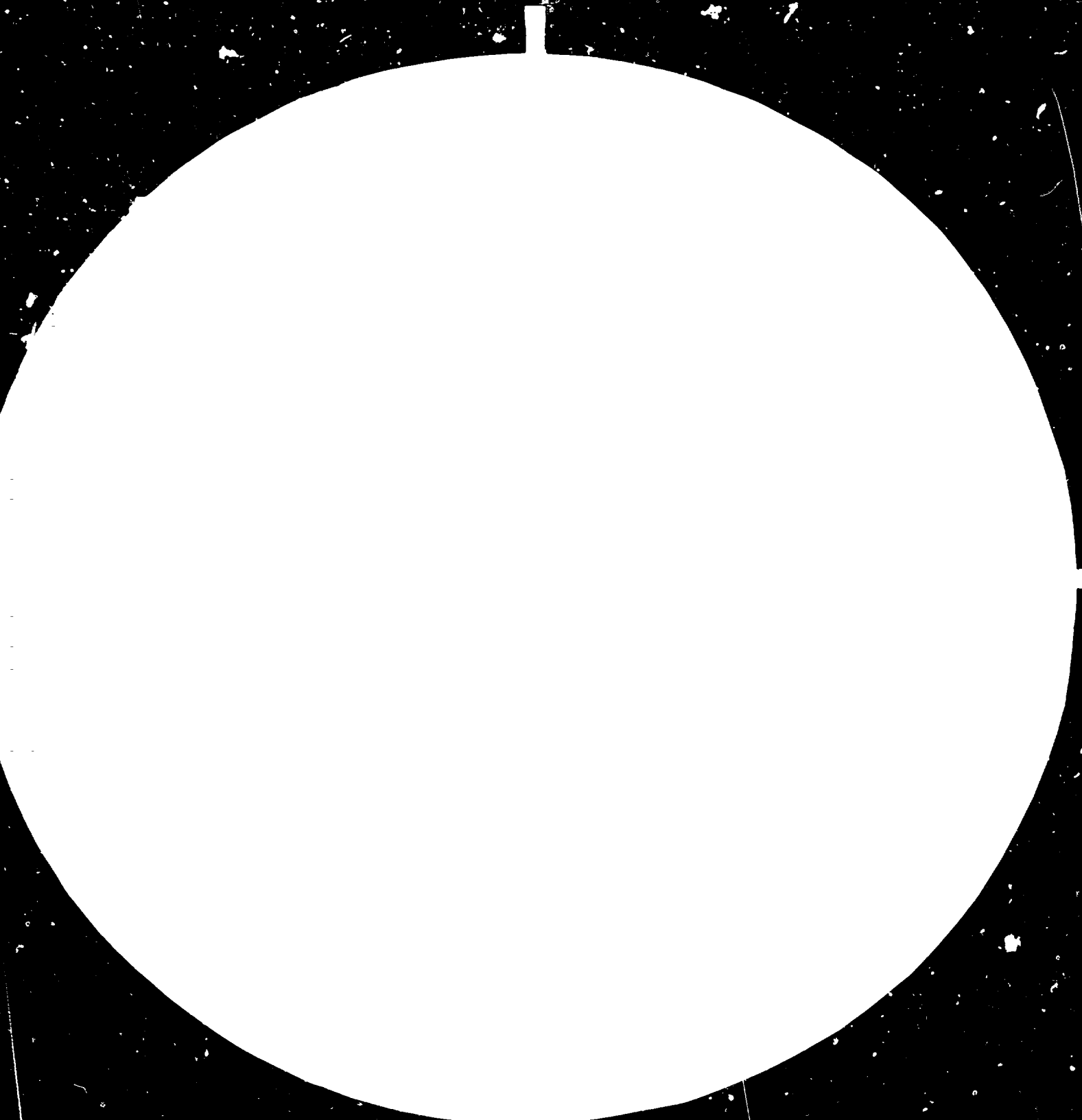
18/ These alternatives would apply in case that disputes are referred for decision to an arbitral tribunal.

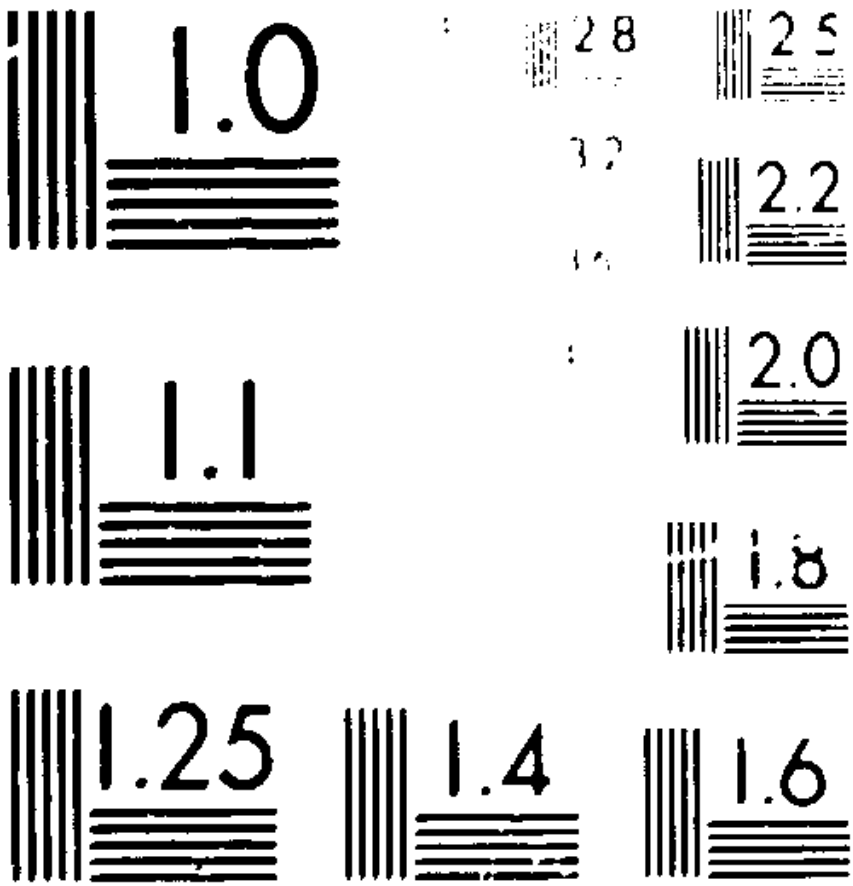
(iii) The award of the arbitrators will be final and binding on the parties hereto. Judgement upon the award may be entered by the court of (country);

(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)).

83.03.29

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Appendix I

PROCESS KNOW-HOW

I. AMPICILLIN TRIHYDRATE

Ampicillin trihydrate is manufactured synthetically from 6-amino penicillanic acid (6-APA), an intermediate which itself is produced from potassium penicillin-G either synthetically or by enzymatic process as detailed below:

PRODUCTION OF 6-APA

A. Enzymatic process

The process consists of two steps namely:

(i) Production of enzyme

(ii) Splitting of penicillin into 6-APA and phenyl acetic acid.

(i) Production of enzyme

The enzyme is produced by escherichia coli bacteria as shown in Fig. I schematic diagram annexure.

E-coli strain from the test tube is transferred into shake flask containing nutrient media under strictly controlled environmental conditions. Broth so obtained is used in three-stage fermentation using 100 L, 500 L vessels called inoculator and seed vessel are mini-fermenters and serves to produce requisite quantity of culture for mass fermentation in the industrial fermenter.

Corn steep liquor, ammonium sulphate and other nutrients are taken in the fermenter and pH adjusted with sodium hydroxide lye. After sterilizing the medium, E-coli culture (inoculum) produced in the seed vessel is transferred under sterile conditions. Fermentation is carried out under controlled conditions by sparging sterile air and addition of phenyl acetic acid, ammonium hydroxide, soyabean oil etc. under sterile conditions. The process is complete within 17-20 hours and broth so obtained is chilled,

filtered by means of high speed centrifuge. Enzyme activity contained within bacterial cell is stabilized with glutaroldehyde. The enzymatic catalyst so obtained is to be kept at low temperature and can be used up to 100 times with a mechanical handling loss of 3 per cent.

(ii) Splitting of penicillin into 6-APA

The splitting can be carried out either in a continuous manner using IMMOBILIZED ENZYME COLUMN Fig. II Block B. In this case, enzymes are stationery embedded on the surface of the glass fibre or polymide fibre nets packed in the column by special treatment. Penicillin solution is circulated and pH controlled till it is completely converted into 6-APA and phenyl acetic acid. An alternative process is shown in Fig. II Block A. The charge consisting of penicillin-G along with enzyme is taken in the reactor and water is added to make up the desired volume. The splitting is carried out at 37° C and pH around 7.6 by addition of ammonia water. The reaction is completed within 2-2.25 hours. The mass is chilled and sent to high speed centrifuge. The supernatant liquor containing 6-APA is collected and the bio-mass (enzymatic catalyst) recovered for re-use.

Separation of 6-APA and phenyl acetic acid

Fig. II Block B. 6-APA and phenyl acetic acid solution obtained either through immobilized column process or by batchwise process as supernatant liquor from centrifuge is mixed with butylacetate and the mass is chilled further from 10° C to 5° C. Sulphuric acid is added to bring down the pH to 4 when 6-APA crystallizes out and is centrifuged. The crystals are further suspended in water and acetone and centrifuged, thus getting first crop of crystals (84-86 per cent yield). Second crop amounting to 6-7 per cent is obtained from the mother liquor which is sent to the separator. Phenyl acetic acid in butyl acetate layer is removed and both are recovered. Butyl acetate layer is regenerated and recycled whereas phenyl acetic acid is used as raw material in the fermentation process. 6-APA in water mother liquor from separator is recovered and recycled after carrying the operation of concentration by the film evaporator or reverse osmosis.

B. Production of 6-APA by synthesis

In a reactor shown in Fig. III, potassium penicillin-G is converted into potassium benzyl penicillin dimethyl silyl ester with dimethyl dichloro

silane and mass is further treated with phosphorous penta-chloride to give imido-chloride derivative. This, on treatment with dimethylaniline gives imino derivatives which on hydrolisis gives 6-APA. The method involves low temperature (-50 to -55° C) and strict anhydrous conditions. 6-APA thus produced is isolated, purified, dried and packed.

PRODUCTION OF AMPICILLIN TRIHYDRATE

6-APA is reacted first with triethylamina to protect the free carboxylic acid group and then acylated with phenylglycine chloride hydrochloride. Ampicillin hydrochloride thus formed is isolated as naphthyl sulphonic acid salt and then converted to ampicillin trihydrate. The solvents methylene chloride, acetone and MIBK used in the process are recovered for re-use. In the alternate process, Dane's salt of phenylglycine chloride is used for introduction of side chain in 6-APA.

Suggestions

6-APA is an intermediate used also for the production of ammoxacillin, cloxacillin and dicloxacillin etc. The plant in case of ampicillin trihydrate is universal and can be used for the production of other semi-synthetic penicillins. It is recommended that the annual capacity of such unit should be 30 tonnes, which is economically viable.

II. TETRACYCLINE HYDROCHLORIDE

A mutant of streptomyces aurofaciens is used to produce tetracycline. The culture is transferred from flask to seed tank having sterilized media. This culture is obtained in the laboratory both by selecting and maintenance of the strain and shake-flask fermentation explained in appendix II. The time for seed cultivation in seed tank is 32-34 hours. The medium for fermenter is prepared and sterilized and inoculated with the culture from seed tank, Fig. II schematic diagram block. The content of tetracycline by the end of fermentation is about 30,000 u/ml. (depending upon type of strain). The fermented broth is transferred to the vessel where it is treated with sulphuric acid followed by oxalic acid and is cooled down. The treated broth is filtered through rotary vacuum drum filter or filter presses. The filterate (called native solution) is collected and antibiotic

is precipitated with ammonia water, and is then filtered through plate and frame filter. The cake so obtained is dried and treated with butanol, oxalic acid, carbon and hydrochloric acid. It is then filtered, crystallized and centrifuged and washed with butanol. The tetracycline hydrochloride is dried in vacuum rotary driers.

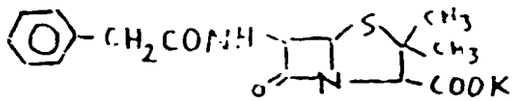
III. DIOSGENIN

The tubers of dioscorea contain diosgenin. The different species of dioscorea, namely, D. deltoide, D. floribunda, D. compositae and D. praxari contain diosgenin in range of 2.5-5 per cent. The process to isolate the active ingredient is quite simple and is described below:

The tubers being quite hard are first softened by soaking in water for about 48 hours before subjecting to disintegration and hydrolysis. The hydrolysis of disintegrated tubers is effected by 6 per cent hydrocholoric acid or sulphuric acid at steam temperature for about 8-10 hours. The hydrolyzed material is washed free of acid, dried and then extracted with n-hexane or toluene or any other suitable solvent. The extraction is done in a soxhlet type of extractor and complete extraction is effected after approximately 30 cycles are completed. The diosgenin is separated by centrifuge.

CHEMICAL SCHEME FOR AMPICILLIN

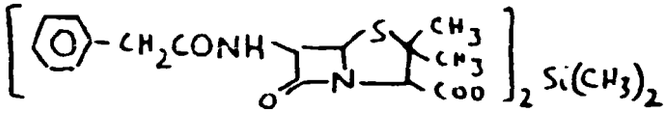
a) 6-APA from Potassium Penicillin G



(Potassium Penicillin G)

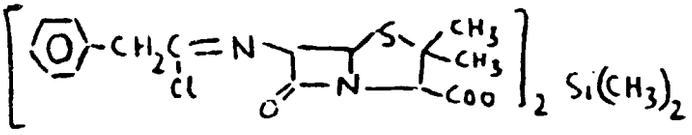
$(CH_3)_2SiCl_2$ (Dimethyl dichloro silane)

Chloroform



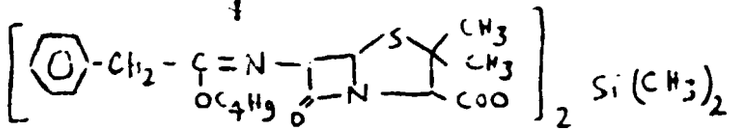
Dimethyl aniline

Phosphorous Pentachloride



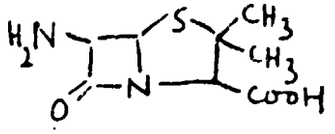
(Imide chloride)

C_4H_9OH (Butanol)



(Iminochloride)

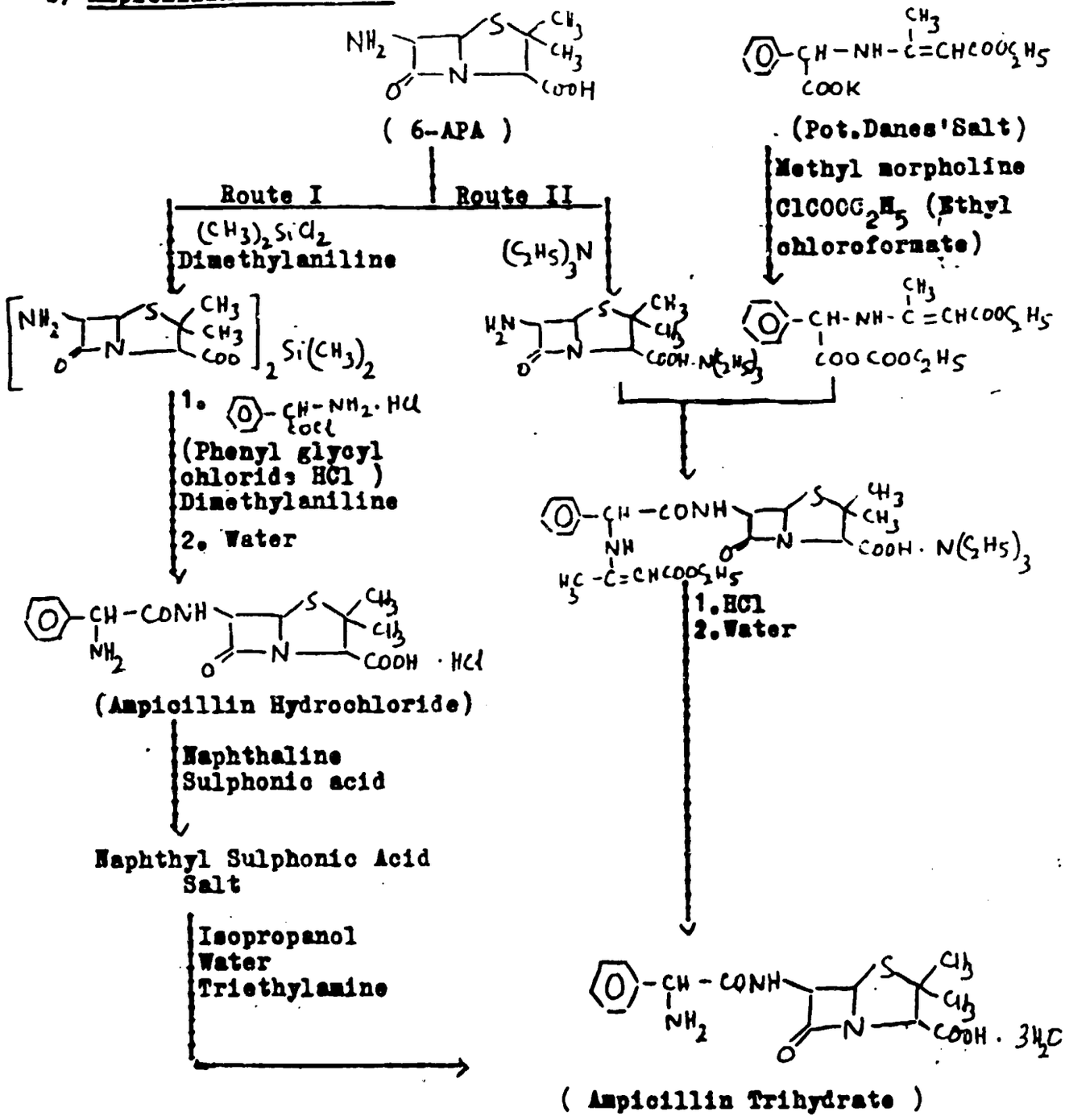
Ammonium Hydroxide/Water



(6-APA)

Fig I: Schematic diagram - Chemical scheme for Ampicillin

b) Ampicillin from 6-APA



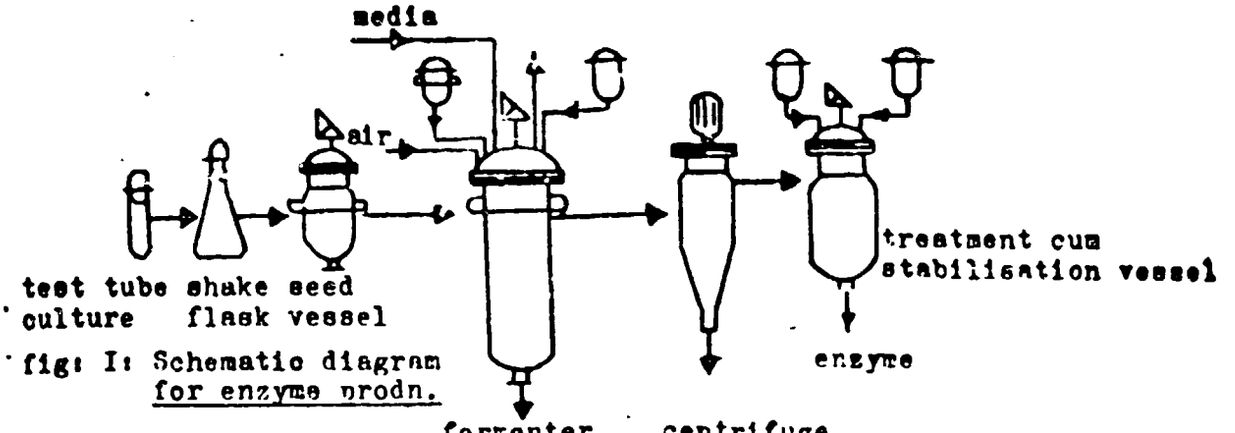


fig: I: Schematic diagram for enzyme prodn.

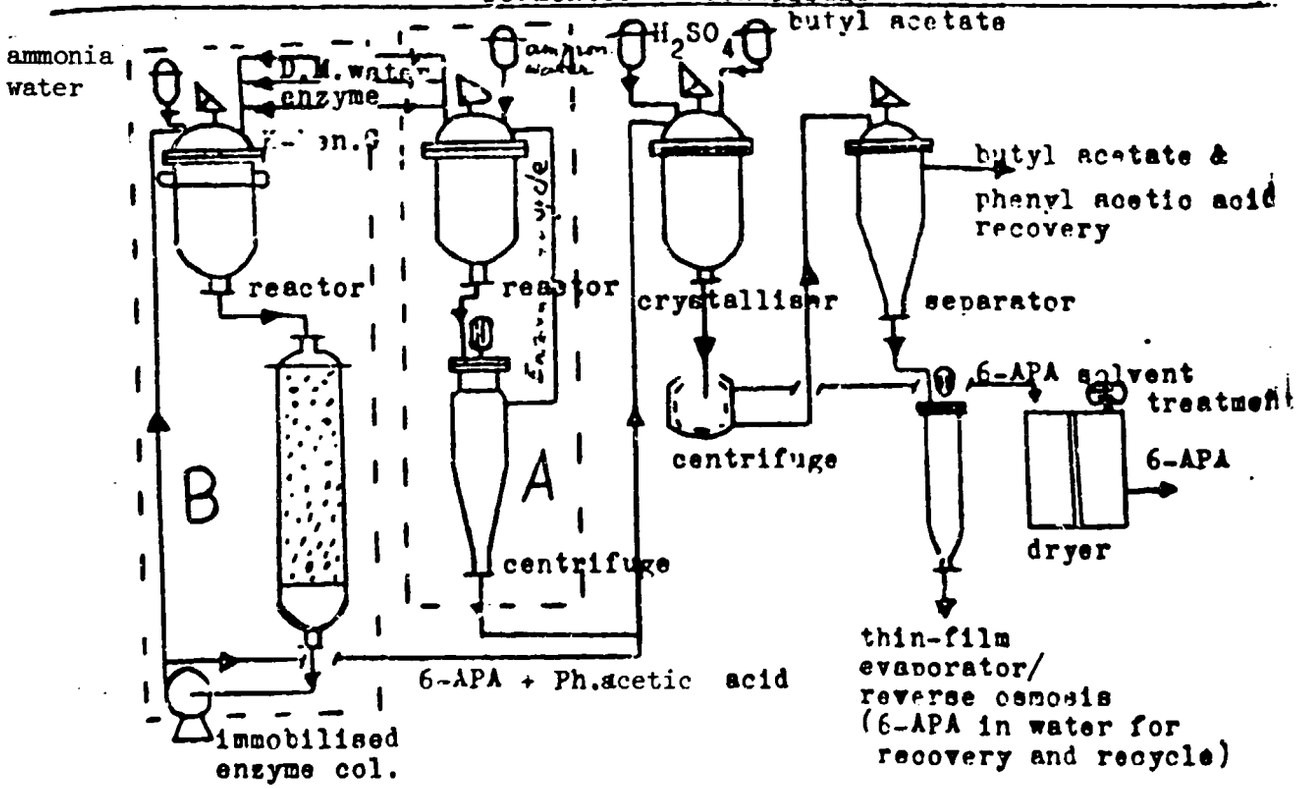


Fig. II : Schematic diagram for the prodn. of 6-APA by enzymatic Process.

Block-A : Ordinary Enzyme Process

Block-B : Immobilised Enzyme Process

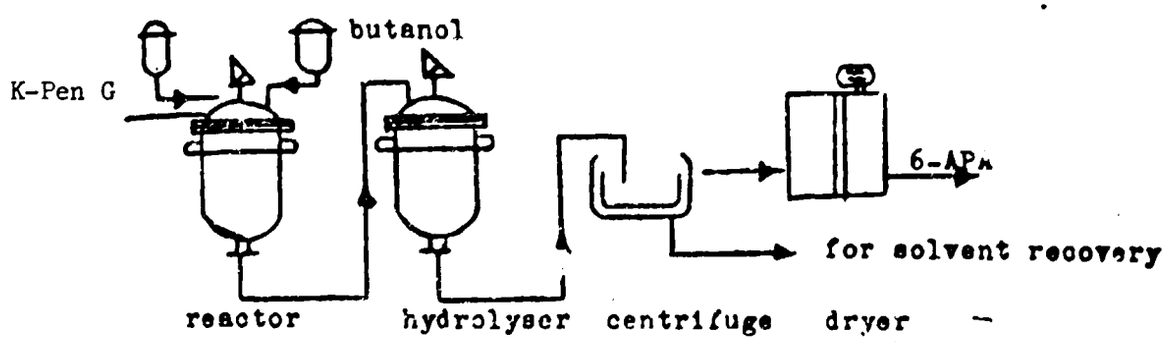


Fig. III : Production of 6-APA by synthetic method.

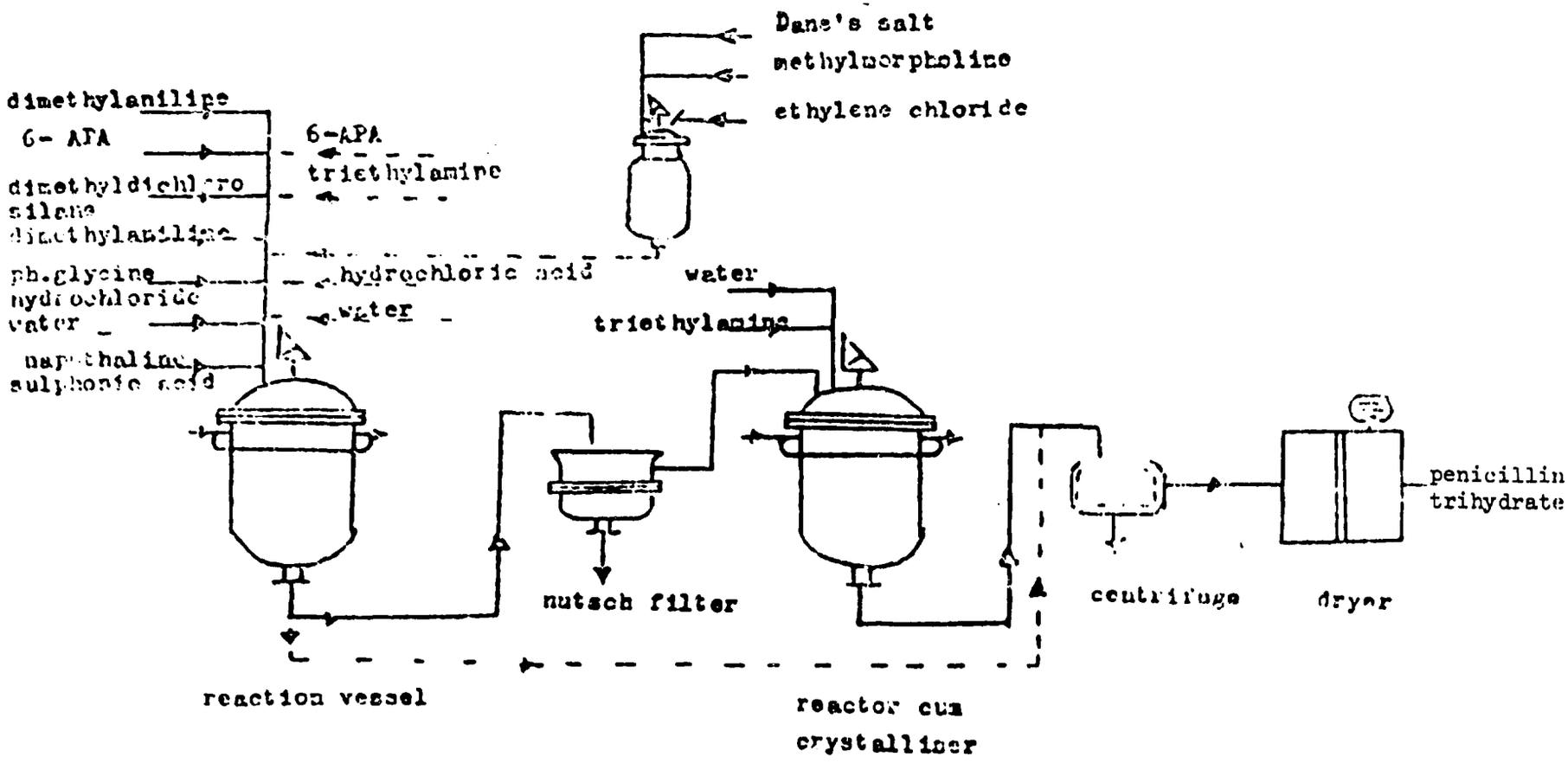


Fig. IV : Schematic Diagram for the Production of Ampicillin Trihydrate from 6-APA.

Legend: ——— route- I

——— route- II

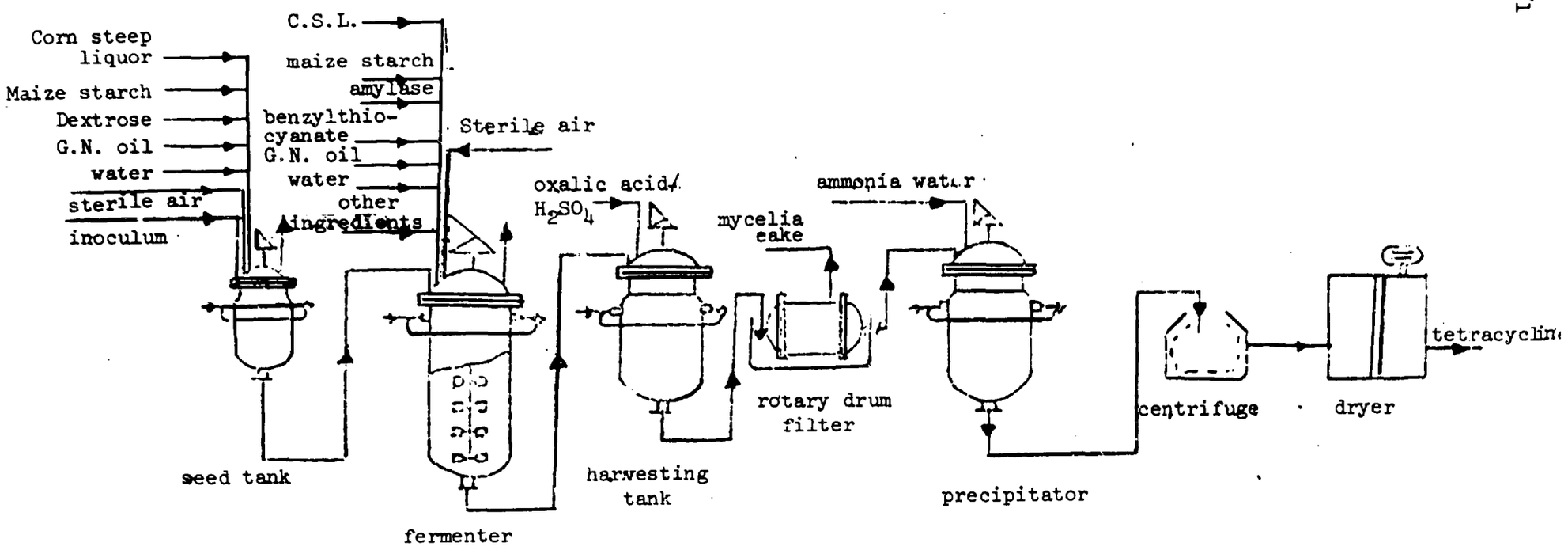


Fig. V: Schematic diagram for the production of tetracycline

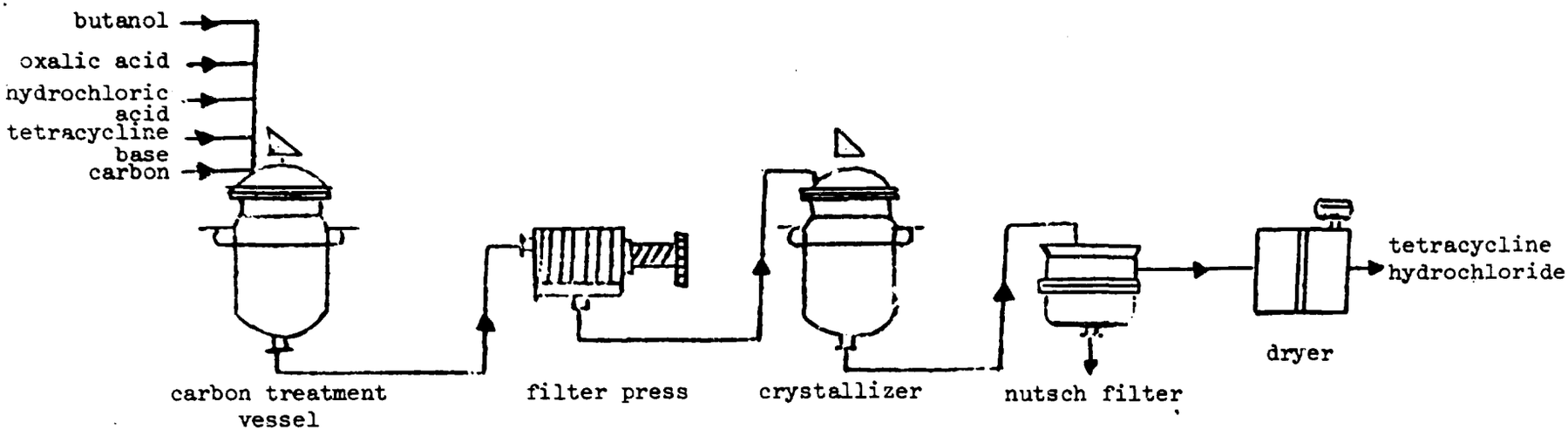


Fig. VI: Schematic diagram for the production of tetracycline hydrochloride from tetracycline base

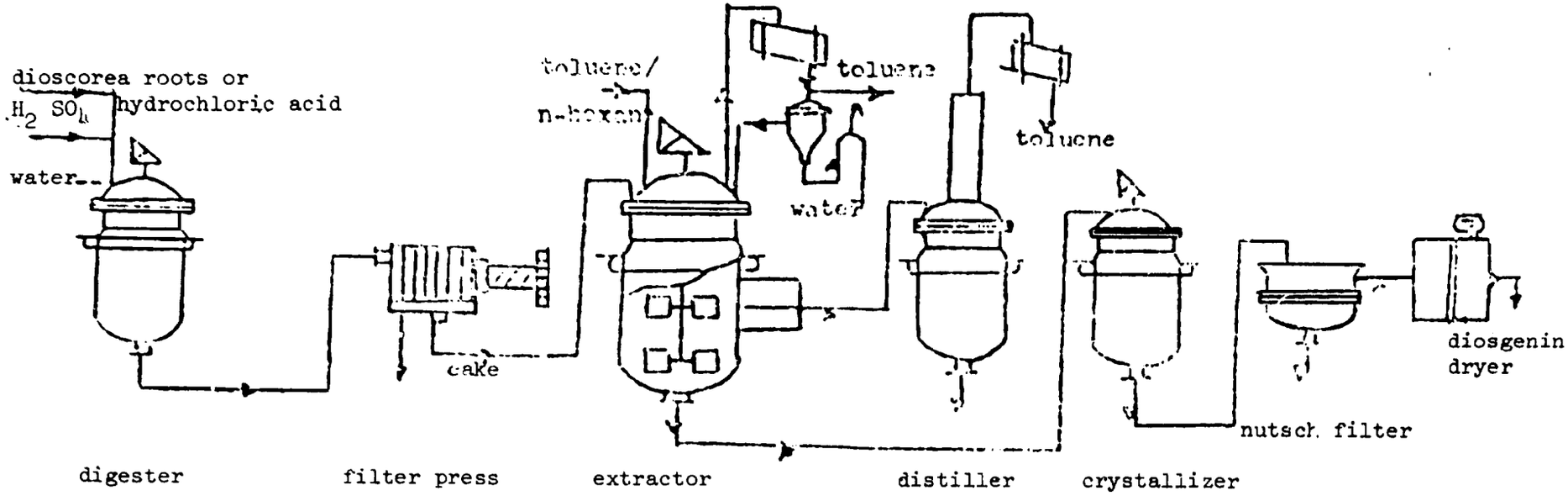


Fig. VII: Schematic diagram for the extraction of diosgenin from dioscorea roots

Appendix II

STRAIN-IN FERMENTATION INDUSTRY

The strain is the smallest collection of individual species of microbes called fungii, which produces chemicals known as antibiotics by the process of fermentation. Its activity is defined in units per ml. They are identified as penicillium, staphylococcus and the antibiotics they produce are penicillin and streptomycin respectively.

The strain of micro-organism used in the industrial fermentation has to go through a rigorous exercise before it is used. The productivity of an antibiotic during fermentation by a microbe is the interaction of its genetic potentiality and the environment within and outside the microbial cells. Augmentation of yield by altering genetic potentiality of a strain is a well-known technique and results of the experiments with such micro-organisms in the area of mutation, microbial genetics and genetic control of secondary metabolites have given valuable information for application to industrial strains. What was 100 units per ml. of penicillin in the fermenter in late 1940 is now 50,000 units in 1980. The increased yield of fermentation has led to the reduction in cost of production. Thus, the strain selection, maintenance and improvement is an important activity in the field of antibiotics. The process of selection and maintenance is given below:

1. Spore isolation
2. Dilution
3. Petri dishes inoculation and incubation
4. Growth of colonies on Petri dishes
5. Slants inoculation and incubation
6. Growth of micro-organism slant culture
7. Spores storage by lyophilization of storage in deep freezer
8. Sterility tests
9. Sterilization of glassware
10. Spores to solid medium or thioglycolate-phenol red medium or fluid thioglycolate medium

Appendix III

FINAL PRODUCTS SPECIFICATIONS AND ANALYTICAL METHODS

1. Specifications of pure tetracycline base
2. Toxicity of pure tetracycline base
3. Tetracycline hydrochloride
4. Moisture
5. pH
6. Absorption
7. Total anhydrotetracycline, epitetracycline, residnal
8. Identification
9. Toxicity

Example for toxicity assay given below:

Toxicity

Prepare a solution in sterile distilled water containing 2 mg per ml. of sample. Use five mice weighing from 18-25 grammes. Inject each 0.5 ml. of solution within 5 seconds in the candal vein. If no animal dies within 48 hours the sample is non-toxic.

If some animals die repeat the test one or more times using fresh animals. If the total deaths is greater than 10 per cent of the sample it is toxic.

Appendix IV

INPROCESS ANALYTICAL METHODS

In chemical industry, final results are dependent upon the control during operation and hence all the inputs as well as products for after each and every unit processes and operation has to be analysed and controlled against the parametics given by the Licensor. In case of deviations, Licensors' know-how also provides effective steps to be taken to correct these deviations. Following examples show various inprocess analytical methods to be performed during the industrial production of tetracycline.

1. Determination of ammonia nitrogen in the fermentation broth.
2. Determination of total sugars in the fermentation broth.
3. Determination of dissolved oxygen in the broth.
4. Spectrophotoretric determination of tetracycline in the fermentation broth.
5. Determination tetracycline in (a) purified filtered broth; (b) spent mycelium; (c) filtered broth; (d) acidified broth; (e) mother liquor, in rich solution and its wastings.
6. Activity determination of crude tetracycline base.
7. Re-crystallized tetracycline base.
8. Karl Fisher method for water determination.
9. Determination of soluble in organic phosphorous in the broth.
10. Determination of phosphorous in the corn steep liquor.

Appendix V

SOLVENTS RECOVERY

Solvents are used as vehicles during a chemical reaction or for extraction or purification. These are very costly in developing countries. In tropical countries due to high temperature evaporation losses are high. For better economics, it is essential that the selection of solvents are proper and the recovery process is efficient. In case of extraction diosgenin, use of n-hexane in the tropical countries was very costly and it has been replaced by toluene. The process of recovery of acetone from water-acetone mixture obtained in the production of ampicilline trihydrate is given below:

Acetone distillation

The distillation unit consists of:

1. Column 900 mm diameter having 15 plates 450 mm apart
2. Heat-exchanger - 38.5 sq. mt.
3. Condensor - 59 sq. mt.
4. Intermediate tank - 250 L
5. Cooler - 10 sq. mt.
6. Pumps for mother liquor feed and reflux and recovery pump.

About 11,000 litres of mixture is charged into the boiler and steam 3 kg/sq. cm is opened into the heater. The distillation is carried out at total reflux during first 30 minutes. The distillation cut is taken when vapour temperature reaches 56-57° C and continued until the vapour temperature reaches 60-65° C.

Recovered acetone - 80 per cent.

Appendix VI

EQUIPMENT LIST WITH DETAILED SPECIFICATIONS

Reactors/Fermenters:

Capacity (volume), dimensions (height, diameter, thickness etc.), flat ends/dished ends, open or close top, bottom outlet/blow leg, on lugs/legs, jacketted/unjacketted, insulated/uninsulated.

Material of construction: S.St. ....., steel, C.I., St.Rl. etc.

Internals: Provided with cooling/heating coils, baffled/unbaffled (with dimension), provided with agitator (type: turbine, propeller etc. rpm) drive power, direct coupling/belt driven, variable speed/constant speed. Thickness of the body and jacket size of ports.

Duty: To carry out reaction at ... temperature and pressure, with liquid/suspension/heterogeneous mass of density ... viscosity etc. The corrosive nature of the liquid and the corrosion allowance is given as follows:
..... ASME Code No. ..... to be followed during fabrication.

Distillation column

Height, diameter, no. of plates, type of plates, spacing of plates, material of construction, size of down-comers. In case of packed towers irri· height, size of the packing material, void volume, no. and size of ...ors etc. Thickness of body and other parts, sizes of ports.

Duty: To distil ... litre per hour of component A from a mixture of ... components. The operating temperature and pressure are ...

Pumps: Type of pumps, head and capacity, NPSH, material of construction, type of motor and power.

Duty: Type of materials to be handled - liquids/slurry/suspension, density, viscosity temperature, corrosive nature, the material handled is (explosive/inflammable/ordinary etc.).

Heat exchangers

Type (shell and tube, plate, paraflow etc.), no. of passes, heat transfer area, material of construction, services used, tube/plate sizes, fabrication codes, shell thickness, port sizes.

Duty: To heat/cool ..... kg/hr of ..... (material) (native of material like organic/inorganic liquids, slurries, suspension, gasses etc.).

To condense ..... kg/hr of ..... (material)

To evaporate ..... kg/hr of ..... (material)

Appendix VII

EFFLUENTS

Synthetic drugs use large quantities of chemicals and intermediates, which along with the products produced are present in the effluents. Some of them are highly toxic and possess very high combined oxygen demand (COD) for their making harmless to attain permissible limit to be put into municipal waste system or river stream or sea. Therefore, these have to be treated before disposal. The chemical effluents could be categorized:

1. Acidic effluent - Requires neutralization which is achieved either by mixing it with the alkaline effluents and if sufficient quantities are not available acidic effluents have to be treated with lime in the neutralization station.

2. Alkaline effluents - Used partly for neutralizing the acidic effluents.

3. Highly toxic effluents - Effluents containing cyanides have to be treated on the spot by ferrous sulphate solution and then to be led to the effluent piping system within the plants. Effluents containing sulphur and sulphides have to be separately treated.

Mostly chemical effluents are treated by biological processes. To the neutralized chemical effluents, from the plant along with alkaline and other process effluents resulting from filterations, reactions, washings, separation, are sent to the effluents treatment unit and mixed in a tank with floor washing, sewerage fical and biologically treated till permissible BOD is obtained. Similarly the effluents from antibiotic plants have large quantities of vegetative organic matters which petrify. These effluents have high biological oxygen demand (BOD) and have to be treated in biological effluent treatment plants mentioned above. These effluents are simpler as compared to effluents from synthetic drugs. The neutralization and biological effluent treatment plant can cost more than $1 million depending upon the size.

Appendix VIII

RAW MATERIALS CONSUMPTION

AMPICILLIN

Raw materials consumption guarantees for each batch of ..... kg of product.

Licensor guarantees the following raw material consumption for ..... kg of 6-APA required for producing ..... kg of product:

- Potassium penicillin-G (96 per cent) kg .....
- N,N-dimethylaniline kg .....
- Dimethyl dichloro silane kg .....
- Phosphorous pentachloride kg .....
- N-Butanol kg ..... (-)
- Sodium hydroxide 40 per cent kg .....
- Methylene chloride kg ..... (-)
- Methanol kg ..... (-)
- Acetone kg ..... (-)

Licensor guarantees the following raw materials consumption for ..... kg of product:

- 6-APA (96 per cent) kg .....
- D-(alfa)-phenylglycine (100 per cent) chloride hydrochloride kg .....
- Triethylamine kg .....
- Dimethyl dichloro silane kg .....
- N,N-dimethylaniline pure kg .....
- p-Toluenesulphonic acid monohydrate kg .....
- Methylene chloride kg ..... (-)
- Dicalite kg .....
- Decolorizing charcoal kg .....
- Amberlite LA - 1 It ..... (-)
- Methyl isobutyl ketone kg ..... (-)

(-) to be recycled for recovery at ... per cent.

TETRACYCLINE

Raw materials consumption guarantees for each batch of ..... kg of product.

Licensor guarantees the following raw materials consumption for producing ..... kg of product:

- Corn steep liquor kg .....
- Maize starch kg .....
- Ground nut oil kg .....
- Calcium carbonate kg .....
- Butanol kg .....
- Oxalic acid kg .....
- Ammonium nitrate kg .....
- Ammonium sulphate kg .....
- Benzyl thiocyanate kg .....
- Manganese sulphate kg .....
- Potassium dihydrogen phosphate kg .....
- Sodium hydroxide kg .....
- Ammonia kg .....
- L.Amylase kg .....
- Charcoal kg .....
- Hydrochloric acid kg .....
- Acetone kg .....
- Magnesium sulphate kg .....

DIOSGENIN

Raw materials consumption guarantees for each batch of ..... kg of product.

Licensor guarantees the following raw materials consumption for producing ..... kg of product:

- D.Deltoide/D.Floribunda/D.Compositae/D.Prazari roots kg .....
- Hydrochloric acid/Sulphuric acid kg .....
- n-Hexane/Toluene kg .....