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08566

Distr.
LIMITED
ID/WG. 282/93
13 October 1978
ENGLISH

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

INTERNATIONAL FORUM ON APPROPRIATE INDUSTRIAL TECHNOLOGY

New Delhi/Anand, India 20–30 November 1978

WORKING GROUP No.2

APPROPRIATE TECHNOLOGY FOR THE MANUFACTURE OF DRUGS AND PHARMACEUTICALS

CHOICE AND ADAPTATION OF APPROPRIATE TECHNOLOGY IN PRODUCTION OF DRUGS AND PHARMACEUTICALS IN DEVELOPING COUNTRIES

Background Paper

78-7020

CHOICE AND ADAPTATION OF APPROPRIATE TECHNOLOGY IN PRODUCTION OF DRUGS AND PHARMACEUTICALS IN DEVELOPING COUNTRIES

by

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INTRODUCTION

The pharmaceutical industry, to provide the optimum requirements of the countries' medical and health services, needs to produce drugs of adequate quality in sufficient quantities and at prices within the reach of the common people.

The markets of developed countries are flooded with innumerable preparations and it will not be possible for any developing country to provide its markets with all of them with its limited resources. Each developing country will therefore have to establish a national list of drugs to meet the country's real needs of the majority of its population. The drugs included in such a list could differ from country to country depending on many conditions such as the pattern of prescription, common diseases, the type of health services, personnel available, financial resources and genetic, demographic and environmental factors. Because of the great difference between countries, the preparation of a drug list of uniform general applicability and acceptibility is not feasible. Therefore each country should undertake the responsibility of evaluating and arriving at a list of national drugs according to its own policy in the field of health. and review it from time to time.
(Ref: Report of Second Panel Meeting of Industrial Experts on the Pharmaceutical Industry. 34 pages. ID/WG.267/4/Rev.1. Annex I, page 21. March 1978

Choice of Technology for different Groups of Countries

After the preparation of a national list, the method of manufacturing chosen will depend on the stage of development of the industry of the country and its technical base. The developing countries have been broadly classified into 5 groups depending on the stage of their development and the steps to be taken by each of them would differ from one another.

Countries of Group I are those that have no manufacturing facilities and therefore are dependent on imported pharmaceuticals in their finished form. These countries also have limitedpublic health services and poor distribution channels. The steps to be taken by them would be :

- (a) to establish procurement procedures of the items in the national list of drugs arrived at as suggested above, to take advantage of purchasing in large quantities;
- (b) to develop quality control facilities to ensure the quality of the drugs purchased; (List of equipment given along with formulation equipment Appendix I)
- (c) to establish units for repacking formulated drugs which will help to build the auxiliary industries of packing materials and standardize their production; (List of packing material is given in Appendix II)
- (d) to set up units to produce infusion solutions and simple formulations on a semi-industrial scale. (Given along with other formulation equipment Appendix I)

Countries of Group II : These are countries that are already packing formulated drugs and are making simple formulations. The steps to be taken by them are :

- (a) to establish formulation units to convert bulk drugs into dosage forms such as tablets, capsules, liquid preparations, ointments and infusion solutions; (Appendix I)
- (b) to establish facilities to control quality from the raw material to the finished product. (Appendix I)

To set up the requisite organization to monitor the stability of the drug.

In cases where products fail to meet specifications they should be recalled from the market.

To achieve the above steps, it is essential to train industrial pharmacists to start and run semi-industrial units and to establish testing facilities. This is a very important infrastructure and UNIDO has been assisting in running courses in some universities, especially at the University of Ghent, in Belgium, Faculty of Pharmaceutical Sciences, giving preferences to candidates from countries belonging to this group of countries.

The University of Ghent has been running such classes for the last five years and trained participants from 82 nations and created confidence in them to start the production of simple preparations, which all the same are mostly needed to save lives in these areas and to set up and operate small infusion producing installation and semi-industrial formulation facilities to produce tablets, capsules, ointments, ampoules and similar formulations. Several of the advanced developing countries have similar facilities and are extending co-operation to other lesser developed countries in this field.

Such semi-industrial plants do not need any elaborate equipment and technical assistance, and equipment for the same is not difficult to get within the developing countries themselves. Such units should also undertake to produce simple antiseptic solutions which could help in preventing the spread of infection. The infusion solutions referred to above are very essential to treat children and even adults who get dehydrated by diarrhoeic disease and unless these infusions are administered immediately lives are lost. Importing such solutions which contain nearly 95% of water would itself cost more to transport and distribute than to produce locally at the hospital pharmacies. In Appendix I a list of equipment required for making infusions and simple formulations is given along with their approximate cost.

The various ingredients involved in making simple formulations like tablets, capsules, liquid preparations, ointments and infusions, including parenterals, are described below :

1. Tablets : Tablets are most frequently administered in oral dosage form and are prepared by compression. Various types of tablets are available, e.g. plain tablets, chewable tablets, sugar-coated tablets, enteric coated tablets, press-coated tablets, layered tablets, film-coated tablets, sustain release tablets, etc..

The tablet dosage form offers several advantages, viz :

(a) easy for dispensing and administering;

(b) easy to pack and ship;

(c) accuracy in having the desired requirement of the active drug for dosage;

(d) easy to preserve the biological activity of the drug or drugs.

The general method of tablet manufacture is as follows :

(a) Raw material : In the manufacture of tablets, besides the active drug or drugs, a number of other raw materials are necessary to form the desired tablets. These are, for example, diluents, binders, lubricants, disintegrating agents, colouring agents, flavouring agents.

(b) Diluents : As is well known, synthetic and natural drugs are highly potent and only small quantities (from micrograms to milligrams) are required for unit dosage form. In order to be able to make a tablet for administration out of small quantities of these active drugs, certain inert materials like lactose, starch, sucrose, mannitol, dicalcium phosphate, calcium sulphate, micro-crystalline cellulose (Avicel), etc are used. These inert materials are called diluents.

(c) Binders : These are substances which keep the components of the tablets together in the tablet form after compression, i.e. the tablets do not break after compression and have sufficient hardness. Examples of common binders are gum acacia, gum tragacanth, gelatin, starch paste, sodium-carboxy-methylcellulose, methyl-cellulose, ethyl-cellulose, polyvinyl pyrrolidone, sodium alginate, etc..

(d) Lubricants : These are substances which prevent adhesion of the powder to the punches during compression and the smooth ejection of the tablets from the dies. Some commonly used lubricants are talcum powder, liquid paraffin, stearic acid and its salts like calcium and magnesium stearate, etc..

(e) Disintegrating agents : Certain substances which help the breaking up of the tablets after administration to the patient are called disintegrating agents. Some commonly used disintegrating agents are cornstarch, gum guar, methyl-cellulose, sodium-carboxy-methyl-cellulose, micro-crystalline cellulose (Avicel), alginates, etc.. The Pharmacopoeias prescribe a limit of 15 minutes for the disintegration of common tablets after administration.

(f) Colouring agents : Colour, besides making tablets look more attractive to the patients, also helps in distinguishing the various tablets before they are administered. Only certified food and drug colours are normally used.

(g) Flavouring agents : Various flavouring agents are being used to make tablets more palatable and to act as a mask against undesirable taste of the ingredients.

The choice of any of the above constituents to manufacture tablets depends upon their compatibility with each other and also with the active drug. This is checked by stability studies of the preparations.

2. Capsules : Capsules are solid dosage forms in which the drug(s) are enclosed in a hard or a soft shell of gelatin. These gelatin shells are called capsules. The capsule dosage form has advantages over the tablet dosage form in that :

i) it keeps the drugs' potency without much formulation effort;
ii) each dosage is in a sealed container ensuring high level of drug protection from atmosphere;
iii) it masks the taste and odour of drugs;
iv) the capsules break in the stomach in less than 5 minutes, thus making the drugs available for absorption quickly.

Capsules are largely used to market single active drugs like antibiotics. However, mixture of drugs either as such or in granular forms are also marketed in capsule form, e.g. vitamins.

Capsules are commonly of three types :

(a) hard gelatin capsules;
(b) soft gelatin capsules;
(c) seamless capsules

Hard gelatin capsules are available in a variety of sizes. The smallest being n° 5 and the largest 000. The choice of the size is dependent on the bulk density of the mixture for a single dosage. Colouring of capsules is adopted extensively as a method of identification for proprietary products.

In slight moisture the capsules stick together. It is, therefore, recommended that they be stored in a dry and cool place.

General process of manufacture :

Hard gelatin capsules : The manufacture of capsules containing drugs involves the following processes :

(a) preparing the powder mixture
(b) filling of the capsules
(c) sealing of the capsules
(d) cleaning of the capsules

The drug for capsules is blended in a blender with a diluent if necessary and with a little lubricant to ensure free flow of the powder while filling the capsule. The blended material is then filled through a semi-automatic or an automatic machine called a capsule-filling machine, now available even in several developing countries. The machine first separates the top and bottom part of the empty capsule and then delivers an accurate weight of the blend in the bottom part of the capsule and subsequently replaces the top part.

The above process is followed by sealing of the capsules. This is done by a solution of gelatin at the joint of the top and bottom parts of the filled capsule. Capsule-sealing machines are easily available. Self-locking capsules do not need however any sealing. Some of the manufacturing houses print their capsules to identify their products. Printing of the capsules can be done before or after filling.

3. Liquids : Liquid preparations are still another form of dispensing drugs. The major advantages of liquid dosage form are :

(a) when the active drug is a liquid;
(b) liquids can be administered in small/large dose as required by the physician;
(c) the drug is available for absorption immediately after administration;
(d) liquid preparations can be sweetened, flavoured and made tasty, facilitating administration of the drug, particularly for children and old persons.

In spite of the advantages described above, there are certain disadvantages of liquid dosage form, viz.:

(a) for a single dosage form liquids are bulkier, when compared with the solid dosage forms. This results in higher costs.
(b) the deterioration of drugs like antibiotics, vitamins and hormones is much faster in the liquid form than in the solid dosage form.

Types of Liquid Dosage form: Liquid dosage forms are mainly of the following types:

(a) solution
(b) emulsion
(c) suspension

A solution is made by dissolving a drug or drugs in a diluent or vehicle in which it is most soluble and compatible. A solution should be clear and free from suspended particles.

An emulsion is a two-phase system prepared by mixing two immiscible liquids, one of which is uniformly dispersed in the other. In order to keep this emulsion stable for a considerable time, certain chemicals are used which are called emulsifying agents, viz., Tween 80, Span 20, benzalkonium chloride, glycerylmonostearate, etc. The most commonly used natural emulsifying agent is gum acacia.

A suspension, like the emulsion, is also a two-phase system in which the solid drug is finely suspended into the liquid phase. In order to keep the solid well suspended, certain chemicals are used which are called suspending agents, like sodium carboxy-methyl-cellulose, methyl-cellulose, carbopol (polyacrylic acid), sodium alginate etc. Natural suspending agents are gum acacia, gum tragacanth etc.

General Process: The basic principle involved in the preparation of a solution is to make a homogenous mixture of the drug/drugs in a diluent or vehicle. Water, alcohol, sugar syrup, glycerine and sorbitol (70%) are the common diluents in use.

Apart from the active drug and diluents, other excipients involved are:

(a) sweetening agent
(b) preservatives
(c) colouring agent
(d) flavouring agent

A sweetening agent is added to make the preparation more tasty. Common sweetening agents are sugar, saccharin and sodium saccharin.

A preservation is added to prevent mould and bacterial growth as the media of a liquid preparation is susceptible to bacterial and fungal contamination. Generally used preservatives are alcohol, hydroxy benzoates, sorbic acid etc.

A colouring and flavouring agent is added to make the dosage form more attractive and acceptable particularly for the children. Only approved, sorbic acid etc.

4. Ointments: Ointments are soft, semi-solid preparations usually containing medicinal agents intended for application to the skin or to the eyes. Ointments for skin are called skin ointments and ointments for use in the eye are called 'ophthalmic ointments'. This however should be sterile and filled under Sterile Conditions.

General process of ointment manufacture: It is not possible to give full manufacturing details in this note. For the sake of convenience, only the general method of ointment manufacture is illustrated.

Raw materials: In the manufacture of ointment, besides the active drug or drugs, a number of other raw materials are necessary to form the desired ointments. These are, for example:

(i) diluent or base
(ii) antioxidant
(iii) preservatives

Diluents or bases: Diluents or bases constitute the major portion of ointments, and influence the absorption of the drugs through the skin. Various types of bases are used, e.g.

(a) Oleogeneous base: consists of mineral, animal or vegetable oils; e.g. soft paraffin, liquid paraffin, lard, olive oil, cottonseed oil etc.

(b) Absorption base: this group includes hydrophilic substances such as wool fat, lanolin.

(c) Washable base: these are water soluble bases and easily removable from skin by washing with water. Common examples are polyethylene glycols. They are compatible with a wide range of active drugs.

(d) Emulsion base: There are two types of emulsion bases. One in which water is the internal phase and oil in the outer phase and is called water in oil emulsion and the other containing oil in the inner phase and water in the outer phase is called oil in the water emulsion. Example of W/O emulsion is hydrous-wool fat, whereas stearic acid-soap emulsion is an example of O/W emulsion. An agent which helps in forming emulsion for both oil and water phase is called emulsifying agent. Sodium lauryl sulphate is an emulsifying agent.

(e) Emulsifying waxes: there are some waxes which form oil in water emulsion when fused with water. Examples are cetyl alcohol, stearyl alcohol, glyceryl monostearates.

(f) Silicon bases: this group includes products which are related to minerals and contain silicon in their molecule. Examples are Bentonite, Veegum etc.

Antioxidants: An antioxidant is sometimes added to the ointment to prevent oxidative deterioration. The selection of an antioxidant is however dependant on several factors like toxicity, irritancy, potency, compatability, odour, discolouration, stability and solubility. Common antioxidants are Butylated hydroxy toluene (BHT), Butylated hydroxyanisole (BHA), Propyl-gallate etc.

Preservatives: Preservatives are added to ointments to prevent contamination, deterioration and spoilage by bacteria or fungi. Most common

preservatives are esters of p-hydroxy benzoic acid (methyl ester or propyl ester) and sorbic acid.

5. Infusions and other parenterals: Parenteral preparations including infusions are sterile pharmaceutical dosage forms which are administered intravenously or intramuscularly. Generally these preparations are known as injections. All parenteral preparations are sterile. There are mainly four types of parenteral products recognized in the Pharmacopocia:

(i) solution of medicaments ready for injection. This is the most common form, e.g. glucose injection, saline injection, etc., known commonly as infusions.

(ii) dry solid medicaments which make a solution upon the addition of a suitable solvent just before administration. These are mostly antibiotic preparations, e.g. penicillin injection, etc.

(iii) suspensions of solid medicaments ready for injection. These are mostly drugs in colloidal or micronised form, e.g. hydrocortisone injection.

(iv) dry, solid medicaments which yield a suspension upon addition of suitable vehicle, e.g. procaine penicillin injection.

Parenteral preparations offer the following advantages over the other dosage forms:

(i) the parenteral route is essential for certain drugs to be absorbed in active form, e.g. streptomycin and neomycin.

(ii) it offers more predictable absorption, as it is independent of the vagaries of gastro intestinal function.

(iii) the effective dose can be more accurately selected and the desired blood concentrations can be obtained quickly.

(iv) it is mandatory in emergencies, e.g. in unconscious or uncooperative patients where an immediate action of the drug is necessary. This is usually achieved by using the intravenous technique - one of the parenteral routes.

(v) the intravenous, parenteral route offers the only method of rapidly increasing blood volume during cases of dehydration referred to earlier.

(vi) it is the only possible method of administering a drug, when the patient is unable to take a drug by the gastro-intestinal route; or cannot retain it when administered orally.

(vii) the intramuscular and the subcutaneous parenteral routes are used to prolong absorption of a drug, especially where sustained release from a depot is needed.

List of ancillary products required to formulate drugs are given in Appendix III.

Supplies to Primary health centres in rural areas and remoter parts of the country: To improve supplies to the centres at reasonable costs, hospital pharmacies have to be established to undertake simple formulations, infusions etc. The selection has to be made with special reference to the Common diseases prevalent in the area. A formulary of drugs preparation commonly required in rural hospitals will have to be prepared, based on the National list of drugs arrived at for the country. The facilities for organising such production are:

(1) Small infusion installations which could serve the needs originally for a group of hospitals through their hospital pharmacies.

(2) Semi-industrial formulation facilities: production of tablets, ampules, ointments, antiseptics (sodium hypochlorite, potassiumpermanganate, chloramine, cresol, etc.), solutions.
These semi-industrial facilities would solve the local needs.
Their production would have no transport difficulties and could be distributed on these regional and local bases.

(3) Quality control (chemical and bacteriological)
Laboratory connected to the hospital pharmacies or semi-industrial units.

These hospital pharmacies or semi-industrial plants would have the great advantage that the locally trained industrial pharmacists, could undertake this work very easily. The development of human skills needed to carry out the operations involved under hygenic and aseptic conditions and operate testing facilities however needs special emphasis and can be achieved only by proper training. A minimum technical help should be available to these units or institutions within the country specially to ensure that the preparations have the necessary bio-availability. The same dosage of active ingredient if not properly formulated can give different results as is illustrated in the graph given in Appendix IV, and makes all the difference between the preparation being effective or not.

Supply and storage of Immunologicals: Proper supply and storage of immunologicals is necessary.

These are heat sensitive and dated products and their storage needs special attention. The rural population hardly get any benefit of these for prevention and treatment of deadly scourges. Later on provision of subdividing them from bulk packing can be undertaken at these centres under sterile conditions.

Other prevention measures: These need water treatment chemicals, pesticides and disenfectants. These could also be formulated locally in a separate unit to meet local requirements.

Group III of the Countries: These countries formulate a broad range of bulk drugs into dosage forms and have also made a beginning to produce simple bulk drugs from intermediates. The steps to be taken by them are:

- (a) to establish multi-purpose plants to produce the bulk drugs required for the health programmes by manufacturing products where the production involves similar chemical reactions;
- (b) to set up units for extraction of active principles from medicinal plants which grow wild or are cultivated in the country;
- (c) to set up centres to utilize slaughter house by-products, such as extraction of active principles of glands and organs and to produce catgut;
- (d) to set up units to produce immunologicals both for prophylaxis and treatment.

Multi-purpose plants: The advantage of multi-purpose plants in a country where the demands are limited, is that the facilities can be utilized throughout the year by changing from one product to another depending on the demand of each product which will always vary from season to season and from year to year depending on epidemics, etc.

It is possible to group a number of simple bulk drugs to be made in one multi-purpose plant from intermediates depending on the similarities of processes and operations involved.

The major groups under synthetic drugs would be sulpha drugs which have chemical similarity and are usually produced with the same type of

equipment starting from the same or similar chemical intermediate. In addition to the sulphas there are many other synthetic drugs which are classified according to their physiological activity like anti-tubercular, anti-malarial, anti-amoebic, anti-diabetic, corticosteroids, anti-pyretics and anti-histamines. The structure of these compounds is different from sulpha drugs as also is their method of manufacture.

It is possible to produce a large number of bulk drugs starting from late intermediates using a multi-purpose plant. A diagram of a glass-lined reactor of a typical multi-purpose plant is given in Appendix V. The material of construction of a reaction kettle is preferably glass lined so that it can withstand many corrosive reactions. It is also possible to carry out reactions in stainless steel equipment and only the final corrosive reactions in small all-glass equipment to reduce capital cost. One can use such equipment for producing a number of drugs whose demands may vary with market conditions by switching from one intermediate to another and varying the condtions of reaction and reactants. An example of such a multi-purpose plant with estimate of its cost to produce certain common drugs is given in Appendix VI.

It is also possible to set up multi-purpose plants to meet the demands of a group of semi-industrial formulation units or hospital pharmacies. They have the advantage of low overheads, little distribution problems and several other advantages over large manufacturing units set up in urban centres.

Plant produots: Production units for active principles of plant products, will depend on the type of plant which is available for extraction and the products that have to be obtained from such extracts. Many of the developing countries are now exporting them in the form of crude herbs to developed countries and in turn importing the active principles. By exporting them even as semi-processed products will improve the export earnings. Later on, as experience is gained, the isolation of the active principles could itself be undertaken within the country to be used for medical treatment as well as to meet the export demands. In such a case the value realization increases several-fold and is one of the important steps of re-deployment of industry from a developed to a developing country which helps in improving the share of industrial production of developing oountries.

In recent years greater importance is being given to plant products as in nature, a plant synthesises complicated molecules from simple ones with highly specific reaction mechanisms. The reactions involved are either difficult or expensive to duplicate by classical chemical methods. In the case of steroid hormones the partial snythesis of the finished hormones starting from a very closely related naturally occurring product diosgenin, is more economical than its total synthesis. Therefore, collection from natural sources or cultivation of dioscorea root for the extraction of diosgenin has been undertaken on a large scale and several plantations have come up in many developing countries where the climatic and soil conditions are suitable. So far, dioscorea root which grows wild on the Mexican mountains, and the Himalayan ranges were collected for the extraction of diosgenin, but depletion of this in the lower accessible ranges has made its collection more and more difficult. The only solution is scientific cultivation of dioscorea tubers and other species of plants like Solanum whose berries contain solasodine, as also, extraction of hecagenin from sisal waste which can also form a starting point for the synthesis of steroid hormones. Another example of this partial synthesis is that of Vitamin 'A' starting from citral present in lemon grass oil. India, Guatamala and other sub-tropical regions have suitable climatic and soil conditions for their cultivation and offer great scope to supply plant material for such partial synthesis of drugs.

There are also certain phyto chemicals where it is more advantageous to extract them as active principles of plant products than obtain them by synthesis. Some of these chemicals can exist in different steric forms and their chemical synthesis, therefore, yields a mixture of isomers, which are very difficult to separate. The product thus obtained by synthesis may be toxic and have a different therapeutic property than what is obtained from nature. In the plants, these reactions take place at normal biological temperatures and pressures and the type and quantity of substances produced will be the one that it needs for its own metabolism, hence normally free from toxic ingredients. In view of these factors, there is great demand for certain plant products in the world in spite of the advances in chemical technology and appearance of cheaper synthetic substitutes. Some of these drugs extracted from plants obtained either by their scientific cultivation or collections from their wild growth are as follows:

Strychnine and Brucine: Nux Vomica, the dried ripe seeds of Strychnos nux-vomica Linne, yeilds the two important alkaloids strychnine and brucine. Although strychnine is a very powerful central nervous system stimulant and was used therapeutically, it has now been replaced by other less toxic and safer drugs. These are produced in the country in large quantities, mainly for export from collection of the seeds from the forests of India, Israel and other countries.

Atropine, Hyoscyamine and Scopolamine: The most characteristic physiological property of the Solanaceous alkaloids is their mydriatic effect - namely, their ability to dilate the pupil of the eye. The solanaceous alkaloids include atropine, hyoscyamine and scopolamine. Scopolamine is also used as a sedative and a tranquilising depressant to the central nervous system.

There is little doubt now that atropine as such does not occur in nature whereas hyoscyamine does and because the latter racemized very readily, hence atropine is obtained from the plant because the hyoscyamine has isomerized during isolation.

As a first stage extraction of crude extracts can be undertaken in developing countries, where these grow wild, for export to developed countries.

Quinine: Cinchona is cultivated over large areas in Indonesia and in India in Darjeeling (W. Bengal), the Nilgiris and Annamalais, in Madras. The factories attached to these plantations in India alone, have a total production capacity of 61 tons per annum of quinine and very much greater in Indonesia. Efforts can be made to increase the production of quinine salts to the maximum extent possible for meeting the growing demand from the foreign markets. Although the use of quinine as an anti-malarial drug has decreased, it is used increasingly for the production of quinidine, used against cardiac ailments such as auricular fibrillation and ventricular tachycardia, and as a bitter for aerated waters and in non-alcoholic beverages.

Reserpine: Reserpine from Rauvolfia vomitoria roots is a tranquilizer which induces sedation without inducing sleep. It is used in psychiatry for the

treatment of schizophrenia and paranoia. Its wide use in drugs against hypertension is well known. Rauvolfia vomitoria is cultivated in Africa and in India in Darjeeling, Kerala and other places and roots of this strain contain 0.7% reserpine as against that reported as only 0.2% of that grown in Africa. Extraction for the isolation of reserpine is fairly simple.

Emetine: Plantations have been established in India in Darjeeling, West Bengal, to grow ipecac to the extent of 20,000 kgs. of dry roots and are largely meeting the requirements for the production of Emetine. Emetine is being extracted at the factories - one in Calcutta and the other in Bombay, with a total annual capacity of 590 kgs. This is principally used in the treatment of amoebic dysentery and in small quantities in expectorants, emetics, etc.

Digitalis Glycosides: In India two units for the extraction of digoxin from locally grown digitalis leaves have been set up in Bombay. In this case, the scientific cultivation of digitalis and the application of modern extraction technology are necessary for the indigenous manufacture of the cardiac drug, digoxin and has been successfully achieved in slopes near the tea gardens which are not usually suitable for cultivation of tea. Although developing countries may not be in a position to isolate the active principle, digoxin, they can make crude extracts for export to countries which produce cardiac preparations.

Caffein: In regions where tea is extensively grown, caffein can be extracted from tea wastes and tea prunings with solvents like benzene or chloromethanes or chloroethanes which is a simple process. Although caffein is made in large factories in developing countries by the synthetic process, there is always a preference for natural caffein in certain drug preparations and the preparation of aerated soft drinks like coca-cola and fetches a higher price. Several such units exist in India near Assam and Kerala States which are tea growing centres. Coffee husk is another source for caffein extraction and caffein is also a by-product in the production of decaffeinated coffee.

Ephedrine: This can be extracted from ephedra which grows wild on the arid mountains of Himalayas in Pakistan and Afghanistan. It has many uses in the production of cough syrups and anti-asthmatic preparations. Here also there is competition from synthetic ephedrine but natural ephedrine has certain preferences.

Schillarin: The bulbs of squill (scilla) grow wild in many sub-tropical regions and need only be converted into crude extract for supply to countries which make this cardiac drug which is very effective when patients do not respond to digoxin.

Other plant products: Multi-purpose plants for the extraction of the active principles of senna, (laxative), belladonna (colic), podophyllum (anti-cancer) etc., are also possible. The total active principles of some of these plant products are already being extracted in India and other countries and a new unit in India envisages, in addition, isolation of the active constituents.

There are many more examples where developing countries can make use of medicinal plants for extracting the active principles and making extracts for converting to more sophisticated products in developing countries.

Utilization of animal by-products and production of biologicals like sera and vaccines: The utilization of slaughterhouse by-products is linked with upgrading of abattoirs in large cities and setting up of primary extraction centres in the immediate vicinity of slaughterhouses. They have to be collected and frozen and preferably processed immediately after an animal is slaughtered.

For instance in the case of insulin production which is so essential for controlling the imbalance of blood sugar level leading to the condition known as diabetes, the pancreatic glands are removed from cattle carcasses immediately after the animals are slaughtered and frozen below $10^{\circ}C$. Insulin is isolated by repeated extraction of the pancreas with cold acidulated alcohol in special mincing equipment. The extract is filtered through a filter press to remove biological matter and the alcohol solution of insulin is concentrated initially through a special rising film type of evaporator followed by further concentration at reduced pressure in a vacuum still. Chilling of the alcoholic concentrate leads to the

separation of the residual fat which is removed by filtration. The insulin is salted out from the filtrate as the crystalline hydrochloride called the salt cake. This salt cake is then dissolved in water and crystalline insulin precipitated by adjustment of the PH to the isoelectric point of insulin. Similarly, many active principles from glands and organs of slaughtered animals such as adrenalin and other hormones, pancreatin, pepsin and other enzymes, liver extracts can be recovered. From the sheep intestines catgut required for surgery and other uses can be produced. Many intermediary products can be obtained like cholestrol from spinal chord or wool fat. Cholestrol can be used for the synthesis of steroid hormones, or Vit. D_3.

Bile can also be used for producing bile acids required for synthesis of hormones, etc. Today most of these raw materials are wasted and at the same time heavy demands made on the limited resources of such products which are produced in developed and few of the developing countries.

Biologicals like sera, vaccines, anti-toxins and toxoids which are so necessary both for prophylaxis and treatment can be produced by the public health laboratories with no elaborate equipment. These include vaccines against smallpox, cholera, anti-tetanus serum and toxoid, anti-diptheria serum and toxoid and anti-rabic vaccine and triple antigen and oral polio vaccine.

Group IV of the countries are those which produce a broad range of bulk drugs from intermediates, and which manufacture some intermediates using local raw materials. The steps to be taken by them are:

(a) set up units for the production of antibiotics by fermentation

(b) set up plants for intermediates covering also the needs of the other chemical-based industries.

The steps that Group IV countries have to undertake really involve more complicated technology and an infrastructure of a developed chemical industry with especially the manufacture of intermediates for drug production is necessary.

Anti-biotics: These products are unlike the synthetic drugs produced with the help of micro-organism using fermentation technology. Inspite of their complete lack of chemical similarity they have anti-biotic activity, i.e. they can interfere with the metabolic processes of specific micro-organisms in that the growth of these organisms is either retarded or suppressed. Unlike synthetic drugs which need a large number of chemicals and complicated chemical reactions anti-biotics mainly need nutrient media and certain solvents and therefore are more amenable to be produced in developing countries than synthetic drugs provided the technology and equipment for manufacture are provided, and workers are trained to maintain strict hygienic and sterile conditions.

The large scale production of antibiotics by fermentation involves growing the antibiotic producing organism in a liquid medium. The correct pure strain of the micro-organism which produces that particular antibiotic substance is chosen and then grown from the master culture stepwise to the fermentor stage. This growth is carried out via a series of intermediate transfers from laboratory shake flasks to seed tanks of increasing size and finally to the fermentor. Each vessel contains a liquid medium with sufficient nutrients required for the optimum growth of the organism and a transfer of the growth from a smaller to a larger tank is carried out at 5-10% of the volume of the larger vessel. All transfers are made under aseptic conditions and, in fact, there are facilities not only for steam sterilization of the vessels, but also all outlets from the tanks are continuously exposed to flowing steam so as to prevent contamination of the broth by other organisms. The plant equipment is made of iron or preferably of stainless steel, and the tanks are equipped with mechanical agitators and dip tubes for aeration of the broth, so as to obtain uniform growth of the micro-organism. Aeration is carried out with compressed air which is first sterilized by filtration through suitable cartridge filters before being passed through the stirred broth. Strict temperature control at all stages of the fermentation is maintained. The pH is also controlled between narrow ranges by the addition of acids or buffer salts. The fermentor has sampling devices so that the progress of the fermentation can be monitored by suitable analytical procedures which depend on the type of fermentation being carried out.

Once analytical assay indicates that the antibiotic concentration in the broth has reached an optimum, the batch is harvested. Usually the antibiotic is in solution so the broth is filtered to separate it from the mycelia which are discarded. The filtrate is then solvent extracted to isolate the antibiotic and the subsequent purification procedures depend on the nature of the antibiotic. The attached flow diagrams (Appendix VII) show the steps involved in the fermentation and recovery of tetracycline base and the formation of tetracycline hydrochloride. It can be seen that tetracycline base is isolated from the filtrate as the calcium complex and then converted back to base. Most of the antibiotics are manufactured by fermentation. However, chloramphenicol and some of the newer, semi-synthetic penicillins like Ampicillin are produced industrially by chemical methods.

The Appendix VIII to X gives general classification of equipment required including those for basic manufacture as also of process control, instruments and laboratory instruments for quality control and product development research.

The major raw materials required for antibiotic production are given in Appendix VII.

Production of chemical intermediates for Synthetic drugs: For the basic production of drugs from locally available raw materials, an integrated development of all the chemical raw materials for the chemical based industries is necessary. In developing countries, the expansions that take place in the manufacturing of basic chemicals as also in the chemical based industries including drugs, have to be linked at the stage of producing intermediary chemicals which is the starting point of chemical based industries(Appendix XII). In other words the development and production of the chemical intermediate are a series of exercises on import substition which has to be progressively achieved. This step can be undertaken as more and more basic chemicals become available and the expansion of chemical based industry makes it possible to set up economic units of production of the intermediates. There are many coproducts that will be involved in such manufacture and they will have to be found proper uses in allied industries. This is a continuous process and is like solving a gigantic jigsaw puzzle

and involves not only development of drug industry but also dyes, plastics, fibres, synthetic rubber, pesticides, etc. The basic raw materials involved are the chemicals based on alcohol, coal and petroleum. This means that not only these resources have to exist, but units get established for making alcohol based chemicals, coal based chemicals and petrochemical reformers and Crackers. Such developments are not possible when these resources do not exist or the country is not big enough for undertaking such projects. This can only be solved by regional cooperation between countries which have the resources and setting up of regional units located at the most convenient centres, whose production then can be shared by the different countries within the region. Exchange of chemical intermediates produced where natural facilities exist between developing countries can also be examined as an alternative.

This problem is not so acute in the production of antibiotics, plant products and those based on animal by-products. The nutrients required by the antibiotics industry are mainly agricultural products and their supply is dependant on overall agricultural production. The other raw materials such as solvents, precursors, filter aids, etc., are not difficult to import from other producing countries at reasonable prices. Similarly, plant products are based on local resources and with the required climatic and soil conditions, can be cultivated or if they grow naturally collected from wild sources. Animal by-products need proper organization of abbatoirs and collection of glands, organs, etc. and their storage under proper conditions to prevent the deterioration of active principles, before they are extracted.

If proper attention is given, these products can be undertaken by developing countries more easily than chemical intermediates to enable the production of synthetic drugs from basic raw materials.

Group V of the countries are those who manufacture the intermediates required for the pharmaceutical industry and produce plant and equipment required. They also undertake local research in order to develop new products and improve manufacturing processes. The steps to be taken by them are:

(a) expand the range of intermediates and the volume of production to be able to meet other developing countries' requirements;

(b) expand the production of chemical plant equipment and machinery both for the production of dosage forms and the production of drugs from basic chemicals;

(c) undertake R and D to develop new processes and screen new products.

Countries at this stage have reached near self-sufficiency with regard to raw materials to start from basic stages, the range of therapeutic groups, developmental and process research, and an effective distribution system. The developing countries arrive at this level of operation (which is comparable to international standards in production technology and the quality of products) after many years of experience with international collaboration. Although they have not reached a stage when they can be self sustaining as regards discovery of new products are concerned, they have achieved a strong technical base, the capacity to produce different chemical intermediates and thereby improved their negotiating power, can select processes most suited to their conditions and have the capacity to absorb any new technology and improve on it with their local R and D facilities. List of intermediate and basic chemicals for production of drugs are given in Appendix VIII and IX.

As regards their capacity to produce machinery and equipment this depends on how well the co-ordinated development of other engineering industries have taken place. In the same way as the manufacturer of basic drugs from primary raw materials in a country depends mainly on the status the chemical industry has reached in the country, the dependence on capital goods to produce drugs depends on the status that the engineering industries have achieved. In the following pages are described briefly the classification of equipment involved.

Production of machinery and equipment

(i) for production of dosage forms

(ii) for production of drugs from basic chemicals

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5. These form a part of the engineering industries and these developments can therefore be undertaken as mentioned earlier only where fairly well developed Engineering Industries exist in the country.

6. Here again such activity is possible if there is an adequate demand from the chemical and chemical based industries and envisages rapid developments especially in the field of dyes, drugs, pesticides, fertilizers and petro-chemicals. The type of equipment under broad headings can be classified under four main categories:

(i) pharmaceutical processing and packaging machinery, (Appendix VIII)
(ii) Laboratory and research instruments, (Appendix IX)
(iii) chemical plant and machinery including specialised, equipment for services and utilities, (Appendix X)
(iv) process control instruments, (Appendix XI)

7. Under each of these categories come a large variety of equipment and instruments. It will be necessary to have a further breakdown of the different categories into individual types depending on the expansions envisaged in the industries to study in detail the present status and future needs. This will be very much dependant on the development of Consultancy, process engineering and design and project management in the country.

8. After having arrived at the probable requirements arise the problems of:

(i) selection of location
(ii) selection of right process and know-how
(iii) planning for finance
(iv) detail process engineering and design for equipment and plant
(v) procurement of right materials and planning for equipment fabrication
(vi) manpower planning, recruitment and training

(vii) Installation of equipment

(viii) test run and start up of plant

(ix) regular routine production

9. Such an activity, however needs capable engineers with experience in a variety of design and development activities.

Patent protection and negotiation for acquiring appropriate technology

Patent protection plays some part in holding up industrial development in some countries which have strong patent laws which cover both user and process patents. But in developing countries there are usually only process patents and in some none at all. In others patent protection on drugs are prohibited for drugs while others have made the patent laws so weak in the field of food and drugs that they - the patents granted - are endorsed with a 'License of Right' and a clause for compulsory licensing exists. The period of validity of the license is also very much reduced. In all these cases what holds up industrial development is the access to'unpatented know-how'rather than what is revealed in the patents. If a country has an adequate technical base to unravel the unpatented know-how and has access to intermediates the permission to use a patent is very simple and the rates paid in such circumstances if at all is something very nominal.

Hence countries which have developed a strong technical base and have access to chemical intermediates are able to negotiate better to obtain the unpatented know-how to establish productions. They have the wherewithal to absorb the new technology and improve on it with the local R and D facilities.

It is only the lesser developed countries which do not have the appropriate background in order to be in a position to understand, untangle and compare the foreign 'know-how' are unable to negotiate proper deals. They often negotiate weekly and grant excessive concessions due to inadequate information on other agreements and lack of ability of those who negotiate, who usually are non-technical people and therefore are unaware of the technical aspects. Shortage of capital or foreign reserves and lack of managerial skills to organise and operate plants are some of the drawbacks which lead to projects being set up where national priorities get little attention and production is undertaken from stages which only increases dependence on foreign suppliers of intermediate products rather than on local resources. Such deals give more benefits to foreign interests rather than to the countries economy.

Countries in this category can easily be helped by the technology division of the UNIDO in the selection of products, type of technology best suited to the country, the better utilisation of local raw materials and help in negotiating better terms and conditions for the acquisition of appropriate technology. This division can also help technical co-operation between developing countries themselves in areas where the technology is more easily adaptable when prevailing local conditions are similar. Certain guidelines for the acquisition of technology which would be of help in negotiations has been suggested by the Second Panel Meeting of Industrial Experts on the Pharmaceutical Industry and outlined below:

(a) For drugs on which the patent has expired, the cost of purchasing technology and manufacturing know-how (often expressed in terms of technical fees and royalties on sale) should be at a reasonable rate, appropriate to the product concerned in view of the patent expiry date;

(b) For drugs on which the patent has not expired, the cost of buying the technology and manufacturing know-how may be higher; however the nearness to the end of the patent life should be taken into account;

(c) When only supply of know-how for formulation is involved, such payments should be reasonable, appropriate to the information supplied;

(d) When further stages of manufacture are undertaken within the country, higher payments are admissible;

(e) The package of terms and conditions should admit different scales of royalties, taking into account the technology involved;

(f) The transfer of technology and manufacturing know-how should be as complete as possible in the sense that the developing country should be entitled to existing and new information on the medical effectiveness of the drug, improvements in the manufacturing process made by the licensor etc.;

(g) Personnel of the developing country should be trained to manage and operate the production facility and to undertake product information, distribution and product research and development activities;

(h) The technology transfered should be adapted to suit local conditions, as and when required, by the supplier of technology collaborating with local expertise of the developing country;

(i) When the drug is manufactured from a late intermediate, the supplier of technology should ensure that the required quantity of the intermediate shall be made available at reasonable prices;

(j) In recognition of the desire by many developing countries to develop exports, the inclusion of such export markets should be considered by both parties when negotiating each technology transfer arrangement. (It is recognized that in several countries the restrictions on procurement of key ingredients such as intermediates from particular suppliers need not apply. This will depend on the technological competence of the company concerned and would in any case be a matter of discussion between the interested parties.);

(k) The supplier of technology should assist the developing country in undertaking the production of late intermediates within the country in a phased programme, so that all or as many stages of production as possible are undertaken within the country.

PROMOTION OF DRUGS UNDER INDIGENOUS SYSTEMS OF MEDICINE

In developing countries a large portion of the population depend on the indigenous systems of medicine. It would go a long way in meeting the medical needs of these countries if some of the medicines used under these systems were standardized and up-graded after a proper screening programme. In addition to determining the efficacy of the products for the purpose for which they are prescribed it will also be necessary to weed out many useless preparations that have come into existence and have been responsible for exploiting the gullible public. The methods to be adopted by different countries will not be the same but some indication to developing countries as to how best they can improve these systems of medicine and make them more effective are suggested below.

1) A system to screen and select the useful preparations should be undertaken. Having done so a formulary should be laid down, to ensure that what is dispensed is of uniform standard and will give the required therapeutic response (about 444 preparations have been listed in a national formulary for indigenous drugs in India).

2) A uniform standard of education in these systems of medicine should be evolved and a Central Register of practitioners should be maintained. A minimum standard of education should be prescribed to practice the system to avoid quacks dabbling in the health of the people.

3) A post-graduate institute or department financed by the government should be established to specialise in different branches of the system of medicine.

4) A Central Council for Research in indigenous systems should be established as an autonomous body engaged in intensive research in the different fields. They should take up, among other schemes, Drug Research, Literary Research, Clinical Research, Mobile Clinical Research and Survey of Medicinal Plants throughout the country.

5) Herbarium sheets, to identify the right herbs required prepared and experimental gardens, for the exploration of medico-botanical wealth should be established. Folklore claims should be scientifically examined. Books containing simple remidies for common ailments should be prepared and published.

6) The Pharmacopeial Laboratories for indigenous medicine should be established with a view to work out standards and develop tests for single drugs and compound preparations used in these systems of medicine. A museum of medicinal plants should be set up to facilitate identification of drugs used in Indian system of medicine.

7) State governments should establish their own pharmacies of indigenous medicines to meet the requirements of drugs for their dispensaries and hospitals. Privately run pharmacies should also be allowed to be set up and encouraged in the country.

8) The drug control in these systems should be enforced by the state governments under the prevailing legislation under the Food and Drug Administration.

9) To cater to the requirements of drugs of these systems and to increase their all-round availability, governments should establish in addition to central pharmacies a public sector undertaking. Financial assistance should be given to state governments for development of similar pharmacies and herb gardens, etc. in their own states.

10) Incorporating certain modern drugs with the indigenous drug has also helped in bringing about improved preparations. This has the advantage of reducing the toxic effects of the ingredients and making the preparations cheaper. Such useful preparations can also be incorporated in the national formulary.

Traditional medicine is extensively used in developing countries as they are cheap and within the reach of the common man. Hence traditional medicine will play an important part in the health services of these countries and how to improve the use of the

locally available substances of natural origin is already receiving the attention of governments of these countries.

The very shortage of modern medicines and their prices being out of reach of many people in developing countries is a major argument for an adequate evaluation and sensible use of these resources within the local health care systems.

Medicinal plants are one of the major components of traditional medicine and represent a complete set of therapeutic and cultural values. No doubt extraction and isolation of their active principles have, in several instances, led to some of their active principles being adopted in modern medicine and synthetic substitutes prepared. But still there is a feeling in the practitioners of these indigenous medicines, and probably rightly so, that they should not be mutilated and reduced to mere phytotherapy but should be used in its original form for them to be beneficial.

APPENDIX I

REQUIREMENT OF EQUIPMENTS IN VARIOUS DEPARTMENTS OF DRUG FORMULATION UNIT.

I. TABLET DEPARTMENT:

Capacity : 1500 million tablets/year
6.25 million tablets/2 shifts/day.
Average Wt/tablet : 350 mg.
2.5 Tonnes/day = 62,50,000 Tablets.

Floor Area : 485 sq.metres.

EQUIPMENT

Granulation.

1.	Platform balance - 1 tonne capacity :	1
	Platform balance - 300 kg. capacity :	1
	Two Pan Balance - 10 kg. capacity :	1
	Chemical balance - .. :	1
2.	Powder Shifter:	
	Comminuting Mill - Jacketed :	1
	" " - Simple .	1
3.	Mixer:	
	Hobart type Mixer with Stirrer. - 500 Litres Capacity:	1
	Extra bowls for above .. :	3
	Hobart type Mixer with Stirrer - 100 Litres Capacity:	1
	Extra bowls for above .. :	1

Steam operated kettle S.S. - 50 Litres	:	1
" " " -100 Litres	:	2
Mortar and Pestle (5 kg. & 10 kg.capacity):		1 each
Cabinet dryer - Thermostatistically controlled - 110°C - (Steam operated 48 trays)	:	2
Fluid Bed Dryer - 120 kg.	:	1
" " - 60 kg.	:	1
Extra Vessels for above	:	3 each.
Drying room (50 sq.metres), thermostatistically controlled, with 6 Trollies of 48 trays.	:	1

Lubrication:

Powder Shifter - 50 kg.	:	1
Granulator	:	2
Hobart Mixer (500 lits)	:	1
Platform balance - 500kg. capacity.	:	1
" " - 10 kg. "	:	1

Compression Section:

Press Coat (900 series)	:	1
Rota Press - 45 station (8000 tablets/minute)	:	1
37 Station Rotary Tablet Machine (2500 Tabs/minute)	:	2
27 Station Rotary Tablet Machine (1500 tablets/minute)	:	2
16 Station Rotary Tablet Machine (500 tabs/minute)	:	2
Single Stroke Compression Machine (90 tabs/minute)	:	1

Hardness Tester	:	4
Vernier Calipers	:	2
Disintegration time unit	:	2
Chemical Balance	:	1
Chilsonator (Roll dia: 20 cmx10 cm. 250 kg/hr)	:	1
Tablet Dedusting Unit	:	4

Coating Section: 1.5 Million Tablets/2 shifts/day.

Coating Pan - 60"	:	1
Coating Pan - 72"	:	1
Jacketed Kettle (20 lit.)	:	2
Colloid Mill	:	1
Polishing Pan with Drive	:	1

Dryer:

48 trays cabinet type	:	2
Two Pan Balance 10 kg.	:	1
" " " 1 kg.	:	1
Chemical Balance	:	1

CAPITAL INVESTMENT IN ABOVE PLANT AND MACHINERY. .. .. Rs.3.62 millions (US $0.42 million)

II. CAPSULE DEPARTMENT:

Capacity : 240 million capsules/year
1 million capsules/2 shifts/day.
Average Wt/capsule : 300 mg.
300 kgs/day.

Floor Area : 255 sq.metres.

EQUIPMENTS:

Platform Balance	- 300 kg.	:	1
Two Pan Balance	- 10 kg.	:	1
One Pan Balance	- 1 kg.	:	1
Mixer -	- 210 lit. capacity	:	2
Double Conc. Mixer	- 100 lit. capacity	:	1
Mortar and Pestle	- 5 kg. capacity	:	1
Chilsonator	- 40 kg/hr.	:	1
Dryers specially designed		:	2
Vacuum Dryer	- 40 trays	:	1
Automatic Capsule Filling Machine (ACF-Cadmach)	- 500 caps/minute	:	2
c Extra accessories for filling other size capsules for above.			
Semi-Automatic Capsule Filling Machine (300 capsules)		:	3
c Extra accessories for other size caps.			
Empty Capsule Loader		:	2
Capsule Inspection Unit with belt		:	2 (1 Penicillin + 1 others)
Capsule Printing Machine		:	2 (1 + 1)
Chemical Balance		:	3
Humidity Recorders		:	6 (Roomwise each)
Capsule Polishing Unit		:	2 (1 Penicillin +1 others)

CAPITAL INVESTMENT FOR ABOVE PLANT AND MACHINERY .. .. .. : Rs.1.52 million : (US $ 0.18 million)

III. LIQUID DEPARTMENT:

Capacity : 1800 Kilo-litres/year
7500 litres/2 shifts/day.
60 ml. and 120 ml.pkgs.
94,000 units/2 shifts/day.

Floor Area : 890 sq.metres.

EQUIPMENT

Weighing Balance	Platform type 500 kg.capacity	: 1
	Double Pan 10 kg. capacity	: 1
	Mono Pan Balance 1 kg. "	: 1
Mixing Tanks S.S. with Stirrer	5000 lit. capacity	: 2
	1500 lit.capacity	: 2
	500 lit.capacity	: 2
Jacketed Tanks with Stirrer	2000 lit. capacity	: 1
	1000 lit. capacity	: 1
Planetary Mixer, Hobart Type	500 lit.capacity	: 1
Colloid Mill	...	: 2
pH Meter	...	: 1
Viscometer	...	: 1
Lob Pump (Pharma Lab.) - 1500 lit/hr.		: 2
Filter Press - 2000 lit/hr.	...	: 2
Eight heeds filling unit (48000 units/shift)		: 1
Automatic Capping Unit	...	: 2
Automatic Labelling Unit	...	: 2
Automatic Carton Opening Machine		: 2
Conveyor belts with checking units		: 2 (7 metres each)
Automatic Gravity filling machine for viscous liquid like Malt.		: 1
Kettle S.S. - 500 litres	...	: 1

CAPITAL INVESTMENT IN ABOVE PLANT AND MACHINERY ... : Rs.1.83 million (US $ 0.21 million)

IV. OINTMENT DEPARTMENT:

Capacity : 60,000 kg/year
250 kg/2 shifts/day.

Floor Area : 200 sq.metres.

EQUIPMENT

Cleaning and Sterilisation:

Isopropyl Sterilizer for tubes	:	1
Powder Sterilizer U.V.Close cabinet of 5 kg. capacity.	:	1

Manufacturing:

Weighing Platform type Balance 200 kg. capacity.	:	1
Weighing Two Pan Balance 10 kg. capacity.	:	1
Weighing Monopan Balance 1 kg. capacity.	:	1
Chemical Balance	:	1 (Sterile & Non-sterile)

Preparation:

Jacketed Mixing Tank with Stirrer 200 kg. capacity.	:	2 (1 Sterile + 1 Non-sterile)
Tripple Roller S.S.Roll	:	2 (" ")
Ball Mill 50 kg. capacity	:	1
Edge Runner Mill 25 kg.capacity	:	1
Jacketed Colloid Mill	:	1
Hot Air Oven (for Ophthalmic preparation) 200°C - 48 trays.	:	1
Autoclave Double-Door	:	1

Filling and Crimping:

Automatic tube filling and crimping machine 4000tubes per hour.	:	1
Chemical Balance - Mono Pan	:	1

CAPITAL INVESTMENT IN ABOVE PLANT AND MACHINERY: Rs.0.59 million (US $0.07 million)

V. PARENTERAL DEPARTMENT: (including infusions)

Capacity : 300 Kilo Litres/year
1250 litres/2 shifts/day.

Floor Area : 305 sq.metres.

EQUIPMENT

Washing:

Automatic Rotary Type High Speed Washing Machine for ampoules and vials	:	1
Demineralisation Plant 300 lit/hr.	:	1
Distillation Plant ..500 lit/hr.	:	1
Rubber Stopper Washing Machine 100 kg/capacity.	:	1

Sterilisation:

Double-Door Autoclave with thermo-recorder 24000 vials capacity. (42"x48"x84")	:	1
DoubleDoor Dry Heat Steriliser 20000 vials capacity(65"x33"x32")	:	2
Storage tank with constant temperature for distilled water 1000 litres.	:	2

Manufacturing:

Weighing Balance Platform type 100 kg. capacity.	:	1
Two Pan Balance 10 kg. capacity	:	1
Single Pan Balance 200 gms.capacity.	:	1
S.S.Tank 200 lit. capacity Jacketed with stirrer.	:	3
S.S.Tank 100 lit. capacity Jacketed with stirrer.	:	3
S.S.Pressure Vessel 100 lit.capacity	:	2
S.S.Pressure Vessel 50 lit.capacity.	:	1
Membrane filtering unit column type.	:	2

Membrane filtering Unit 193 mm.	: 2
Membrane filtering unit 141 mm.	: 2
Vacuum Pump with high capacity	: 1
Air compressor	: 1

Filling and Sealing:

Automatic multi-head vials filling and rubber stoppering unit with sealing unit.	: 1
Three head ampoules filling and sealing machine.	: 2
Laminar Flow (6 feet)	: 3 units.

Leak Test:

Vacuum Operated Vessel	: 1
Inspection Unit for physical checking	: 10

CAPITAL INVESTMENT IN ABOVE PLANT AND MACHINERY. .. .. .. : Rs.2.29 millions (US $ 0.27 million)

VI. POWDER & GRANULES SECTION:

Capacity : 60 Tonnes/year
250 kg/2 shifts/day
or 12,500 bottles.

Floor area : 165 sq.metres.

EQUIPMENT

Mixer (210 litres capacity)	: 2 (1 Penicillin + 1 others)
Dryer (48 trays)	: 2 (" ")
Augur type Automatic Bottle Filling Machine.	: 2 (" ")
Conveyor Belt	: 2 (" ")
Semi-Automatic Capping Machine	: 2
Granulator	: 2 (1 Penicillin + 1 others)

CAPITAL INVESTMENT IN ABOVE PLANT AND MACHINERY: .. .. : Rs. 0.48 million (US $ 0.06 million)

VII. QUALITY CONTROL DEPARTMENT:

A. Chemical Analysis Divisio

Mettler balances	:	3
Melting Point apparatus	:	2
Hot Air Oven	:	3
Vacuum Oven with vacuum pump	:	1
Distilled water unit	:	1
Muffle furnace	:	1
Oxygen flask wich platinum basket	:	2
Platinum dishes and crucibles	:	6
Various types of Glassware		
Waterbath (Electrical)	:	3
Gas Plant	:	1
Other miscellaneous equipments.		

B. Instrumental Analysis Division:

Gas Chromatograph	:	1
I.R.Spectrophotometer	:	1
U.V.Spectrophotometer	:	1
Flourimeter	:	1
pH Meter	:	2
Refrectometer	:	1
Paper Chromatographic equipment	:	1
Thin Layer Chromatographic equipment	:	1
Air permeability apparatus for surface area.	:	1
Polarimeter	:	1
Viscometers (Redwood, Ostwald and Brookfield 1 each).	:	3
Tablet Disintegration machine	:	2
Tablet Dissolution rate machine	:	1

Tablet Hardness Tester	:	1
Tablet Friability Test Machine	:	1
Tablet Inspection Belt	:	1
Karl Fisher Moisture determining apparatus.	:	1
Flame Photometer	:	1
Vernier Callipers	:	2
Micrometer Screw	:	2
Potentiometric Titration Unit	:	1

C. Microbiological Analysis Division:

Asceptic cabinet for sterility testing	:	1
Hot air ovens	:	2
Incubators (to maintain temperature from 0-50°C).	:	4
Autoclaves (Sterilisers)	:	2
Microscope with camera lucida	:	1
Projection Microscope	:	1
Refrigerated High Speed Centrifuge Machine. (20,000 r.p.m.)	:	1
Zone reader	:	1
Refrigerator	:	3
Coulter counter	:	1

D. Pharmacological Analysis Division:

Automatic Temperature Recording Machine for Pyrogen Test.	:	1
Kymograph for test for depressor substances.	:	1

Animal House:

Cages : (a) Galvanised cages for rabbits cats and guinea pigs.

(b) Polypropylene or galvanished cages for mice.

Animals:	Rabbits for Pyrogens	:	36
	Cat for Depressor test	:	6
	Mice for toxicity	:	200
	Guinea Pigs for toxicity	:	50

CAPITAL INVESTMENT IN ABOVE PLANT AND MACHINERY .. .. .. : Rs. 0.81 million. (U.S. $ 0.09 million)

VIII. RESEARCH & DEVELOPMENT DEPARTMENT (FORMULATION)

Area : 150 sq.metres.

EQUIPMENT

Tablet Compression Machine - Single Stroke	:	1
Rotary Tablet Machine - 16 station.	:	1
Mixer	:	1
Granulator	:	1
Coating Pan	:	1
Oven Small size (Range 40°C-200°C)	:	1
Capsule Filling Machine (200 Capsules) capacity	:	1
Balance - 5 kg. capacity	:	1
Chemical Balance Single Pan - 200 Gms. capacity.	:	1
Triple Roller Mill - small size.	:	1
Colloid Mill - small size.	:	1
Jacketed Vessel & Stirrer - 5 lit.capacity	:	1
Ball Mill - 2 kg. capacity	:	1
Tube Filling Machine - semi-automatic	:	1
Tube Crimping Machine- semi-automatic	:	1
Liquid Filling Machine (range 1 to 30 ml.)	:	1
Capping Machine for Vials & Bottles)	:	1
Mini-Bottle and Vial Washing Machine	:	1

Autoclave Small size	:	1
Ampoule Sealing Machine	:	1
Incubator 30°, 45°, 60°, each	:	3
Refrigerator small size.	:	1
Humidity & Temperature Control Cabint	:	1
Library Books & Periodicals	:	

CAPITAL INVESTMENT IN ABOVE PLANT AND MACHINERY. .. .. : Rs. 0.32 million (US $ 0.04 million)

IX. CENTRAL PACKING DEPARTMENT

Area : 750 sq.metres.

EQUIPMENTS:

Strip Packing Machine (Six Tablets)	:	6
Conveyor Belts (5 Metre each)	:	12
Automatic Tablet Counting and Filling Machine.	:	2
Automatic Capsule Counting and Filling Machine.	:	1
Automatic Capping Machine	:	2
Tin Sealing Machine	:	1
Gumming Machine	:	2
Automatic Carton Opener	:	3
Automatic Label & Carton Printing Machine	:	2
Automatic Printing & Labelling Machine for Vials and Ampoules.	:	3
Heat Sealer for Plastic bags	:	3

CAPITAL INVESTMENT FOR ABOVE PLANT AND MACHINERY .. .. .. : Rs. 1.18 million (US $ 0.14 million)

X. MAINTENANCE & COMMON UTILITY SERVICES DEPARTMENT:

Area : 375 sq.metres.

EQUIPMENT:

Lathe (165x600 mm) (Kirloskar)	: 1
Lathe (300x200 mm) "	: 1
Drilling Machine (2") (Praga)	: 2
Bench Grinder (150 mm) (Wolf)	: 1
Flexible Grinder - medium size (Wolf)	: 1
Portable Drill Machine:	
Upto 13 mm. size (Wolf)	: 1
Upto 38 mm. size (Wolf)	: 1
Portable Blower - small size (Wolf)	: 1
Electric Welding Machine 12 KVA 3 Phase Oil cooled (Advani)	: 1
Gas Welding Set (standard size)	: 1
Air Compressor - 20 HP, 3 Phase, 60 CFM, 150 PSI (Ingersoll Rand)	: 1
Vacuum Pump - 10 HP, 3 Phase, 177.0 CFM, Ultimate vacuum - 0.005 (J.B.Sawant Engg.)	: 1
Gas Plant - 8A Size Gas produced 141.5 c.metre per hr. (Ganson)	: 1
Boiler - 2 tons capacity (Wanson or WIMA India)	: 1

Water Treatment Plant:

(i) Demineralised water plant - 1000 litres per hour.

(ii) Water Softening Plant - 10000 litres per shift.

(iii) Distilled water plant - 500 litres per hour.

Airconditioning Plants - 3 plants.
80 tons capacity.

CAPITAL INVESTMENT IN ABOVE PLANT AND MACHINERY .. .. .. : Rs.3.69 million (US $ 0.43 million)

Ref: Project Profile for a Drug Formulation Unit by I.A. Modi, Cadilla Laboratories, Ahmedabad, India

APPENDIX II. LIST OF PACKAGING MATERIAL FOR REPACKING ACTIVITY

Sl. No.	Type of Formulation	Containers	Closures	Outer Packaging	Shippers	Remarks
1.	Sterile Antibiotics Powders in Vials.	USP Type III Vials (20 mm-d) 5,10 and 20 ml. capacity.	(a) Rubber Stoppers (b) Aluminium Seals	(a) Vial Labels (b) Printed Carrier Cartons	(a) Corrugated boxes (b) Gummed tape.	Except for rubber stoppers, the quality of all materials satisfactory. Rubber stoppers to be improved to suit automatic stoppering machines.
2.	Parenteral solutions.	1. USP Type I vials (11mm-d) 5,10 & 20 ml. capacity	(a) Gum Rubber Stoppers (b) Aluminium Seals (c) Aluminium Dust Caps.	(a) Labels (b) Printed Individual Cartons (c) Inserts (d) Carrier Cartons	(a) Corrugated boxes (b) Gummed tape.	—
		2. USP Type I glass ampoules (amber or white flint) 1,2,5,10 & 25 ml. capacity.	End sealing by jet flame	(a) Labels (b) Carrier Trays (Paper or Plastic) (c) Carrier Labels (d) Inserts	(a) Corrugated boxes (b) Gummed tape.	There is still some difficulty in the procurement of ampoules made in automatic machines for use with high speed filling & sealing machines.
3.	Sterile Transfusion solutions.	Neutral glass infusion bottles or Special Plastic bottles-500ml. capacity	(a) Rubber plugs (b) Aluminium caps (c) Aluminium Dust Caps	(a) Labels (b) Individual cartons (Printed) with corrugated liners (c) Dispensers (d) Inserts	(a) 7-ply corrugated boxes with cushion liners. (b) Gummed tape.	—
4.	Elixirs, Syrups & Suspensions; Ophthalmic or Otic Solutions, etc.	1. White or Amber bottles-10, 25, 50, 100,250,500 & 1000ml.	(a) Bakelite or metal caps with paper wads. (b) Pilfer-proof closures.	(a) Labels (b) Individual cartons (printed) with corrugated liners. (c) Inserts	(a) 7-ply corrugated boxes with cushion liners. (b) Gummed tape.	(a) Measuring spoons & cups (plastic) for dispensing. (b) Dropper assembly in case of drop dispensing.

Sl. No.	Type of Formulation	Containers	Closures	Outer Packaging	Shippers	Remarks
		2. Polyethylene squeeze bottles 10 & 20 ml. capacity (Printed).	(a) Polyethylene screw caps (b) Dust caps	(a) Individual printed cartons (b) Inserts	(a) Corrugated carrier boxes. (b) Gummed tape.	—
		3. "Drop-tainers" with droppers	Bakelite screw caps	(a) Labels (b) Individual printed cartons (c) Inserts	(a) Corrugated carrier boxes. (b) Gummed tape.	—
5.	Tablets, Capsules, Suppositories, etc.	1. White or Amber bottles.	(a) Corks or Polyethylene plugs (b) Pilfer-proof caps with silicagel bags	(a) Labels (b) Printed individual cartons. (c) Inserts	(a) 7-ply corrugated boxes with cushion (b) Gummed tape.	—
		2. Polystyrene containers with polyethylene bags.	Polystyrene screw with silicagel bags	Printed Carrier cartons (Paper or Plastic)	(a) Corrugated paper boxes. (b) Gummed tape.	—
		3. Printed Laminated paper plastic or Aluminium foil laminates in rolls.	Heat sealing	(a) Catch covers (Printed) (b) Inserts (c) Carrier cartons.	(a) Corrugated paper boxes (b) Gummed tape	
		4. Plastic tablet dispensers (printed)	—	(a) Carrier cartons (printed) (b) Inserts	(a) Corrugated paper boxes. (b) Gummed tape.	Specially used for Saccharin and other readily needed Tablets.
6.	Ointments, Creams and Pastes.	1. Printed Collapsible tubes (inside lacquered Aluminium or tinned steel)	Bakelite or HDPE screw caps with seals.	(a) Individual cartons (b) Inserts (c) Carrier cartons (d) Carrier labels.	(a) Corrugated boxes. (b) Gummed tape.	Individual cartons can be dispensed with if nested packing is used.

Sl. No.	Type of Formulation	Containers	Closures	Outer Packaging	Shippers	Remarks
		2. Glass Jars (Amber)	Bakelite or HDPE Screw caps with wads	(a) Individual cartons (b) Inserts (c) Carrier cartons (d) Carrier labels.	(a) Corrugated boxes (b) Gummed tape.	—
7.	Powders for suspension, Dusting powders granules, etc.	1. Amber or White bottles.	(a) Rubber wads (b) Bakelite screw-caps (c) P. P. seals	(a) Labels (b) Individual cartons (c) Inserts (d) Printed carrier cartons.	(a) Corrugated boxes. (b) Gummed tape.	—
		Plastic (LDPE) squeeze bottles	(a) Plastic plugs (b) Polyethylene screw caps	(a) Labels (b) Individual cartons (c) Inserts (d) Printed carrier cartons	(a) Corrugated boxes. (b) Gummed tape.	—
		3. Polyethylene Laminated paper bags, pouches, etc. (Printed)	Heat sealing	(a) Inserts (b) Printed carrier cartons	(a) Corrugated boxes. (b) Gummed tape.	
8.	Tinctures, extracts and infusions.	N. M. Amber bottles 500 ml. capacity	P. P. caps	(a) Labels (b) Cellophane wrap	(a) Wooden boxes. (b) Signod straps	—
9.	Nutritional products Foods, Biscuits.	1. Bags made of polyethylene or other Laminates.	Heat sealing	(a) Inserts (b) Printed carrier cartons	(a) Corrugated boxes. (b) Gummed tape.	—
		2. Printed tins or printed composite containers	(a) Metal lids (b) Paper wads	—	(a) Corrugated boxes. with liners (b) Gummed tape.	—

Sl. No.	Type of Formulation	Containers	Closures	Outer Packaging	Shippers	Remarks
		3. Printed Waxed paper or Laminated Aluminium Foil Wrape.	Adhesive wrap sealing.	—	(a) Corrugated boxes. (b) Gummed tape.	—
10	Aerosols & Sprays (Pressure packs)	Printed container made of tinplated steel, extruded seamless Aluminium, coated glass or Synthetic plastics with Polyethylene dip tubes.	Spray valves with Polyethylene actuators & pistons.	(a) Inserts. (b) Printed carrier cartons.	(a) Corrugated boxes. (b) Gummed tape.	Aerosol packs need Propellents which are usually compressed fluorinated hydrocarbon gases. Glass containers are preferred for Pharmaceutical pressure packages.

NOTE: (1) Jute paper lined wooden cases are used for shipping specially in rainy season.
(2) Cellophane wrapping of individual containers was being done for all packings. Now no longer used. Plastic film "peel wraps" are being tried.

Ref: Indian Pharmaceutical Industry - 1973. D.G.T.D. Government of India

APPENDIX III: LIST OF ANCILLARY PRODUCTS REQUIRED TO FORMULATE DRUGS

Diluents

Lactose
Starch
sucrose
Manintol
Dicalcium phosphate
Calcium sulphate
Microcrystalline cellulose (Avicel)

Binders

Gum acacia
Gum tragacanth
Gelatin
Starch paste
Sodium carboxymethyl cellulose
Methyl cellulose
Ethyl cellulose
polivinyl pyrolidene
sodium alginate

Lubricants

Talcum powder
liquid paraffin
stearic acid
calcium stearate
magnesium stearate

Coloring Agents

only certified food and drug colors

Flavouring Agents

Make dosage forms more paletable act as a mark against undesirable taste of the indgredients.

Capsules

Hard gelatin capsules
Soft gelatin capsules
seamless capsules

Emulsifying agents

Tween 80
span 20
benzalkonium chloride
glycerylmonistearate
gum acacia

Suspending agents

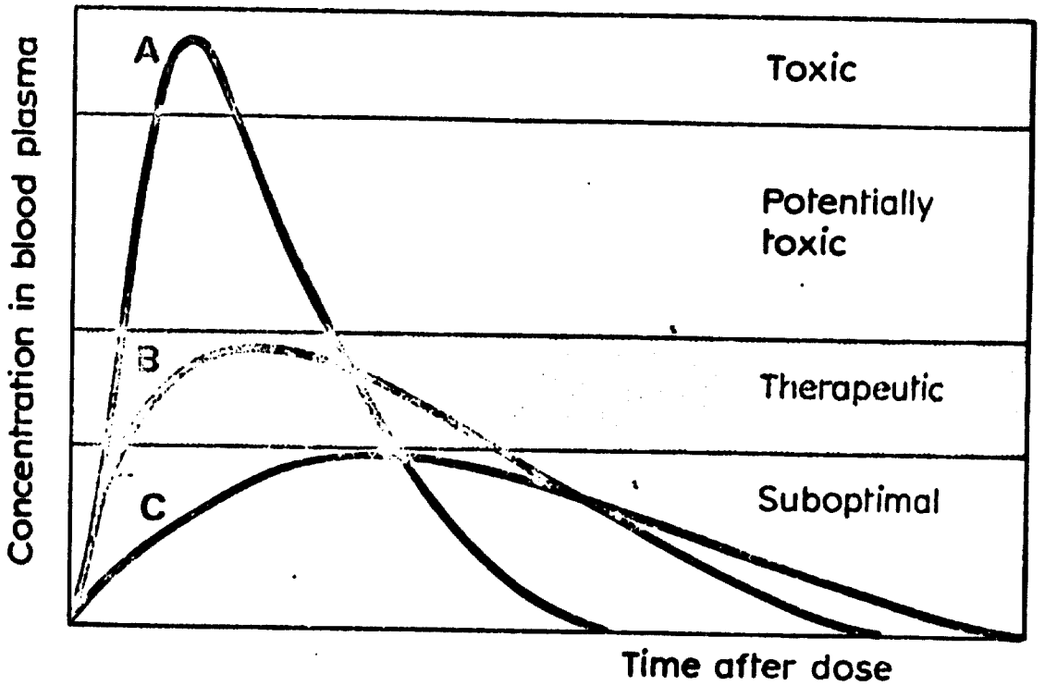
sodium carboxy-methyl-cellulose
Methyl-cellulose
Carbopal (polyacrylic acid)
sodium algriate
gum acacia
gum tragacanth

Preservations

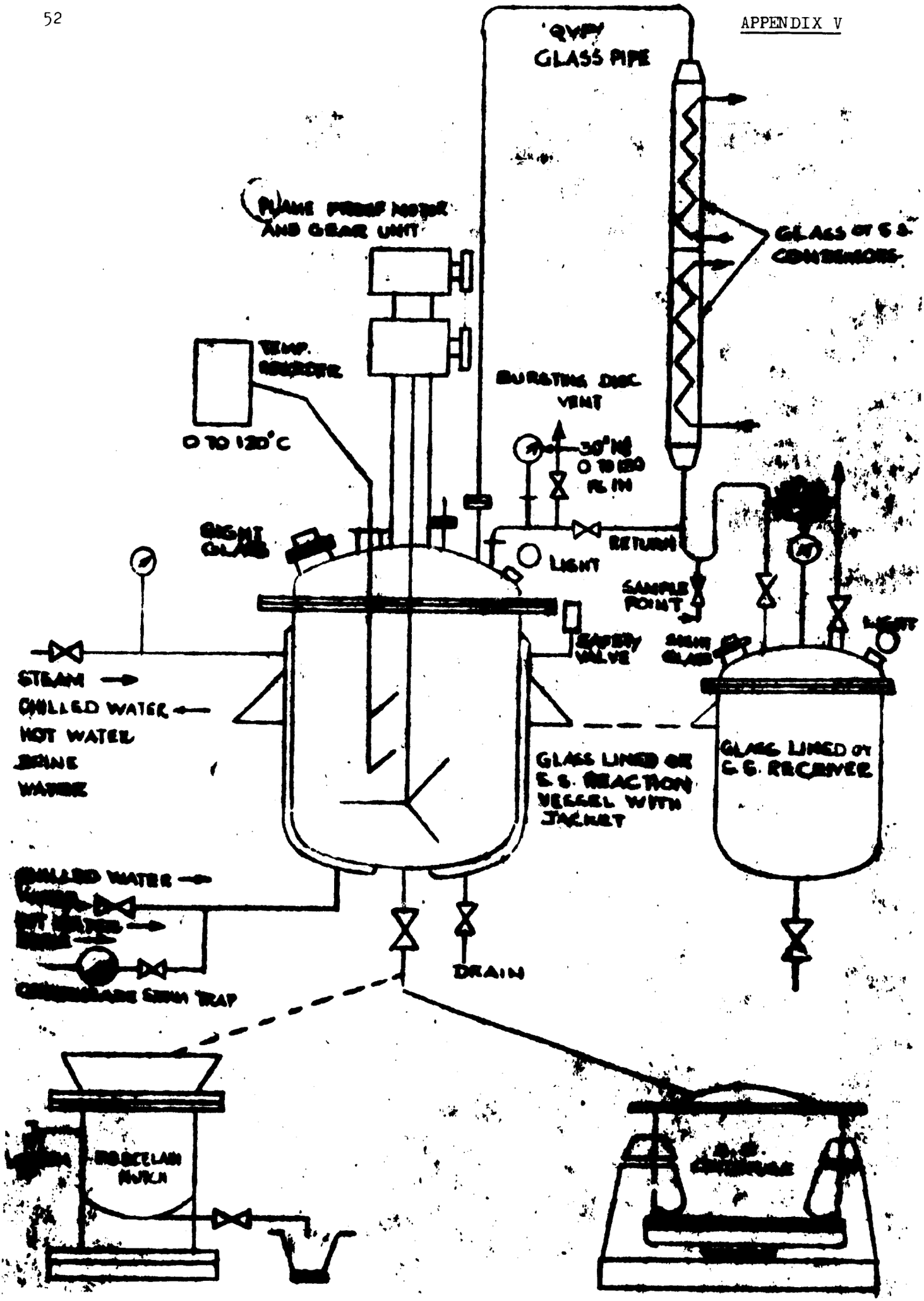
alcohol
hydroxy benzoates
sorbic acid

APPENDIX IV.

BIO-AVAILABILITY OF A DRUG FORMULATION DEPENDING ON THE AUXILLARY INGREDIENTS, PARTICLE SIZE, METHOD OF FORMULATION, ETC.



All three drug formulations A, B and C release the same total dose into the bloodstream. But drug A is released so fast that it reaches toxic levels, while drug C is released so slowly that it never reaches the level at which it has any effect. Only drug B is medically useful.



MULTIPURPOSE REACTION AND DISTILLATION UNIT

LIST OF EQUIPMENT FOR MULTIPURPOSE PLANT

ESTIMATED COST OF EQUIPMENT

A. Process Equipment

1.	Glasslined reactor 1000 litres, jacketted with anchor agitator, condenser, receiver 500 litres.	2 Nos.
2.	SS Reactor jacketted with stirrer, 100 litres MS Receiver 500 litres	2 Nos.
3.	MS Distillation unit (1000 Litres) with receiver (5000 litres)	3 Nos.
4.	Cast Iron Reactor jacketted anchor type stirrer, MS receiver 500 litres	1 No.
5.	SS 316 centrifuge 1000 mm dia	2 Nos.
6.	MS rubberlined centrifuge 1000 mm dia	1 No.
7.	Steamheated Dryer 72 Aluminium trays (80x80x3)	2 Nos.
8.	Vacuum steam heated tray drier with trays as above	2 Nos.
9.	SS Crystallizer with jacket and anchor type stirrer 5000 litres	3 Nos.
10.	Pressure leaf filter SS	2 Nos.

Total FOB Bombay US $ 200,000

1.

Drugs that can be produced.

1. Methyl Salicylate
2. Aspirin
3. Paracetamol
4. Nicotinomide
5. Isoniazed
6. Phanaceton
7. Phenyl butazone
8. Lidocaine

} 200 tonnes/yr

B. Services Equipment

1.	Water ring Vacuum pump 80 m^3/hr.	2 Nos.
2.	Air compressors with receiver 30 cfm 30 psi with receiver	2 Nos.
3.	Steam generating plant 600 Kg/hr. with water softener and accessories	1 No.
4.	Refrigeration plant for chilled water 20 TR with cooling tower	1 No.
5.	Water circulation pumps	6 Nos.
6.	DM water plant	1 No.
7.	Electrical Distribution Panel LT/HT circuit breaker	Set

Total FOB Bombay US $ 90,000/-.

C. Laboratory Equipment:

1.	Balances	2 Nos.
2.	Glassware	Set
3.	Vacuum Pump	1 No.
4.	Muffle Furnace	1 No.
5.	Electric Oven	1 No.
6.	pH meter	1 No.
7.	Misc. Instruments thermometers, melting point apparatus etc.	Set

Total FOB Bombay US $ 20,000

Ref: Multipurpose Basic Pharmaceutical Plant Project Proposal Sarabhai International Baroda, India

APPENDIX VI.

Requirement of Raw Materials for the Manufacture of Antibiotics

Penicillin

Streptomycin

Tetracyclines

Neomycin

Raw Materials:-

Carbohydrates

Strach

Dextrin

Dextrose

Cane Sugar

Protein Sources

Scya Flour

Corn Steep Liquor (50%)

Ground nut meal

Salts

Ammonium Sulphate

Sodium Sulphate

Ammonium Chloride

Manganese Sulphate

Zinc Sulphate

Sodium Bi-phosphate

Sodium Chloride

Potassium Acetate

Potassium Dihdrophosphate

Acids

Sulphuric Acid (Tech)

Nitric Acid (Tech)

Hydrochloric Acid (Tech)

Oxalic Acid (Tech)

E.D.T.A.

Alkalies

Calcium Carbonate (Tech)
Sodium Hydroxide (Tech)
Potassium Hydroxide (CP)
Calcium Oxide (Tech)

Gases

Ammonia

Chlorine

Nitrogen

Carboxide

Solvents

Butanol

Butylacetate

Methanol

Isopropyl Alcohol

Octanol

Quaternary Ammonium Compounds

Arquad/Citramide

NID/Tretolite

Filter Aid

Dicalite/Hyflosupercel

Decolorising Agent

Active carbon

Resins (Replenishments)

IRC-50

IR-45 or equivalent

IR-124 or equivalent

Deacidite FF

Zeocarb-225

Antifoamers

Wax Emulsion

Vegetable Oils

Miscellaneous

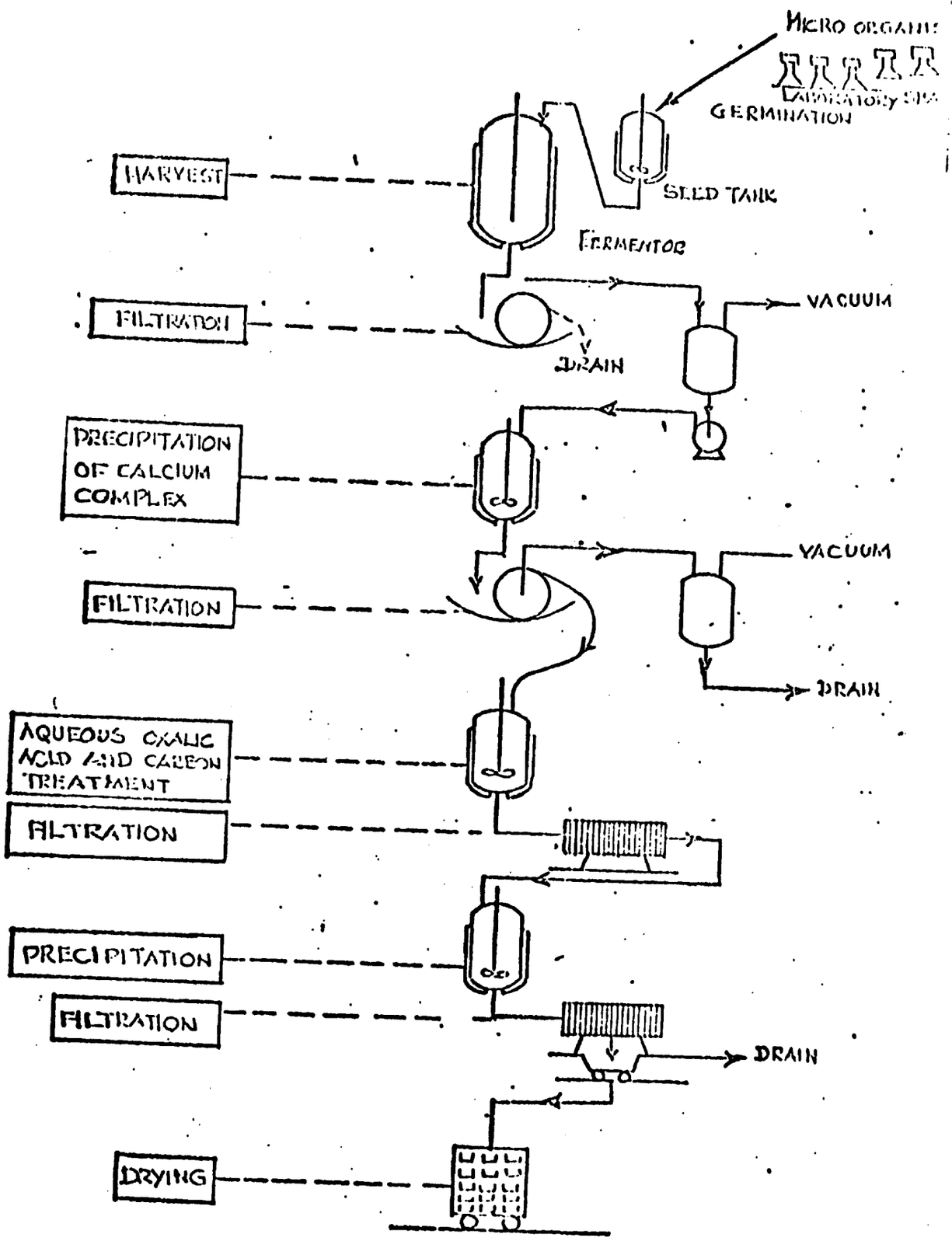
Formaldeyde (30%)

Potassium Phenyl Acetate

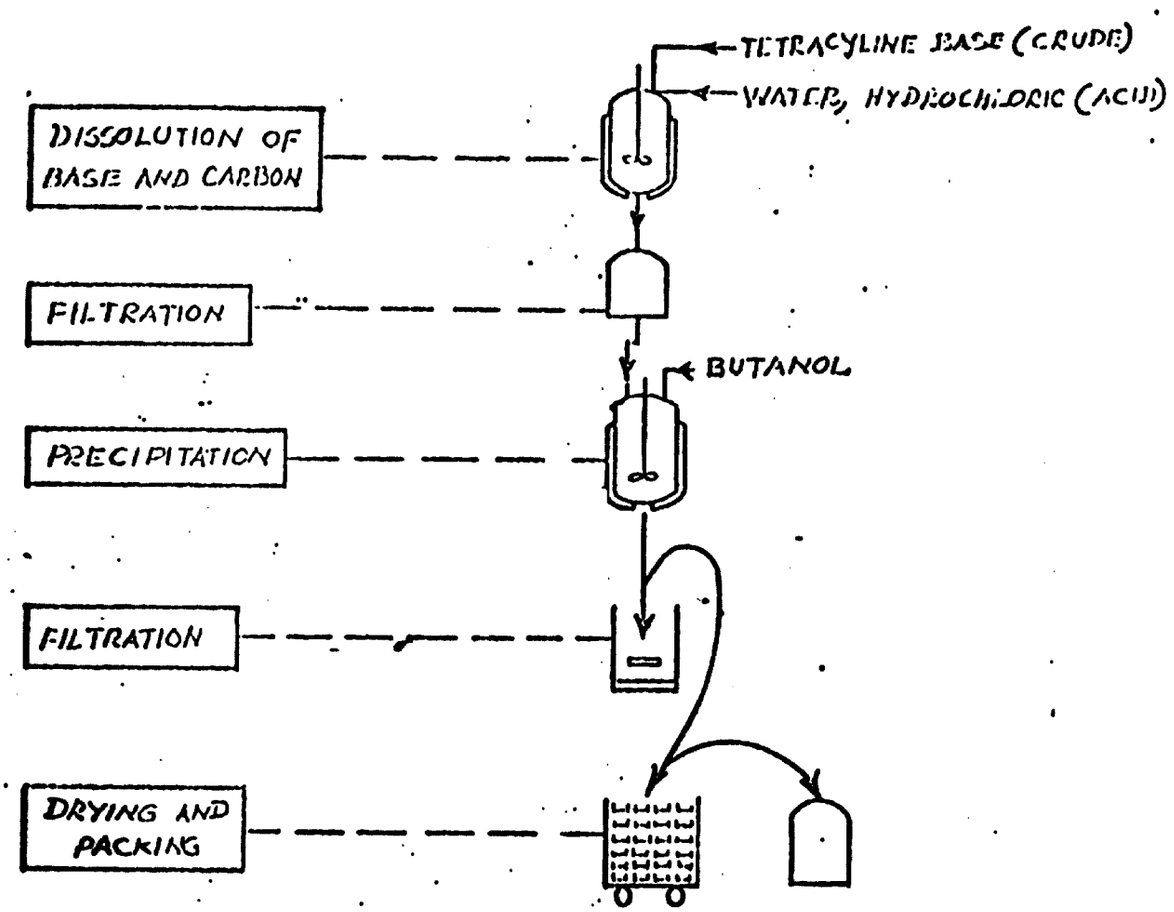
Phenyl acetamide and Phenyl acetic acid

FERMENTATION, RECOVERY OF TETRACYCLINE BASE (CRUDE)

FROM PERMENTOR LIQUOR



PREPARATION OF TETRACYCLINE HYDROCHLORIDE
FROM TETRACYCLINE BASE (CRUDE)



APPENDIX VII. LIST OF INTERMEDIATES AND BASIC CHEMICALS FOR PRODUCTION OF DRUGS

Unit - Tonnes

Name of Chemical/Intermediate
A. Alcohol based
1. Acetic Acid
2. Acetic anhydride
3. n-butanol
4. Butyl acetate
5. 2-Ethyl hexanol
6. Ethyl acetate
B. Methane and Methanol based
1. Methanol
2. Formaldehyde
3. Methylamine
4. Dimethyl sulphate
5. Methylene dichloride)
6. Methyl chloride)
C. Other derivatives based on alcohol
1. Monochloroacetic acid
2. Aceto acetic ester cyanoacetic ester
3. Methyl dichloro acetate
4. Aceto acetic ester
5. Diethyl malonate
D. Coke-oven products and their derivatives
1. Benzene
2. Toluene
3. Phenol
E. Petro Chemicals Products
1. Benzene
2. Toluene
3. Orthoxylene
4. Ethylene oxide
5. Acrylo Nitrile
6. Acetonitrile
7. Butanol
8. Acetone
9. MIBK
10. Ethyl chloride
11. Phenol

12. Nitro Benzene
13. Meta amino phenol
14. M.C.B.
15. Aniline
16. Acetanilide
17. Para-nitro tolene
18. Meta Nitro Toluene
19. Ortho Nitro Toluene

Other products based on Toluene and Benzene

20. Acetophenone
21. Amino chlorobenzophenone
22. C and P nitro phenol
23. p-Chloro phenol
24. p-Chlorobenzene sulfonamide
25. 2-5 dichloro nitrobenzene
26. Methyl benzene sulfonate
27. p-nitro aceto phenone
28. Benzaldehyde
29. Benzoic Acid
30. Benzyl chloride
31. Benzyl cyanide
32. p-chloro benzoic acid
33. 2:4 Dichloro benzoic acid
34. p-nitro benzoic acid
35. m-nitrobenzoic acid
36. p-toluene sulfonamide
37. Phenyl acetamide
38. Phenyl acetic acid and its salts

DRUG INTERMEDIATES

Hydrazine hydrate 50%
Phenylhydrazine
Pyrazolone
Paraphenetadine
Para Amino phenol
Thiosemicarbazide
Acetyl Sulfanilamide
Cyano Acetic Ester
Acetyl Acetone
Acetobutrolactone
Diethylamine
Triethylamine
Monoethylamine
Malonic ester
Sulfaguanidine
Diethyl Carbamly chloride
Trichloroacetone

High pressure synthetics plant

1. Beta Picoline
2. Alpha Picoline
3. Pyridine
4. Gamma Picoline

Along with dye intermediates

1. Methyl dichloroacetate
2. Phosgene
3. P. Toluene sulphanamide
4. Ethyl chloroformate

Along with (Textile Auxiliaries)

1. Quaternary Ammonium Compounds

APPENDIX VIII. LIST OF MACHINERY REQUIRED FOR FORMULATION OF DRUGS AND PRODUCTION OF DRUGS

PHARMACEUTICAL, PROCESSING AND PACKAGING MACHINERY:

Type of equipment

1. Tablet presses and accessories
2. Coating and Polishing pans
3. Capsule filling, band sealing and capsule printing machines.
4. Tablet and capsule counting devices.
5. Ointment making and filling machines.
6. Automatic bottle washing, filling and labelling machines for oral liquids.
7. Equipment for sterile preparations
8. Powder filling machines
9. Pilfer proof capping machines
10. Strip packaging machines and accessories.
11. Low Humidity equipment.

Appendix IX

LIST OF EQUIPMENT FOR CONTROL OF QUALITY

LABORATORY INSTRUMENTS FOR RESEARCH AND QUALITY CONTROL:

Type of equipment

i) Microscopes, including Binocular Microscopes

ii) pH Meters & accessories like glass electrodes etc.

iii) Refractometers

iv) Viscometers

v) Photo electric Colorimeter.

vi) Flame photometer

vii) SpectroPhotometers :

a) Absorbtion & emission type.

b) Infrared spectrophotometer

c) Spectronic 20

viii) Paper & thin layer chromatograph.

ix) Column Chromatograph

x) Gas Chromatograph

xi) Karl-fischer moisture determination Apparatus.

xii) Tablet disintegration and friability testing equipment.

xiii) Refrigerated Lab centrifuges.

xiv) Zone readers.

xv) Automatic sample collectors.

xvi) Auto analyzers & automatic titration apparatus.

xvii) Laboratory hard-ware like ovens refrigerators, Lab. centrifuges, deep freezes, ovens, Vacuum ovens, Chemical balances, incubators, Sterilizers, shakers, blenders, Constant temp. baths, standard sieve sets, etc.

Type of equipment

xviii) SPECIAL RESEARCH INSTRUMENTS :

a) Coleman Nitrogen analyser

b) Warburg Outfit unit with accessories.

c) Coleman Carbon Hydrogen analyser.

d) Mettler micro and Semi-Microbalances.

e) Horacous Semi-Microcombustion Unit.

f) Cenco Moisture balance

g) Laybold lab. 2 stage vacuum pumps.

h) Labline universal penetrometer.

i) Special Stereo Microscopes

j) Dialyzers, with accessories.

k) Impactograph

l) Aerosal Lab equipment

m) Apparatus for testing timed release of tablets.

n) Electrophoretic Apparatus.

o) Tensiometer

Appendix X

LIST OF MACHINARY REQUIRED FOR BASIC PRODUCTION OF DRUGS

CHEMICAL PROCESSING PLANT AND MACHINERY:

Type of equipment

1. Reaction vessels, pressure vessels, storage tanks, silos, bins etc.
2. Specialized Anti-corrosive equipment like Glass lined, rubber lined, plastic coated and fibre glass based equipment.
3. Agitators of various types with reduction gears.
4. Transfer equipment such as pumps made of SS, rubber lined, PVC, MS, CI or Bronze; blowers, conveyors, elevators and other material handling equipment.
5. Water ring vacuum pumps, steam ejectors and high vacuum pumps.
6. Separation equipment including filter presses, centrifuges, screens and cyclones, dust collectors, clarifiers liquid/liquid extractors etc.
7. Heat Exchangers, distillation columns, evaporators and crystallizers.
8. Thermal equipment including rotary vaccum dryers, fluidized bed dryers, spray dryers, drum dryers etc.
9. Size reduction equipment including crushers, ball mills, tube mills, Hardinge mills, pebble mills, hammer mills, reductionizers, etc.
10. Electrical equipment including motors, generators, diesel generators, electric transformers, switch gears, various types of starters, cables, explosion proof motors and accessories.
11. Pipes, valves and fittings of various types and of different materials of construction.
12. Ventilation equipment including fans, blowers, air handling equipment etc.
13. Services equipment like Steam Boilers, refrigeration compressors and oil free air compressors, cooling towers etc.
14. Water deionisation, softening and effluent treatment plants.
15. Electrolytic cells to produce hydrogen etc.

Appendix XI

PROCESS CONTROL INSTRUMENTS :

Process control instruments used in chemical and pharmaceutical industry can be classified as those which are used for the measurements of (a) Temperature (b) Pressure (c) Vacuum (d) Flow of gas and liquids (e) Liquid level indicators (f) pH (g) Concentration of solutions and gas mixtures (h) Relative humidity (i) Density of gases (j) Electrolytic conductivity (k) current (l) voltage etc. Normally the control mechanisms used are either thermostatic, mechanical, pneumatic, electrical or electronic. Some of the important types of control instruments are indicated below

Type of equipment
1. Simple indicating instruments for pressure and vacuum, dial thermometers, PH meters, conductivity meters, Ammeters, flow & level indicators..
2. Temperature, pressure and flow recorders and controllers.
3. pH recorders and controllers.
4. Rotameters and liquid level controllers.
5. Off gas analysers :
6. Continuous recording electrolytic conductivity meters.
7. Smoke density meters and controllers.
8. Gas balance & specific gravity meters.
9. Humidity controllers and recorders.
10. Oxygen probes.
11. Foam sensers and controllers.
12. Automatic process cycle controllers (both electric and and electronic)
13. Temperature compensated totalizers and rate indicators.
14. Long distance transmission and

Type of equipment
15. Mini computers for process control

APPENDIX XII

MAIN RAW MATERIALS REQUIRED FOR THE MANUFACTURE OF ALL DRUGS

APPENDIX II

Sr. No.	Name of the Raw Material	Name of the drug or Intermediate for which it is used.	Annual requirement for 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
1.	Acetanilide	Sulpha Drugs	400	1. H.O.C. 2. Cibatul 3. Dipak Labs. 4. Universal Chemicals		
2.	Acetaldehyde	Sulpha Drugs Indomethacin	50	1. Union Carbide 2. Synthetics & Chemicals.	Adequate	—
3.	Acetic Acid	Phenacetin Chloroquin Sulpha Drugs	20000	1. Sirsilk 2. Andhra Sugar 3. Somaiya Organics 4. Union Carbide 5. Indian Organic 6. Myscre Acetate 7. Godavari Sugar	Adequate	—
4.	Acetic Anhydride	Chloramphenicol Sulphacetamide, Paracetamol, Acetazolamide Thiacetazone Aspirin Vitamin B_1 Phenacetin	3650	1. Andhra Sugar 2. Sirsilk 3. Myscre Acetate & Chemicals 4. Colour Chem	Adequate	—

Remarks : A — Basic manufacturers of the drugs to take up production of the intermediate.

B — New production capacities to be approved and set up.

C — Expansion of capacities to be approved

D — Indigenous production yet to be started.

E — Permanent method of allocation of production to be devised without excise problems.

F — Use can be eleminated by indigenous substitutes.

G — To import.

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
5.	Acetoacetic Ester	Amidopyrin Novalgin 4-Dietnylamine-l-methyl butylamine	1500	1. I.D.P.L. 2. I.O.C. 3. Colour Chem.	Adequate	—
6.	Acetonitrile	Sulfas	1200	—	—	A
7.	Acetone	Vitamin A, B., Vitamin C, Ephedrine Amodiaquin		1. Herdillia 2. Sirsilk 3. Nocil 4. Cordite Factory		
8.	Acetophenone	Para-nitro-acetophenone	700	1. D. D. Shah & Co. 2. Herdillia	—	B
9.	Acetone Semicarbazone	Nitrofurazone	30	1. I.D.P.L.	Adequate	—
10.	Acetoin	Sulphamoxazole	27	—	—	B
11.	Acetyl Acetone	Sulphadimidine	610	1. I.D.P.L.	Insufficient	B, C
12.	Acetyl Butyro Lactone	—	30	—	—	B
13.	Acetylaminophenol or Paracetamol	Amodiaquin	400	1. Burrows Wellcome 2. Chemo-Pharma 3. Duphar Interfran 4. Themis 5. Dipak Labs. 6. I.D.P.L.	Adequate	—
14.	Acetyl Chloride	Vitamin A	10	1. Excel 2. K. P. Chemicals	Adequate	—
15.	Activated Carbon	All Drugs	700	1. Laxmi Carbon 2. Narbada Valley 3. Patco Carbon 4. Hypine Carbon	Adequate	—
16.	Acrolein	Folic Acid	15	1. I.P.C.L.	—	D

Sr No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
17.	Acrylonitrile	Vitamin B_{12} Sulphas	60	1. I.P.C.L.	—	D
18.	Adipic Acid	Iodipamide	50	1. Pharma Chem. Labs.	Insufficient	B, C
19.	Alcohol (absolute)	All drugs	1500KL	1. Sugar Mills	—	E
20.	Aluminium (metal)	Chloramphenicol	430	1. Indian Aluminium 2. Hindalco	Adequate	—
21.	Allyl bromide	Secobarbitol	25	—	—	B
22.	Aluminium Chloride (Anhydrous)	Chloramphenicol Prenylamine	150	1. Excel 2. I.D.I.	Adequate	—
23.	Amino-chloro-benzophenone	Chlordiazepoxide Diazepam	12	—	—	A
24.	d-2-Aminobutanol	Ethambutol	20	—	—	B
25.	4-Amino-2-6-dimethyl-pyrimidine	Sulphasomidine	120	1. Cibatul	Insufficient	A, C
26.	Aminohydantoin Sulphate	Nitrofurantoin	60	1. I.D.P.L.	Insufficient	A, C
27.	O-Aminophenol	Di-iodohydroxyquinoline	300	1. Mermaid Chemicals (THEMIS)	Insufficient	C
28.	M-Aminophenol	PAS & Esters	800	1. H.O.C.	Adequate	—
29.	P-Aminophenol	Paracetamol (P-Acetylaminophenol No. 6) Diloxanide	300	1. H.O.C. 2. Industrial Pharma. Chem. 3. Themis 4. K. P. Chem.	Adequate	—
30.	2-Aminopyridine	Mepyramine	15	—	—	B
31.	2-Aminopyrimidine	Sulphadiazine Sulphadimidine	1800	1. I.D.P.L.	—	B
32.	2-Aminothiazole	Sulphathiazole derivatives	200	—	—	B

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
33.	Ammonium Thiocyanate	Acetazolamide Thiacetazone Vitamin B_1	80	1. Cibatul Other small scale units	Adequate	—
34.	Ammonia gas	All drugs	960	1. Fertilizer Plants	Adequate	—
35.	Ammonium sulfate	Antibiotics	3500	1. Fertilizer Plants	Adequate	—
36.	dl Alanine	Vitamin B_5	90	—	—	B
37.	Aniline	Acetanilide	6000	1. H.O.C.	Insufficient	B, C
38.	p-anisidine	Indomethacin	25	1. Amar Dye	—	B
39.	Anthranilic Acid	Methaquolone Hcl.	20	1. Dipak Labs. 2. K. P. Chemicals	Adequate	—
40.	Anisaldehyde	Mepyramine	20	1. S. H. Kelkar 2. Hindustan Lever	Adequate	—
41.	Arquad 16 (c) (Quaternary Ammonium Compounds)	Tetracyclines	2000	1. Hico Products	Adequate	—
42.	Beet Molasses	Vitamin B_{12}	2000	—	—	D
43.	Benzene	Vitamins Analgesics Sulfas Thiacetazone	2170	1. Udex Plant, Guj. Refinery 2. Aromatic Plant, IPCL 3. H.S.L.	Inadequate	B
44.	Benzaldehyde	Chloramphenicol Analgin	610	1. S. H. Kelkar & Co. 2. D.C.M. 3. Orgorama	Insufficient	B, C
45.	Benzoic Acid and salts	Diazepam Chloridiazephoxide	10	1. Morani Chemicals 2. Btx Chemicals	Adequate	—
46.	Bromine	Chloramphenicol Diphenhydramine	560	1. Tata Chemicals 2. Western India Match. Co.	Inadequate	B

APPENDIX II (Continued)

Sr. No.	Name of the Raw Material	Name of the drug or Intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
47.	Benzyl Chloride	Chloramphenicol Bephenium Hydroxy-Napthoate Benzyl Cyanide Phenobarbitone	270	1. D.C.M. 2. Orgorama 3. IOC	Adequate	—
48.	Benzyl Cyanide	Pethidine Phenobarbitone Phenylacetic acid Phenformin	1000	1. D.C.M. 1. Orgorama	Adequate	—
49.	2-Benzyl pyridine	Pheniramine maleate	15	—	—	B
50.	Boric Acid	Anti-dysentry drugs	100	1. Sorax Morarji 2. Wesix Chemicals	Adequate	—
51.	2-Bromopentane	Barbiturates	45	—	—	B
52.	Butyl acetate	Penicillin	2340	1. Kolhapur Sugar Works 2. Somaiya Organics 3. Union Carbide 4. Godavari Sugar	Adequate	—
53.	n-Butyl alcohol	Penicillin Tetracycline Vitamin B_{12}, B_2	2470	1. Godavari Sugar 2. Nocil 3. Union Carbide 4. Somaiya Organics 5. Kolhapur Sugar Works	Adequate	—
54.	t-Butyl alcohol	Hydrochlorothiazide	50	—	—	B
55.	n-Butylamine	Tolbutamide, Methyldopa	130	—	—	A, B
56.	2-butane 1,4 diol.	Vitamin B_6	90	—	—	A
57.	Butyl-malonic-Diethyl Ester	Phenylbutazone	60	—	—	A
58.	Butyl oxide	Ephedrine	5	—	—	A

Sr. No.	Name of the Raw Material	Name of the drug or Intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
59.	n-butyl bromide	Pheny.butazone Oxyphenyl butazone	400	—	—	B
60.	Calcium cyanamide	Sulfamoxazole	20	—	—	—
61.	Calcium oxide	Antibiotics	100	1. Radha Chemicals 2. Several Indigenous Units	Adequate	—
62.	Calcium carbonate	Antibiotics	500	1. Sturdia Cemicals 2. Radha Chemicals 3. Burma-Lime 4. Triveni Tissues.	Adequate	—
63.	Capryl Alcohol	Vitamin B_{12}	15	—	—	F
64.	Carbon di-sulphide	Tolbutamide	45	Almost All Rayon Mfrs.	Adequate	—
65.	Citrimide (Quaternary Ammonium Compound)	Penicillin & Other antibictics.	870	1. Hico Products 2. Ahura Chemicals	—	F
66.	Cellosolve (Ethyl Cellosolve)	Tetracyclines	2200	Sardesai Bros.	—	F
67.	m-chloraniline	Amodiaquin Chloroquine Hydrochlorothiazide	135	1. AmarDye:Chem 2. Atul Products	Adequate	—
68.	Chloral hydrate	Diloxanide	70	1. Alembic 2. Shree Chemical Ind. 3. Hindustan Insecticides	Adequate	
69.	Chloracetyl chloride	Xylocaine	20	—	—	A
70.	P-chlorobenzoic acid	Analgesics Indomethacin	15	—	—	A
71.	P-chlorobenzene sulphonamide	Chlorpropamide	40	—	—	A
72.	2-chloro-ethanol	Metronidazole	25	—	—	A

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1973-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
73.	1-chloro-2-dimethylamino-ethane	Chlorpheniramine maleate	15	—	—	B
74.	Chloroflurethane	Phenacetin DDS Paracetamol	1200	1. H.O.C. 2. Themis	Adequate	
75.	Chloroflurethane	Halothane	1	—	—	G
76.	2-chlorophenothiazine	Chlorpromazine	15	—	—	B
77.	P-chlorophenol	Clofibrate	5	1. Piramal Organic Chemicals	—	B
78.	2-chlorpropyl-dimethylamine hydrochloride	Chlorpromazine	30	—	—	B
79.	Chlorosulphonic acid	Sulfa drugs, DDS, Hydrochlorothiazide Furesamide Chlorpropamide	30000	1. Atul Products 2. Dharmsey Morarji 3. Andhra Sugars	Insufficient	B
80.	Chlorpropionic acid					
81.	5-chloro 2,4-disulphonamido-aniline	Chlorothlazides	60	—	—	A
82.	Choiesterol	Ethisterone Spiranolactone	20	1. CIPLA	Insufficient	B, C
83.	Citric Acid	Tetracycline Citrates		1. Citric India	Insufficient	B, C
84.	Cinnamaldehyde	Prenylamine Lactate	5	—	—	B
85.	Cobalt nitrate	Vitamin B12	2	1. Technico Enterprises	Adequate	—
86.	Corn Steep Liquor	Antibiotics	7000	1. Maize Products 2. Anil Starch 3. Bharat Starch	Adequate	—

Sr. No.	Name of the Raw Material	Name of the drug or Intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks
87.	Copper Powder	Chlorpromazine	10	—	Adequate	—
88.	Cotton Seed Flour (vegetable protein source)	Amphotericin Tetracyclines	100	1. RRL (Hyd) 2. Dorr-Oliver	Adequate	
89.	m-cresol	—	80	1. Shalimar Tar Products	Insufficient	B
90.	Cyanoacetic acid	Theophilline	45	—	—	A
91.	Cyanacetic ester	Folic Acid Sulphadimethoxazine	100	1. I.D.P.L.	Insufficient	A, B
92.	Cyanacetamide	Ethionamide	60	—	—	A,B
93.	Dextrin	Antibiotics	1000	1. Maize Products 2. Anil Starch	Adequate	—
94.	7-Dehydrocholestrol	Vitamin D	—	—	—	B
95.	Dibutyl Ether	Ephedrine	—	—	—	A,B
96.	2-4 Dichlorobenzoic acid	Furesemide	10	—	—	A,B
97.	Dichloromethyl acetate	Chloramphenicol	220	—	—	A,B
98.	4-7 Dichloroquinoline	Amodiaquin	160	I.D.P.L.	Insufficient	A
99.	2-5 Dichloronitrobenzene	Chlorpromazine	25	—	—	A,B
100.	Dicyandiamide	Sulphaguanidine Sulphadimidine Phenobarbitone Phenformin	1440	I.D.P.L.	Insufficient	A,B,C
101.	Diethylamine	Diethylcarbamazine Xylocaine Amodiaquin Nikethamide Diethylamino-ethanol	540	I.D.P.L.	Insufficient	B,C

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
102.	Diethanolamine	Pethidine	1.5	India Carbon	Insufficient	B,C
103.	2-Diethylamino-ethanol	Procaine Hcl. 4-Diethylamino-1-methyl butylamine	280	1. Hico	Insufficient	B,C
104.	4-Diethylamino-1-methyl-butylamine	Chloroquin	110	1. I.D.P.L.	Insufficient	B,C
105.	Diethyl carbonate	Furazolidone	40	—	—	B
106.	Diethyl ethoxymethylene malonic ester	Chloroquin Amodiaquin	220	1. I.D.P.L	Insufficient	C
107.	Diethyl Malonate	Phenyl butazone Diethylethoxy methylene malonic ester. Vitamin B2	660	1. I.D.P.L.	Insufficient	B
108.	Diethylmethylamine	Pethidine Ethionamide	880	—	—	A
109.	Diethyl oxalate	Phenobarbitone Vitamin B2 Ethionamide	880	—	—	B
110.	Dimethylamine 100%	Chloramphenicol Bephenium hydroxy-napthoate	20	1. FCI, Bombay	Adequate	—
111.	3-4 dimethylaniline	Anti-hystamines	5	—	—	B
112.	2-6 dimethylaniline	Anti-hystamines Sulphadimethoxazine	5	—	—	B
113.	Dimethyl chlorosilane	—	—	—	—	B

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
114.	Dimethylamino-chloroethane hydrochloride	Mepyramine	5	—	—	B
115.	Dimethyl formamide	Antibiotics, Steroids.	50	—	—	B
116.	1-Dimethylamino-2-chlor-propane hydrochloride.	Promethazine & salts.	10	—	—	A
117.	Dimethyl polysiloxane	—	5	—	—	B
118.	3-Dimethyl aminopropyl chloride	—	10	—	—	B
119.	Dimethyl sulphate	Vitamin B, Novalgin Amidopyrin Dilcoumide	1800	1. Ind. Solvents & Chemicals Pvt. Ltd. 2. Ganesh Chemicals	Insufficient	B
120.	Dimethyl sulfoxide	Vitamin A Dilcoumide	75	—	—	A,B
121.	Dinitrobenzol chloride	Vitamin D	2	1. H.O.C.	Adequate	—
122.	Diphenyl oxide	Chloroquin Amodiaquin	300	1. Durgapur Chemicals	Insufficient	B,C
123.	Diphenylamine			1. ACCI	Adequate	—
124.	Diosgenin	Steroids	200	1. Burrows Wellcome 2. Sandoz 3. CIPLA	Insufficient	B,C
125.	Ergosterol	Vitamin D		1. Dupher Interfran	—	B
126.	Epichlorhydrin	Xanthinol nicotinate	15	—	—	B
127.	Ether (solvent)	Vitamins & Analgesics	150	1. Alembic 2. Industrial Solvents	Adequate	—

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
128.	Ethyl acetate	Vitamins	550	1. Acetochemicals 2. Union Carbide	Adequate	—
129.	Ethyl Bromide	Phenobarbitone Vitamin A Ethambutol	45	1. Excel 2. Tata Chemicals	Adequate	—
130.	Ethylene Dichloride	Chloramphenicol INH Diethylcarbamazine Bephenium Hydroxy-naphthoate Chloroquin Amodiaquin	350	1. Calico 2. Dhrangdhra 3. Excel 4. NOCIL 5. Mettur Chem. 6. Chem Plast	Adequate	—
131.	Ethylene diamine	EDTA Caffeine and Thiophylline	450	1. Bharat Vijay Mills	—	B
132.	Ethylene diamine tetracetic acid.	Antibiotics	200	1. Hico. 2. Assoc. Lab. Requisites.	Adequate	—
133.	2-ethyl hexanol	Antibiotics	100	1. NOCIL 2. Union Carbide	Adequate	—
134.	Ethyl orthoformate	Diethyl ethoxy-methylene malonate	60	—	—	B
135.	Ethyl chloroformate	Vitamin B_6	175	—	—	A
136.	Ethylene Oxide	Chloramphenicol 4-Diethylamino-1-methyl butylamine Furazolidone Vitamin B_1	200	1. NOCIL	Adequate	—
137.	Ethylene chlorohydrin	Diethylamino ethanol	600	1. NOCIL	—	B
138.	Ethyl Palmitate	Vitamin A	20	—	—	B
139.	Ethyl Isopropyl-malonate	Amylobarbitone	15	—	—	A

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
140.	Ethyl Methyl Ketone	Ethionamide Vitamins	225	—	Adequate	—
141.	Filter Aid (Hyflosupercel and Dicalite)	All Drugs	4000	1. Celsil. Chem.	Insufficient	B,C
142.	Formamide	Hydrochlorothiazide and other chlorothiazides.	120	1. New Asarva.	Insufficient	B
143.	Formaldehyde 30%	Streptomycin Chloramphenicol Amodiaquin Tetracycline INH	750	1. H.O.C. 2. Atul Drug House 3. Allied Resins & Chem. 4. Nuchem Plastics 5. Konkan Chemicals 6. Formalino & Fine Chemicals.	Adequate	—
144.	Formic Acid	PAS & Esters. Diethylcarbamazine Vitamin B1 Hydrochlorothiazide	600	1. New Asarva, 2. Periyar Chemicals 3. Camphor & Allied Products	Adequate	—
145.	Fumaric Acid	—	500	1. Chemicals & Aromatics	Adequate	—
146.	Fumaronitrile	Vitamin B6	200	—	—	—
147.	Furfurylamine	Furosemide	15	—	—	A
148.	Gelatine (Pharmaceutical grade)	Vitamin A Gelatine capsules	1000	1. Rallis India 2. Arrow International 3. Protein Products of India 4. Shaw Wallace	Adequate	—
149.	Glucose (Dextrose)	Vitamin C Ca. gluconate Antibiotics.	20000	1. Anil Starch 2. Maize Products	Adequate	—
150.	L-Glutamic Acid hydrochloride	Folic acid	45	—	—	B

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
151.	Guanidine Nitrate	Folic acid	45	—	—	B
152.	Guanidine carbonate	Sulfas	120	—	—	B
153.	Hexamethylene-Tetramine	Chloramphenicol	560	1. Atul Drug House 2. Allied Resins & Chem.	Adequate	—
154.	Hydrazine Hydrate	INH Thiacetazone Nitrofurantoin	300	1. IPCL 2. Bengal Immunity 3. Pfizer	Insufficient	B, C
155.	Hydrazine Sulphate	Acetazolamide and others.	230	1. IPCL	Insufficient	B, C
156.	Hydrobromic Acid	Methyl Dopa	520	1. Tata Chemicals	Adequate	—
157.	Hydrogen peroxide 30%.	Tolbutamide	190	1. National Peroxide	Adequate	—
158.	Hydroxyethylhydrazine	Furazolidone	40	—	—	A —
159.	p-Hydroxy-napthoic acid.	Bephenium Hydroxy naphthoate.	20	—	—	A, B
160.	3-Hydroxymethyl pyridazine	Pyrazinamide	25	—	—	A, B
161.	Hydroxylamine-hydrochloride	Hydroxy urea Sulfadimethazine	12	—	—	G
162.	8-Hydroxyquinoline	Halogenated Oxyquinolines	300	1. Industrial Pharm. Chem. Ltd. 2. Themis	Insufficient	C
163.	Hydroquinone	Vitamin A	5	1. Satyadev Chemicals 2. Kesar Sugar Works.	Adequate	—
164.	Hexane	Soya flour vitamins	385	1. Esso 2. Burma Shell	Adequate	—
165.	Iodine	Iodochloro and Dichlorohydroxyquinoline	280	—	Not available	G

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
166.	Isoamyl Formate	Imipramine	5	—	Not available	G
167.	Isopropyl alcohol	Chloramphenicol Tetracyclines, etc.	1250	1. NOCIL	Adequate	—
168.	Isopropyl Ether	Vitamins	15	1. NOCIL	—	B
169.	Isophytol	Vitamin E	5	—	—	G
170.	Ketoacetol	Vitamin A	10	1. Alkali Metals (P) Ltd.	Adequate	—
171.	Lard Oil	Antibiotics	—	1. Many Oil Mills	Local vegetable oils can be used.	F
172.	Lithium Metal	Vitamin A	5	1. Alkali Metals (P) Ltd.	Insufficient	B
173.	Lactic acid	Calcium Lactate Calcium sodium Lactate	100	1. Orchem Industries	—	B
174.	Levulinic acid	Indomethacin	5	—	—	B
175.	Maleic Acid	Pheniramine maleates Chlorpheniramine maleates	15	—	—	B
176.	Magnesium Metal	Vitamin A	5			
177.	Malonic ester	Riboflavin Amytobarbitone and other barbiturates	60	1. IDPL	Insufficient	B, C
178.	Methoxy Pyridoxin	Vitamin B_6	50	—	—	A
179.	Methyl Alcohol	Streptomycin Chloramphenicol Vitamin A Vitamin C Ephedrine Pethidine Vitamin D Chloroquin	5000	1. FCI Bombay	Insufficient	B

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
180.	Methylamine 40%	Ephedrine Caffeine Theophylline	125	1. FCI Bombay	Adequate	—
181.	N-Methylalanine	Vitamin A	0.5	—	—	C
182.	Methylbenzene sulphonate	Amidopyrin Novalgin	2400	1. I.D.P.L.	Insufficient	B,C
183.	2-Methylimidazole	Metronidazole	35	—	—	B
184.	Methyldichloroacetate	Chloramphenicol Vitamin A	170	1. Atul Products	Adequate	—
185.	Methyl acrolein	Sulfamerazine	150	—	—	B
186.	Methyl Aminophenol	PAS & Salts	1000	1. H.O.C.	Insufficient	C
187.	B-Methyl amino ethanol	Xanthinol Nicotinate	15	—	—	B
188.	Methylene chloride	Vitamin A	1125	1. Mettur Chem.	Adequate	—
189.	Methylethyl pyridine	Vitamin A	5	—	—	G
190.	Methyl formate	Chloramphenicol	80	—	—	B
191.	Methyl Isobutyl Ketone	Tetracycline PAS & Esters Tolbutamide Chlorpropamide	1200	1. NOCIL	Adequate	—
192.	Methylaminochloroacetate	Vitamin A	100	—	—	A
193.	Methyl cyanoacetate	Sulfadimethoxazine	15	—	—	A
194.	Methylene dichloride	Antibiotics	1000	1. Mettur Chemicals	Adequate	—
195.	Methyl ethyl ketone	Vitamins Ethionamide	250	—	—	B

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
196.	B-Methyl Napthalene	Vitamin K	10	—	—	B
197.	2-Methyl-1-3-propanediol	Meprobamate	80	—	—	A,B
198.	Monochlorobenzene	Chloramphenicol	1700	1. H.O.C. 2. Durgapur Chem. 3. Vijay Indus.	Adequate	—
199	Monochloracetic acid	Analgesics Vasodilators Xylocaine	295	1. Cellulose Products 2. Excel 3. I.O.C. 4. Sardesai Bros 5. HICO	Adequate	—
200.	Monoethyl amine		500	1. IDPL	Adequate	—
201.	Monoethanolamine	Piperazine salts	150	1. India Carbon	Adequate	—
202.	Nickel catalyst	Vitamin C 4-Diethylamino-1-methylbutylamine	150	1. Hindustan Lever 2. Navsari Oil Products 3. FCI 4. United Trading Co.	Adequate	—
203.	Nickel alloy (Raney nickel)	Several synthetic drugs.	5	Small scale units	Adequate	—
204.	p-nitroacetophenone	Chloramphenicol	720	—	—	B
205.	Nitrobenzene	Phenyl butazone	200	1. H.O.C. and many Small Scale units.	Adequate	—
206.	p-nitrobenzoylchloride	Folic Acid	60	1. H.O.C.	Insufficient	A
207	5-Nitrofurfuryl Diacetate	Furazolidone Nitrofurazone.	100	—	—	A,B
208.	Nitromethane	Anti-hypertensives	25	—	—	B
209	Nitroethane	Methyl Dopa	250	—	—	B

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
210.	Nitropropane	Methyl Dopa	200		—	B
211.	Nitrogen gas	Methyl Dopa	10	Many SS manufacturers Aims Oxygen, Indian Oxygen	Adequate	B
212.	O-Nitrophenol	Iodo-chloro & Diiodo-hydroxyquinoline		1. Chemo Pharma 2. Other Small Scale Units	Insufficient	B, C
213.	p-Nitrotoluene	Thiacetazone Procain Hcl. Imipramine	300	1. H. O. C.	Adequate.	D
214.	p-nitrobenzoic acid.	Procaine Hcl.	200	1. Hoechst 2. Synbiotics 3. HICO	Adequate.	—
215.	m-nitrobenzoic acid.	Iodipamide	40	—	—	A
216.	Novaldiamine	Chloroquin Phosphate	100	—	—	A,B
217.	Oxalic Acid	Vitamin B_2 Diethyloxalate Tetracyclines.	2500	1. Excel 2. New Asarwa,	Adequate	—
218.	Oils (Maize, Peanut or Soya)	Antibiotics	2000	Many Indigenous Oil Mills and Maize and Starch plants.	Adequate	—
219.	Palladized Charcoal	Vitamin A	1	1. Ravindra Herauces	Adequate	—
220.	Palladium Chloride	Chloramphenicol etc.	130	1. Ravindra Herauces	Insufficient	B,C
221.	Palmitoyl Chloride	Vitamin A	10	1. Amar Dye-Chem.	Insufficient	B,C
222.	Pancreas (Animal gland)	Insulin	750	Organized Slaughter houses.	Adequate	—
223.	Paraformaldehyde	Vitamin A Vitamin B_6	40	1. Atul Drug House 2. Allied Resins	Adequate	—

Sr. No.	Name of the Raw Material	Name of the drug or Intermediate for which it is used.	Annual requirement by 1978-79 (in tonnes)	Manufacturers in India	Present indigenous capacity available	Remarks*
224.	Paraldehyde	Vitamins	100	Somaiya Organics	Adequate	—
225.	Phenol	Paracetamol Salicylic acid Iodo-chloro & Di-iodohydroxyquinoline Bephenium-Hydroxynaphthoate Chloroquin	3600	1. Herdillia 2. Durgapur Chem. 3. Neyveli Lignite	Adequate	—
226.	Phenothiazine	Promethiazine and salts.		1. Alkali & Chemical Corpn. of India (ACCI)	Adequate	—
227.	Phenoxyacetic acid.	Penicillin V	50	A few units in Small Scale Sector have started production	Adequate	—
228.	Phenylacetyl carbinol	Ephedrine	45	—	—	B
229.	Phenylacetamide	Penicillin	400	1. DCM 2. Hyderabad Chem.	Insufficient	B,C
230.	O-phenylene diamine	Thiobendazole	5	—	—	A or G
231.	Phenylacetic acid and its pot. salt	Penicillin	900	1. Standard Pharmaceuticals 2. DCM	Insufficient	C
232.	D-Phenylglycine	Ampicillin	70	—	—	B
233.	B-Phenylethylamine	Phenformin Diethylcarbamazine	20	—	—	B
234.	Phosgene	Phenobarbitone	150	1. Atul Products 2. Alembic Chemicals	Insufficient	B
235.	Phosphoric acid.	Antimalarials	165	1. Excel 2. Wesix Chemicals 3. Star Chemicals	Adequate	—
236.	Phosphorous oxychloride	Chloroquin	500	1. Excel	Insufficient	B

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used	Annual requirement by 1973-74 in tonnes	Manufacturers in India	Present indigenous capacity available	Remarks*
237.	Phosphorous pentasulphide	Vitamin B1	80	1. Excel	Adequate	—
238.	Phosphorous Pentoxide	Nikethamide Ethionamide	45	1. Excel	Adequate	—
239.	Phosphorous Trichloride	Methaqualone Hcl.	5	1. Excel 2. Atul Products	Adequate	—
240.	Phosphorous Pentachloride	Ethionamide	24	Excel	Adequate	—
241.	Phytyl bromide	Vitamin E	5	—	—	G
242.	Phenyl acetone	Prenylamine	1	—	—	G
243.	Phenylhydrazine	Sulfas	70	—	—	B
244.	B-Picoline	Nicotinic acid/amide Nikethamide	500	1. Warner Hindustan	Inadequate	B,C
245.	G. Picoline	I.N.H.	550	1. Warner Hindustan	Inadequate	B, C
246.	Piperazine Hexahydrate	Diethylcarbamazine Piperazine salts	150	1. IDPL 2. Bayer 3. BDH	Adequate	—
247.	Pipyridine	Ethionamide	30	—	—	B
248.	Potassium Acetate	Antibiotics Ethionamide	1260	Many Small Scale Units	Adequate	—
249.	Potassium Borohydride	Vitamin A Chloramphenicol	20	—	—	P
250.	Potassium Hydroxide	Antibiotics Vitamin B_2 Synthetics	2000	1. Standard Mills 2. Atul Products	Adequate	—
251.	Potassium Carbonate	PAS & Esters Penicillin	1700	1. Standard Mills 2. Swadeshi Chemicals	Adequate	—

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
252.	Potassium dihydrogen phosphate	Antibiotics	470	—	—	B
253.	Potassium Permanganate	Pyrazinamide Nicotinic acid	150	1. Swadeshi Chemicals 2. Kirti Chemicals	Adequate	—
254.	Potassium Cyanate	Tolbutamide Chlorpropamide	240	—	—	—
255.	Potassium Cyanide	Vitamin B_{12}	15	—	—	G.
256.	Potassium Thiocyanate	Tolbutamide Chlorpropamide	25	1. Maharashtra Fire Chem. 2. Caliron Chemicals	Insufficient	B
257.	Potassium Ferricyanide	Antibiotics	20	1. Maharashtra Fine Chem.	Adequate	—
258.	Procaine HCL.	Penicillin	375	1. Hoechst 2. HICO 3. Synbiotics	Insufficient	C
259.	Proporgyl Bromide	Vitamin A	10	—	—	A
260.	N-propylamine	Chlorpropamide Probenecid	45	—	—	B
261.	Pyridine	Sulfa Drugs	300	1. Warner Hindustan 2. Hindustan Steel	Insufficient	B, C
262.	Pyrazine mono carboxylic acid	Pyrazinamide	20	—	—	B
263.	Quinoline	Hydroxyquinolines	300	1. Consolidated Solvents	Insufficient	B
264.	Resins IR-45 or Equivalent IR-124 or Equivalent IRC-50 or Equivalent IRA-402/410	Streptomycin and other antibiotics	20 25 175 30	1. Ion Exchange India 2. Tulsi Industries —	Adequate	F
265.	Salicylic acid	Aspirin Sod. Salicylate	2000	1. Alta 2. Indosol Chem. Corpn. 3. Gujarat Salicylates	Adequate	—

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used	Annual requirement by 1978-79 in tonnes	Manufacturers in India	Present indigenous capacity available	Remarks*
266.	Silicones	Antibiotics	2	1. Metroark	Adequate	—
267.	Sodamide	Pethidine		1. Excel	Adequate	—
268.	Sodium borohydride	Vitamins	0.5	—	—	G
269.	Sodium Benzoate	Vitamin A	15	1. Morani Chemicals 2. B.T.X Chemicals	Adequate	—
270.	Sodium Bromide	Analgesics	35	1. Tata Chemicals	Adequate	—
271.	Sodium Citrate	Antibiotics	50	Many Small Scale Units	Adequate	—
272.	Sodium Acetate	Chloramphenicol	600	Many Small Scale Units	Adequate	—
273.	Sodium cyanide	Phenobarbitone Vitamin B_{12} Phenylbutazone Diloxanide	300	1. Pigments & Cyanides 2. IPCL	Insufficient	B
274.	Sod. Diethyldithio-carbamate	Vitamin A	30	—	—	A
275.	Sod. Ferrocyanide	Tetracycline	20	1. Pigments & Cyanides	Insufficient	B
276.	Sodium hydrosulfite	Antibiotics	210	Many Small Scale Units	Adequate	—
277.	Sodium Metal	Metamizol Folic acid Phenobarbitone Vitamin B_1 4 Diethylamino-I-Methyl Butylamine Amidopyrin	500	1. Alkali Metals (P) Ltd. 2. Sodium Metals (P) Ltd.	Adequate	—
278.	Sodium Methoxide	Vitamin A Phenylbutazone Sulfas Analgesics.	60	—	—	B
279.	Sodium sulphide	Analgesics.	2000	Many Small Scale Units.	Adequate	—

APPENDIX II (Continued)

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by 1978-79 in tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
280.	Sodium metabisulphite	Vitamins	10	Many Small Scale Units.	Adequate	—
281.	Sorbitol	Vitamin C	2400	1. Sarabhai M. Chemicals 2. Hindustan Antibiotcs 3. Maize Products	Adequate	—
282.	Sodium hydroxide (tech.)	All drugs.	30000	Many Large Units.	Adequate	—
283.	Sodium carbonate	All drugs.	70000	1. ICI 2. Tata 3. Dhrangadhra Chemicals. 4. Saurashtra Chemicals.	Adequate	—
284.	Sodium Nitrate	Vitamin B_{12} Folic Acid	150	1. F.C.I. 2. Deepak Nitrates	Adequate	—
285.	Sodium Nitrite	Chloramphenicol Phenacetin Analgin	1500	1. F.C.I. 2. Deepak Nitrates	Adequate	—
286.	Sodium Phosphate	Antibiotics	600	1. India Alkalies 2. Saurashtra Chemicals	Insufficient	B
287.	Soyaflour (edible)	Antibiotics	10000	1. Madhyadesh Syndicate 2. Alembic Chemicals	Adequate	—
288.	Sulfuric acid	All drugs	20000	Many Large Units.	Adequate	—
289.	Sugar (cane.)	Antibiotics	10000	Many Large Units.	Adequate	—
290.	Stearyl alcchol	Vitamin C and other drugs.	60	Many Large Units.	Adequate	—
291.	Stannic chloride	Analgesics	120	—	—	B
292.	Sulphur	Anti.T.B.drugs	40	—	—	G
293.	Tartaric Acid	Chloramphenicol	30			B
294.	Thiosemicarbazide	Sulfas Anti TB drugs.	100	1. Unichem 2. Many Small Scale Units	Adequate	—

APPENDIX II (Continued)

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.	Annual requirement by IDPL/P.Ts in tonnes	Manufacturers in India	Present indigenous capacity available	Remarks*
295.	Toluene	Analgesics	150	1. IPCL 2. Hindustan Steel 3. Gujarat Refinery	Adequate	—
296.	O.Toluidine	Methaqualone	30	1. Amar Dyechem 2. Atul Products	Adequate	—
297.	Trichloroethylene	Chloramphenicol Emetine Bephenium Hydroxynapthcate Phenylbutazone.	250	1. Calico 2. Dhrangadhra Chemicals	Adequate	—
298.	P-Toluensulphonamide	Tolbutamide	100	1. Atul Products 2. Standard Chemicals 3. Meremy Chemicals 4. Many Small Scale Units.	Adequate	—
299.	Trimethylquinol	Vitamin E	5	—	—	A
300.	Thionyl chloride	Procaine Hcl. Pethidine Hydrochlorthiazide 4-Diethylamino-l-methyl-butylamine	90	1. Schroff's Ind. Chemicals.	Adequate	—
301.	Thiazole-4-carboximide	Thiobendazole	5	—	—	A
302.	Triethylamine	Tetracycline Vitamin B.	200	1. IDPL	Adequate	—
303.	L-Tyrosine	Anti-convulsents (L-Dopa)	3	—	—	a
304.	Ucon (defoamer)	Antibiotics	50	—	—	G
305.	Urea	Chloramphenicol Vitamin B,	200	1. Fertilizer Companies	Adequate	—
306.	Urethane	Meprobamate	—	—	—	G

APPENDIX II (Continued)

Sr. No.	Name of the Raw Material	Name of the drug or intermediates for which it is used.	Annual requirement 1978-79 tonnes.	Manufacturers in India	Present indigenous capacity available	Remarks*
307.	Vanillin	Methyl Dopa Anti-hypertensives	450	—	—	B
308.	Wax Emulsion (Mobilper S)	Antibiotics	1200	1. Ahura Chemicals 2. Hico Products	Adequate	—
309.	O-Xylene	Chloramphenicol Vitamin B_2 Phenylbutazone	250	1. IPCL (Aromatics Plant) 2. Coke Oven Plants 3. Gujarat Refinery.	Adequate	D
310.	m-xylidine	Xylocaine	15	1. Sudarsan Chemicals	Adequate	—
311.	Zinc Dust.	Phenylbutazone Chloramphenicol	400	—	—	B
312.	Zinc chloride	Vitamins	5	1. Small Scale Units. 2. Tata Chemicals	Adequate	—

Ref: Indian Pharmaceutical Industry 1973. Compiled and published by Development Council (Drugs and Pharmaceuticals) P.C.T.D. Government of India

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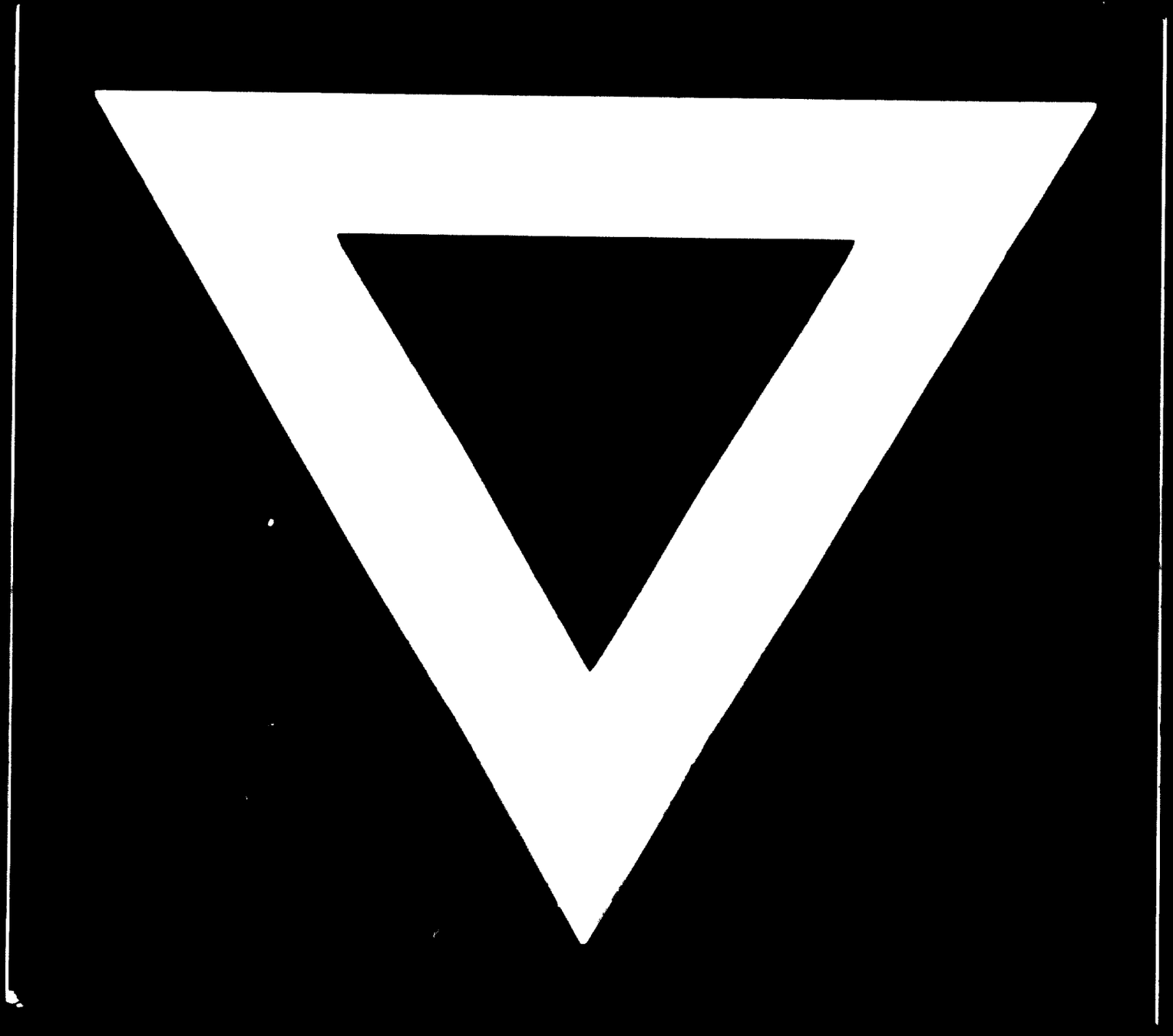

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