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THE STEPS INVOLVED IN ESTABLISHING A PHARMACEUTICAL INDUSTRY IN DEVELOPING COUNTRIES*

by

The UNIDO Secretariat

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PREFACE

In this paper the developing countries are classified into different groups depending on their present stage of development of the pharmaceutical industry.

The steps involved in fostering their growth to become more self-sustaining are suggested.

The first step is for each country to draw up a national list of drugs to establish priorities for procurement and production covering the major health requirements of each country. These lists cannot be uniform for all countries nor remain fixed for all time. The list will have to be revised continuously in keeping with the changing pattern of consumption and advances in the field of medicine.

Countries with no pharmaceutical manufacturing facilities should start repacking facilities of formulated drugs and use this as a training ground for building up the ancillary industries.

Countries which have started repacking formulated drugs should enter into formulation of imported bulk drugs into dosage forms and manufacture some simple bulk drugs from intermediates.

Countries which have gained some experience in the pharmaceutical field and have trained personnel in different disciplines involved in production of drugs should undertake extraction of active principles of plant products and animal by-products and utilise their natural resources.

Countries which have gained experience in basic production should extend the range of product including the production of antibiotics.

Countries which have an advanced pharmaceutical industry should expand the range of intermediates, processing machinery, and pharmaceutical equipment and undertake research in the improvement of processes and screening of new drugs.

The paper also deals with aspects of production of machinery and equipment, training of technical personnel, promotion of indigenous systems of medicine, regulation of imports, price control and distribution, regulation of quality and production control and regulation of technology transfer.

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I: PRESENT STAGE OF DEVELOPMENT OF THE PHARMACEUTICAL INDUSTRY IN DEVELOPING COUNTRIES

1. Developing countries can be classified broadly into the five following groups on the basis of the stage of development reached by the pharmaceutical industry in these countries.

2. Group 1: Countries which have no manufacturing facilities and therefore are dependant upon imported pharmaceuticals in their finished form. In many of these countries there is insufficient trained personnel, limited public health services and poor distribution channels. Examples of countries in this group are: Africa: Burundi, Chad, Lesotho, Rwanda, Sierra Leone, Somalia, Swaziland, Togo, Central African Republic; Latin America: Honduras; Trinidad; Asia: Bhutan, Mongolia; Asia/Middle East: Jordan, Democratic Republic of Yemen.

3. Group 2: Countries which have started to repack formulated drugs and process bulk drugs into dosage forms. Examples of Countries that have made a beginning as manufacturers are: Africa: Madagascar, Sudan, Tanzania, Uganda, Zambia; Latin America: Haiti, El Salvador, Guatemala; Asia: Afghanistan, Burma, Malaysia, Nepal, Sri Lanka, Vietnam.

4. Group 3: Countries which manufacture a broad range of bulk drugs into dosage forms and manufacture some simple bulk drugs from intermediates. Examples of countries in this group are: Africa: Algeria, Ghana, Morocco; Latin America: Colombia, Ecuador; Peru; Asia/Middle East: Iran, Iraq.

5. Group 4: Countries which produce a broad range of bulk drugs from intermediates and who manufacture some intermediates using locally produced chemicals. Examples of Countries in this group are: Africa: Egypt, Tunisia; Latin America: Argentina; Asia: Pakistan, Turkey

6. Group 5: Countries who manufacture most of the intermediates required for the pharmaceutical industry and undertake local research on the development of products and manufacturing processes. Countries in this group are: Latin America: Brazil and Mexico; Asia: India.

7. This classification shows that countries which are largely agricultural have so far reached only Stage 1 or Stage 2. Governments

in these countries have generally launched campaigns to end epidemics, but an adequate number of hospitals and medical practitioners are still lacking.

8. Countries which have a better nucleus of medical services have generally reach Stage 3. In these countries, between 20 per cent to 75 per cent of pharmaceutical products are used in hospitals or public dispensaries. The consumption of drugs, however, is still very low and in order to promote the development of the pharmaceutical industry, some regulation of imports is usually required.

9. Once stage 3 is reached, development of the industry gathers its own momentum. Technical skills are built up in the various areas of formulation and production, packaging and movement of finished products, bulk manufacture of some drugs, quality control and development of new products to suit the local health priorities. Side by side the Government must evolve legislation to control the conditions of manufacture and the quality of finished products.

10. The development of the pharmaceutical industry stimulates the development of anciliary industries producing laboratory and packaging materials and production equipment. Employment opportunities are created, particularly for students of science and technology.

II: THE STEPS INVOLVED IN ESTABLISHING A PHARMACEUTICAL INDUSTRY IN DEVELOPING COUNTRIES

1. Drawing up a list of essential drugs to meet the health needs of a country and the introduction of generic names.

11. Before any manufacturing activity is undertaken the most important step is to draw up a list of essential drugs to meet the health needs of the country.

12. Any national list of essential drugs, however carefully it is drawn up, taking into account the morbidity rates of different diseases, can only be very tentative and has to be continuously revised because the rate of obsolescence of products in this industry is very high. This is caused not only by the continuous discovery of new products with better therapeutic effect and lower toxicity but also for a drug which is in continuous use, after a time the invading micro-organisms develop resistance as also the patients using them get sensitised resulting in manifestation of allergic reactions.

13. Continuous change takes place in the range of drugs used; more than 75% of the drugs used today were not even known 20 years ago. According to present day usage, only about 5% of the total output of pharmaceutical industry represents plant products and the leading share of about 55% is taken by synthetic products, and the rest of about 40% by antibiotics and other biological preparations.

14. Moreover, the pattern of consumption of drugs itself changes over a period depending on the public health measures undertaken by the Government such as improving drinking water supply, disposal of sewage, prophylaxis against infectious diseases, etc. Added to this are factors like improved education, improved standards of living, better food habits and so on. With these developments the consumption of anti-infective agents will go down but at the same time the need for drugs for the treatment of degenerative diseases such as vascular, cardiac and those related to the central nervous system, will increase with better expectancy of life.

15. In most developing countries, the major health needs can be satisfied by about 100 essential drugs. This list in Annex A, is provided as an example. It covers an estimated 90 per cent of India's requirements.

16. The development of the pharmaceutical industry will be facilitated if there is a concentration of effort in producing the essential drugs that are required in large volume in each particular country.

The Introduction of generic names

17. (i) Single Formulation

If a list of essential drugs is used, it is clear that a large number of brand names for the same drug preparation may confuse the medical profession which tends to become overwhelmed with literature from the different producers on the same drug taxing his memory.

18. In India, the producer of a drug preparation has, according to the Drugs Act, to show on the label in equally bold letters the generic name of the drug along with its brand name. Similar legislation exists in many other countries.

19. In India, where there is a price control on drugs, no special considerations are given to a branded product over a generic product in fixing its price. The price control order under which all prices are fixed takes into account the prices of raw materials going into the production of the preparation and a fixed sum for each of the processing operations involved in making the dosage form. Therefore a branded product is more expensive only when this is specifically justified.

20. It sometimes happens that pharmaceutical producers in India use a standard known as the 'house standard' for the raw materials which are usually higher than the minimum fixed under the pharmacopoeia. This, to a certain extent, increases the total cost of the raw materials going into the manufacture. Also there are sometimes some additional processing operations such as micronising etc., which are undertaken to arrive at the finished dosage form. This may in turn also result in a higher cost. As far as cost of promotion and distribution and profits are concerned, usually a level of mark-up fixed by the Government is added to the ex-factory cost of production. Therefore, the cost of a branded product may differ from manufacturer to manufacturer for the same drug formulation.

21. In India, an excise duty is levied on the finished preparation at a higher rate on a branded product than that levied on a product sold under a generic name; this encourages more products to be made and sold under a generic names and making a product sold under a brand name more expensive.

The reasons why the use of brand names is allowed to continue for single formulations in India are:

22 1. The better bioavailability of a drug formulation. Many producers of branded products claim a better bioavailability and therefore a well known branded product is more often prescribed by a physician who feels that it will suit the particular requirement of his patient in preference to a product sold under a generic name which only uses raw materials conforming to the minimum prescribed pharmacopoeial standards and uses the minimum processing operations to arrive at the final dosage form. In certain countries for certain drugs, the producer is asked to prove that his different brand of product has the same bioavailability as another branded product.

22. 2. When all products are sold under generic name, the choice may then be left to the dispensing chemist who may be influenced more by the return he gets in selling the product of a particular producer rather than the interest of the patient.

22. 3. Another important factor is quality control. In some countries where there is no strict enforcement of quality control of drugs, many sub-standard and spurious imitations appear in the market. The manufacturer generally zealously guards against such imitations appearing in the markets and competing with his branded products and gets such activity curbed by the Government. For this reason, a ban on the sale of branded preparations is likely to result in complaints coming from the medical profession and the public.

Multiple-Drug Formulations

23. When we come to multiple-drug formulations whose composition may vary in different preparations, the use of only generic names becomes more difficult. Even if an essential drug list is compiled, it will also be necessary to produce multiple-drug formulations. A national formulary can be drawn up listing a limited number of such formulations (say, 500-)that are used in Government hospitals and the National Health Services; but in India where this practice is followed the specialist still has the right to prescribe a preparation which is outside the national formularies to suit the specific needs of his patients.

24. The advantages and disadvantages of Introducing of generic names.

With this background, it will be seen that the advantages and disadvantages of relying on generic rather than brand names will have to be carefully considered by any country contemplating such a measure. Whilst such a measure could bring benefits for simple products like analgesics, its use for more complex products raises many difficulties.

25. It should be remembered that legislation normally requires the name of the manufacturer to be indicated on the packing. Even if generic names are used the product of a well-known manufacturer may still be preferred by the physician to the consumer even if it sells at a higher price. The replacement of brand names by generic names will not therefore necessarily achieve the main advantage which is claimed, namely a reduction in price of pharmaceutical products. Where brand names already exist, the use of only generic names could seriously harm small producers whose name is not as well known as the name of their branded product.

2. Repacking of Formulated Drugs and local production of Packaging materials

26. In countries where there is no manufacturing activity so far, repacking of drugs will serve as a training ground preliminary to the production of formulated drugs and help in building up the ancillary industries of packaging material and standardise their production.. For example, to start with, if there is already a glass industry the right size of bottlesand a plastic moulding industry the right type and sizes of caps can be developed and progressively more sophisticated packaging materials like foil for strip packing, vials and accesories for filling antibiotics and multidose injections, collapsible tubes for ointments, etc. A list of packaging material and also the type of packaging equipment required are shown in the Annexure "B", and F'.

27. This will also serve as a check list to decide if any particular country or region has the necessary infra-structure to undertake the activity and in case they are lacking, take steps to organise their availability.

3. Processing of bulk drugs into dosage forms

28. With the advent of new and more potent drugs, the compounding of prescriptions in pharmacies has steadily declined. The therapeutic efficacy of these drugs is not only linked with the pharmacological activity of the basic drugs, but also with the properties of the dosage form in which they have to be administered. It has become increasingly clear that attention has to be paid to the influence of total composition and processing upon the activity of the basic drug. In other words, a basic drug will have to be so manipulated by physical means that upon administrations optimal biological response will be obtained.

29. Processing of the basic drugs into pharmaceutical preparations has, therefore, become a very important aspect of the industry. Not only the physical properties given to the drug during the formulation process are very important and essential for its desired effect, but quite often, the auxiliary ingredients used in the formulation are responsible for the bio-availability of the active drug as also its stability. In certain preparation, even the particle size is important in influencing the rate of absorption, and hence its therapeutic effect.

30. The choice of the auxiliary ingredients, and excipients, as also methods of preparation, are arrived at by each manufacturer through research and investigation. Pharmaceutical manufactureres have to do considerable work in this field, especially in making the products suitable for indigenous conditions. The dosage form of a drug has indeed become so important that while prescribing treatment, the medical profession has now to give as much attention to the choice of the dosage form as to the basic drug itself.

31. Any visitor to a pharmaceutical factory will be impressed by the care and attention paid to the manufacture and processing of drugs, and the latest techniques adopted. No efforts is spared to ensure the highest standards in hygiene and manufacturing processes. Pharmaceutical processing calls for high precision machinery of amazing complexity, a few examples of which are:

32. Tablet-making and coating machines, which compress into tablet drugs in correct dosage at several thousands a minute and coat them to maintain their keeping qualities and also make them palatable.

33. The capsule-filling machines, where small gelatine capsules are filled with the exact quantity of the drug in powder or other forms and subsequently closed if they are lock capsules or hermetically sealed by colour bands.

34. The ampoule-filling machines which fill exact quantities of pure sterile solution into millions of small fragile glass containers which are first individually washed and sterilized, and afterwards sealed by flame. These, in turn, are printed or labelled and packed with great skill. Injectables are also filled in multidose vials and freeze dried.

35. Many other examples of new techniques adopted by the Pharmaceutical Industry could be given to indicate that it is well served by modern machinery. The capacity for processing is usually more than adequate to be able to handle any increased requirements. List of ancillary products required to formulate drugs are given in Annex B (cont'd).

36. The commonly used dosage forms are:

I. Tablets

Tablets are most frequently adminstered 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, filmcoated 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, disentegrating 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 corn starch, gum guar, methyl-cellulose, sodium-carboxy-methyl-cellulose, micro-crystalline cellulose (Avicel), alginates etc. The Indian Pharmacopoeia prescribes 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 choiceof 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.

36. II. Capsules

Capsules are solid dosage forms in which the drug/drugs 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 No.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. Some of the manufacturing houses print their capsules to identify their products. Printing of the capsules can be done before or after filling.

36. III. 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 homogeneous 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 preservative 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 colours are to be used.

36. IV. 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'. These 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

i) 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) Oleaginous bases: consists of mineral, animal or vegetable oils; e.g. soft paraffin, liquid paraffin, lard, olive oil, cottonseed oil etc.

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

c) Washable bases: 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 bases: 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 monostearate.

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

ii) 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.

iii) 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.

36. Parenterals

Parenteral preparations are sterile pharmaceutical dosage forms which are administered under or through one or more layers of the skin or mucous membrane. Generally these preparations are known as injections. All parenteral preparations are sterile. There are mainly four types of parenteral products recognized in the United States Pharmacopoeia.

i) solution of [illegible] ready for injection. This is the most common form e.g. glucose injection, saline injection, etc.

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 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.

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.

For processing drugs into dosage forms a large number of all types of equipment are available and can be imported easily by developing countries. The great advantage in the processing activity is that the same equipment can be used even if there is a change in the bulk drug required, if any substitution becomes necessary resulting from factors already mentioned above concerning the fast obsolescence of drugs required and change in the pattern of consumption to treat the people of any community. Annexure F [illegible] the general description of processing and packaging machinery.

4. Production of simple bulk drugs starting from imported intermediates

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

39. The major groups under synthetic drugs would be sulpha drugs which and 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.

40. It is possible to produce a number of bulk drugs starting from late intermediates using a multipurpose plant. A diagram of a typical multipurpose plant is given in Annex H. The material of construction is preferably glass lined so that it can withstand many corrosive reactions. 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 conditions of reaction and reactants.

5. PLANT PRODUCTS (PHYTO CHEMICALS)

41. In nature, a plant synthesises, complicated molecules from simple ones with highly specific reaction mechanism . The reactions involved are either difficult or expensive to duplicate by classical chemical methods. In the case of steroid hormones the partial synthesis 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 when the climatic and soil conditions are suitable. So far, dioscorea root which grows wild on the Mexican mountains, 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 hecogenin 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.

42. There are also certain phyto chemicals where it is more advantageous to extract them as active principles of plant products than obtain 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:

43. Nux Vomica, the dried ripe seeds of Strychnos nux-vomica Linne, yields 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:

44. 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 tranquillising depressant to the central system.

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

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

Quinine:

45. 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 tonnes 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:

46. Reserpine from Rauwolfia 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. Rauwolfia 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 in only 0.2% of that grown in Africa. Extraction for the isolation of reserpine is fairly simple.

Emetine:

47. Plantations have been established in India in Darjeeling, West Bengal, to grow ipecac to the extent of 20,000 kgs. of dry roots etc. 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 500 kgs. Ipecac is principally used in the treatment of amoebic dysentery and in small quantities in expectorants, emetics, etc.

Digoxin:

48. Indian 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 Bombay. Digitalis is a temperate zone 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.

Caffeine:

49. In regions where tea is extensively grown, caffein can be extracted from tea wastes and tea prunings with solvents like benzene or chlorinated hydrocarbons 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 food preparations and the preparation of aerated soft drinks like coca-cola which commands 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 bye-product in the production of decaffeinated coffee.

Ephedrine:

50. 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 syraps and anti-asthmatic preparations. Here also there is competition from synthetic ephedrine but natural ephedrine has certain preferences.

Scillarin:

51. 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:

52. 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.

52. 1. 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.

6. Utilisation of animal by products and production of biologicals like sera and vaccines

53. The utilisation of slaughterhouse by products is linked with upgrading of abattoirs in large cities and setting up of primary extraction centres in immediate vicinity of slaughterhouses. They have to be collected and frozen and preferably processed immediately after an animal is slaughtered.

54. 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 precipitation 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 use 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.

55. 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 exist on the limited resources of such products which are produced in developed and few of the developing countries.

56. 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.

7. Anti-biotic

57. These products are unlike the synthetic drugs produced with the help of micro-organisms 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.

58. 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 stage/ 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 sterilised 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.

59. 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 (Annexure J) 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 (Annexure K) and some of the newer, semi-synthetic penicillins like Ampicillin are produced industrially by chemical methods.

60. The enclosures give general classification of equipment required for basic manufacture as also of process control instruments and laboratory instruments for quality control and product development research.

61. The major raw materials required for antibiotic production as given in Annexure, C. A more detailed list of raw materials grouped drug wise in an alphabetical order is given in Annexure E.

8. Production of chemical intermediates for Synthetic drugs

62. 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. In other words the development and production of the chemical intermediates are a series of exercises on import substitution 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.

63. 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 organisation 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.

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

9. Production of machinery and equipment

(i) for production of dosage forms

(ii) for production of drugs from basic chemicals

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

66. 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 are given in Annexure E.

Equipment needed can be classified under four main categories:

(i) pharmaceutical processing and packaging machinery.

(ii) Laboratory and research instruments

(iii) chemical plant and machinery including specialised equipment for services and utilities.

(iv) process control instruments

67. Under each of these categories come a large variety of equipment and instrumer s. 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.

68. 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

69. Such an activity presupposes that the country has capable engineers with experience in a variety of design and development activities.

III: FACTORS AFFECTING THE DEVELOPMENT OF PHARMACEUTICAL INDUSTRY IN DEVELOPING COUNTRIES

1. TRAINING OF TECHNICAL PERSONNEL

70. The Pharmaceutical Industry needs besides people trained in Pharmacy and Pharmaceutical Technology those trained in other disciplines of science as well such as Chemistry, Chemical Engineering, Pharmacology, microbiology, Engineering, etc. Many developing countries like India have also institutions for these purposes and their Syllabus and Courses of studies will serve as a model for starting new institutions in other developing countries where none exist today. Institutes training in branches other than Pharmacy and Pharmaceutical Technology will have to be common for other chemical and chemical based industries as well and presupposes that corresponding developments in those branches are also taking place.

71. As the training of personnel will take considerable time the Industry will have to be started using personnel who have obtained training elsewhere and also possess some practical experience.

72. Once the training institutes come into being the qualified people should be absorbed and given in plant training to give them practical experience.

73. Managerial skills are very important for the Pharmaceutical Section and should not be neglected. Maintenance of Hygienic Conditions throughout the factory and Aseptic Conditions where sterile preparations are made, requires a lot of discipline being instilled among the employees. Therefore, it needs greater skill to manage Pharmaceutical Factories than other Chemical Factories and entails higher responsibilities. A good training in management techniques and control of labour are therefore essential.

2. PROMOTION OF INDIGENOUS SYSTEMS OF MEDICINE

74. 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. Incorporating modern drugs with indigenous drugs has also helped. 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 an example of what steps India is taking in this direction would give some indication to other countries as well as to how best they can use these systems of medicine more effectively. The example is illustrated below.

75. The development of Indigenous Systems of Medicine has gained a considerable tempo since Independence. The Government of India have been providing progressive funds for the development of the Indian Systems of Medicine, including Ayurveda. Due to popularity of the Ayurvedic Systems of Medicine amongst the masses, the Government of India have decided that scientific medicine (allopathy) and Ayurvedic, Unani and Homoeopathic systems of medicine should contribute towards the development of the National Health Services in the country. In addition, Indian Systems of Medicine have also been recognised for purposes of reimbursement of medical treatment under the Central Services (Medical attendance) Rules, 1944. Facilities for Ayurvedic treatment have been provided for C.G.H.S. beneficiaries.

Training and Research

76. A Central Council of Indian Medicine was established by the Government of India by an Act of Parliament mainly to evolve uniform standards of education in these systems of medicine and to maintain a Central Register for these systems. The Council has already prescribed minimum standards of education for Ayurveda, Siddha and Unani. These standards are likely to be introduced in all I.S.M. colleges shortly.

77. Besides two full-fledged post-graduate institutions in Ayurveda at the Banaras Hindu University, Varanasi, and Gujarat Ayurveda University, Jamnagar, there are 15 post-graduate departments in Ayurveda, two in Unani and two in Siddha functioning in Andhra Pradesh, Kerala, Madhya Pradesh, Maharashtra, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh, West Bengal and Orissa. These institutions and departments turn out about 150 post-graduates every year. They specialise in different branches in these systems of Medicine.

78. All the post-graduate institutions and departments are wholly financed by the Government of India and undergraduate colleges are either financed or run by the State Governments. The Government of India have also provided partial financial assistance to 16 colleges run by voluntary organizations under these systems of medicine for construction of college buildings and purchase of equipment, etc. So far financial assistance, amounting to Rs. 35 lakhs, has been given to the various under-graduate colleges run by voluntary organizations for construction of college buildings and purchase of equipment, etc.

79. There are, at present, 83 colleges in Ayurveda, one in Siddha and 12 in Unani. Majority of the colleges of Ayurveda are affiliated to the respective Universities in the State in which they are established. More than 2,000 Ayurvedic, Siddha and Unani graduates are coming out every year from these institutions.

80. The Government of India have established a National Institute of Ayurveda at Jaipur and a National Institute of Homoeopathy at Calcutta. Similar Institutes in Naturopathy, Siddha, Unani and Yoga has also been established as a Registered Society in Delhi.

81. A Central Council for Research in Indian Medicine and Homoeopathy established as an autonomous body is engaged in intensive research in the different fields in the Ayurveda, Unani, Siddha and Homoeopathic medicines, including yoga. The Central Council has established 15 full-fledged research institutions for carrying out multi-disciplinary research. Apart from these, about 120 research schemes are functioning in different parts of the country under the Council. The Council has also taken up, among other schemes, Drug Research, Literary Research, Clinical Research, Mobile Clinical Research and Survey of Medicinal Plants throughout the country. The Council has finalised

working standards of 444 preparations, prepared 5,633 identified herbarium sheets, cultivated about 1,225 plants in experimental gardens, surveyed about 150 forest division areas of the country for the exploration of medico-botanical wealth and collected about 1,500 folklore claims. Besides, the Council has prepared an Ayurvedic Medical Kit and published books containing simple remedies in Homoeopathy, Unani and Siddha for common ailments. A similar book in Ayurveda is under publication.

82. The first volume of the Standard Ayurvedic Formulary for 444 compound formulations has been finalised and is under publication. The Unani and Siddha Formularies are also being finalised.

83. The Nature Cure Advisory Committee in the Union Ministry of Health and Family Planning is responsible for the development of Nature Cure. Grants have been given to about 30 Nature Cure Centres for nature cure research beds and training.

84. The Pharmacopoeial Laboratory for Indian Medicine was established at Ghaziabad during 1968 with a view to work out standards and develop tests for single drugs and compound preparations used in Indian Systems of Medicine. They have already developed a small museum of medicinal plants which will facilitate identification of drugs used in Indian Systems of Medicine.

85. Almost all the State Governments have established their own pharmacies of indigenous medicines to meet the requirements of drugs for their dispensaries and hospitals. In addition, more than 600 privately run pharmacies are also functioning in the country.

86. The Drug Control of these systems is being enforced by the State Governments under the Drugs and Cosmetics Act.

87. In addition to various hospitals and dispensaries mentioned earlier, the Government of India have also established 5 Ayurvedic and one Unani dispensary under the Central Government Health Scheme at Delhi. Ayurvedic Units have been set up in Allahabad, Kanpur, Calcutta, Madras, Nagpur, Bombay and Meerut under the C.G.H.S Ayurvedic dispensaries are also functioning under the Coal Mines Development Authority and Employees State Insurance Scheme. The Government of India have also amended the Central Government Medical Attendance Rules to provide the benefits of reimbursement of expenditure

incurred by the Central Government employees for their medical attendance and treatment and of their families in non-allopathic system of medicine.

Future Programme

88. It has been decided to amend the rules of the Central Council for Research in Indian Medicine and Homoeopathy with a view to set up five Boards for Ayurveda, Unani, Siddha, Yoga and Homoeopathy with a view to give an autonomous status to these systems.

89. Apart from financing the existing post-graduate research institutions/departments, Government also propose to establish in the near future two more post-graduate departments in different States.

90. To cater to the requirements of drugs of these systems and to increase the all-round availability, Government propose to establish a Central Pharmacy at Ranikhet as a Public Sector Undertaking. The Government also propose to give financial assistance to State Governments for development of Pharmacies and herb garden, etc. in their own states up to a ceiling of Rs. 8.00 lakhs per Pharmacy.

Plan allocation

91. The Planning Commission have recommended an allocation of Rs. 635 lakhs for the Central Schemes relating to Indian Systems of Medicine in the Fifth Five-Year Plan. In addition, an amount of Rs. 450 lakhs has been approved in the Fifth Five-Year Plan under the Centrally sponsored schemes for the upgrading of departments for post-graduate training and research in Indian Systems of Medicine and development of pharmacies and herb garden. Besides, an amount of Rs. 1550.07 lakhs has also been provided in the State Sector for Indian Systems of Medicine Schemes relating to education, medical aid and pharmacies.

3. Regulation of imports and price control and Distribution

92. The import and price policies of the country will have to be framed and revised from time to time to assist in the integrated development of the industries and not to come in the way of rapid industrialization of the country. Where production has been achieved using local raw materials imports of the concerned finished products should be progressively reduced. Where the industry is in the early stages of development and is unable to meet the full requirements the imports should be restricted to only meet the balance requirements. This is no doubt a difficult job but there are many ways of achieving it. One of the solutions would be to canalize the imports through state owned organizations, of products already produced but not adequate to meet the demands through state owned trading or manufacturing organisation in case these products are made by the latter but are able to meet only part of the demand. As the prices of products locally produced will in the earlier stages be higher due to various causes, the prices should be pooled with the imported production which in turn will benefit the consumer. Bulk buying by state owned organizations of products not adequately produced or those which are likely to be over invoiced will help in obtaining them at lower prices than they would have normally entered the country and restrict the imports to meet only the needs without discouraging the local industry to operate to full capacity or expand production. If there is a tendency on the part of the local industry under a protected market to make excessive profits a system of price control should be introduced. In the case of packaging and formulation activity it should be based on the cost of raw materials going into their manufacture, packing material and fixed sums arrivedat, for each of the processing operations involved as well as a mark up on the ex-factory cost to cover other expenses like marketing, promotion and profits. In the case of basic manufacture the price of the bulk drug should be arrived at based on cost of raw materials, production costs and reasonable return on investment. This pricing should be such as to give more encouragement for basic manufacture and not stop the units at mere formulating activity.

93. As an example the list of items whose imports are canalised by the state agencies and by the state owned pharmaceutical sector in India are shown in Annexure -I .

4. QUALITY CONTROL OF IMPORTED AND LOCALLY MANUFACTURED DRUGS

94. The overall aim of the drug control organization in a country should be to infuse a sense of confidence in the quality of drugs that are manufactured by firms, notwithstanding the size of operations of the unit. The interests of patients are of paramount importance as its aim is to cure the patients quickly by administering those drugs in whose quality the medical profession has confidence. It is the responsibility of the drug control administration, both at the Central and State levels, to ensure that the quality of drugs manufactured by all firms is uniformally satisfactory. In the case of drugs, a little latitude shown to a manufacturer may spell all the difference between life and death. Concerted efforts have to be made by the Centre and the State Governments to maintain uniform standards of inspection, licensing of drug firms and the weeding out of firms which are technically or otherwise incompetent to manufacture drugs, to enable the medical profession to have full confidence in the quality of all the drugs that are available in the country.

95. Quality control of drugs assumes considerable importance when we have to compare the same drug made by different manufacturers. Units in the industry must have a built-in system for quality control right from the raw materials to the finished stage and also the requisite organization to frequently study the stability of the drug when it moves in the market and for recalling any drug from the market from different parts of the country whenever necessary. Units in many developing countries lack these essential facilities without any built-in quality control and without any regard to the keeping quality of the drug. The result is obvious. It is not enough if a drug complies with the standards when it is made but it is equally important that its potency is guaranteed when it is consumed in any part of the country and under various climatic conditions. Such a quality control check can be enforced only if the officer in overall charge of the organisation and the Drugs Inspectors have the necessary background knowledge and are properly trained. Frequent inspections of manufacturing establishments and stability studies of products and enforcing stringent precautions at the first and subsequent inspections must constitute the most important duties of such officers.

96. The technique of manufacturing drugs is becoming more and more highly specialised and complex and newer techniques in manufacture and testing of drugs are being introduced continuously. Organized manufacture of drugs of high potency has greatly increased the social responsibility of the Drug Control Organization and compels it to exercise rigid control over the practices of drug manufacturers and also act as an adviser to the industry to strive for constant improvement of its performance. All these need an expert in the field of drugs and the responsibility cannot be assigned to personnel whose competence in this complex field is questionable.

Scope of the Drugs and Cosmetics Act

97. "Drugs Control" is a social measure intended to ensure that the community at large obtains drugs of standard quality. With this object in view a Drugs Act should be enacted, the Rules under it framed for enforcement of the legislation. The Act should regulate the import into and manufacture, distribution and sale of drugs in the country.

Control Mechanism and Division of Responsibility

Central:

98. Under this Act, the Central Drugs Standard Control Organization, headed by a Drugs Controller should be responsible for:

(i) Controlling the quality of imported drugs, and drugs moving in Inter-State Commerce

(ii) Co-ordinating the activities of the States advising them on matters relating to the uniform administration of the Act in the country

(iii) Laying down regulatory measures and standards of drugs, and

(iv) Granting approval to 'New Drugs' proposed to be imported into or manufactured in the country.

States:

99. The State Drug Control authorities should be responsible for controlling the quality of drugs manufactured, sold or distributed in the country. This control is exercised through a system of licensing of manufacturing and sale premises through Drugs Inspectors.

100. The officer in over-all charge of Drug Control in a State constitutes the king-pin of the Organization. He should be responsible not only for enforcing the quality control measures over drugs but also for the development of the drug industry, having regard to the raw materials and natural resources available in the country. Lack of adequate technical knowledge on the part of the top officer will result in ill-equipped and ill-organized firms being licensed to manufacture drugs. The check that is experienced over the first licensing or the renewal of licences determines the quality of products that are turned out by the firm though frequent inspections of the manufacturing firms are also necessary to ensure that the quality control discipline is ingrained in all the personnel working in the firms. Considering these aspects, the need for laying down the qualifications for the 'Licensing Authority' needs no emphasis.

The qualifications of the licensing authority in each State should be laid down in the Drugs and Cosmetics Rules and if necessary an enabling provision should be introduced in the Drugs and Cosmetics Act for this purpose. The qualifications should be the same as that required for Drugs Inspector under the Drugs and Cosmetics Rules, the idea being that experienced Inspectors should be made eligible for appointment as the Drugs Control Authority. The overall authority in the State should also be the 'Controlling Authority' for Drugs Inspectors and no Drugs Inspector should be permitted to institute a prosecution without the express order in writing from the 'Controlling Authority'.

101. Apart from laying down the qualifications for the Licensing Authority the licensing firms, the Licensing Authority should be guided by a small technical committee which among others should include a senior officer from the Central Drugs Control Organization. It would be even better if the licensing of drug manufacturers in each state is decided by a Board. This licensing Board should consist of (i) Drug Control Authorities of the State concerned; (ii) Drug Control authorities of the State in the region; (iii) a senior representative of Drugs Control Authority of the country. This procedure of screening applicants for manufacturing

licences will greatly help in weeding out firms which are incompetent or ill-equipped to manufacture drugs and also obviate inter-state complaints. The manufacturers of injectibles including glucose solutions, anti-biotics, etc. (Schedule C items) should not be licensed to manufacture unless they have their own arrangements for testing them. Other items - non-schedule C items, may be permitted to be got tested by manufacturers through commercial laboratories. Such commercial laboratories should be required to maintain efficient standards with regard to technical staff, equipment and environments and should be approved by the Drug Control Organization at the Centre.

102. The Drug Control Organization should be divorced from the Directorate of Medical and/or Health Services and constituted into a separate department functioning directly under the control of the Ministry/Department of Health. Such an alignment of the Drug Control Organization will be conducive to greater co-ordination between the Government and the Drug Control Organization, eliminate delays that are inevitable in an arrangement where the Drugs Controller functions under someone else's control and help in answering the criticism that the power to license drug manufacturing firms is vested in the authority that also purchases drugs.

Adequate number of duly qualified Inspectors on attractive pay scales

103. should be appointed so that there would be one Inspector for 200 selling premises. However, more appointment of Drugs Inspectors without concomitant efforts to bring their technical knowledge up-to-date will not help in toning up quality control measures. "Drugs" is a field where innovations in the techniques of manufacture and testing drugs are a daily feature and if the inspectors are not conversant with them they will cease to command the respect of the industry which engages top-grade technical personnel. A programme for training Inspectors has to be organised by the Central Drugs Control Organization.

104. More exhortation to the States advising them to build up testing facilities will not have the desired effect. The Centre should assist the States in developing combined food and drugs laboratory by extending financial assistance to them. If such States ask for financial aid from the Centre for expanding some of their departments, the Central Government should consider such requests favourably.

105. The States should constitute a legal-cum-intelligence Cell for carrying on the campaign against spurious drugs. Recommendations setting forth the manner in which the campaign against spurious drugs should be organised are given separately. The Central Government should assist the States in organising this campaign by extending financial assistance to them.

106. There is a need for maintaining close contact with the medical profession, consumer groups etc. Unless this contact is established the public may not be aware of the governmental efforts that are being made in this direction.

107. Enlistment of the co-operation of the public, the members of the medical profession and other social bodies such as Consumer Councils etc. in tightening drug control measures and in combating spurious drugs should engage the attention of the Central and State Governments.

Spurious drugs and Problems connected with the Campaign against them

108. The term "Spurious Drugs" does not specifically occur in the Drugs and Cosmetics Act. However, the term 'misbranded drugs' covers what is commonly intended by the term 'Spurious Drug'. In brief, spurious drugs would include:

(a) A drug whose label shows it to be manufactured by a firm which is non-existent

(b) A drug which is found to be different from what is claimed on the label.

(c) A drug which is manufactured by a party other than the manufacturer shown on the label.

(d) A drug which is a close colourable imitation of a well established drug or brand of drug and which is likely to deceive the consumer into the belief that he is buying the established drug or brand of drug

(e) Defective drugs which are treated in such a manner as to conceal the damage or defects of drugs which are made to appear of better or greater therapeutic value than they

really is (Penicillin contaminated with other material and labelled as pure penicillin of certain potency is a case in point.)

109. "Sub-standard Drugs" are those which do not conform to the standards laid down in the Drugs and Cosmetics Act. While the manufacture of spurious drugs is essentially a clandestine operation indulged in by unlicensed manufacturers or dealers, sub-standard drugs may be manufactured by licensed manufacturers. "Spurious drugs" is a law and order problem, just like any other illegal activity, such as counterfeiting of currency or smuggling of banned articles. The Drugs Inspector whose primary duty is to educate and assist honest and ethical drug manufacturers operating against valid licences to improve their quality and performance, is ill-equipped to tackle the problems of spurious drugs on his own. The reason for this is that the manufacture of spurious drugs is mostly an under-cover activity and that for tracking down the hide-outs where drugs are faked, the operations should start from the end of dealers who are suspected to be selling or distributing such spurious drugs. The activities and the external 'Contacts' of such dealers should be kept under surveillance through plain clothes watchers or policemen. From the 'leads' that are obtained, the hide-out where the drug-faking activity is carried on should be traced and raids carried out by the police or the Drug Control Organization with the help of the police. Prosecutions may have to be launched, in many cases, simultaneously under the provisions of the Drugs and Cosmetics Act, the Trade Marks Act the Penal Code etc., so as to ensure that the accused does not escape clutches of a single legislation on technical grounds. In short, the campaign against spurious drugs will be effective only if the Drugs Inspectors, apart from being fully conversant with the ins and outs of drugs manufacture and testing, are also well-acquainted with the provisions of other legislations such as the penal code, the evidence act, the Criminal Procedure Code etc., and also know the pitfalls in processing prosecutions. The secret of success of the campaign against spurious drugs lies in the maintenance of close liaison with the police authorities. This implies that an 'Intelligence-cum-legal' unit must operate in each State. This organization should consist of 'watchers' who would be well-conversant with the drug trade and its practices. As already stated above, reports of movements of spurious drugs are more frequent in the State where drug control has been lax. The information given to the states about the positive clues relating to spurious drugs, such as the names of parties dealing with spurious drugs or the areas where they move should be taken note of and action taken quickly.

5. Regulation of new production facilities for formulation of drugs and organic bulk production

110. As an industry the pharmaceutical sector falls entirely in the category of a chemical based industry. In developed countries the pharmaceutical industry has come into being after the chemical industry and engineering industry have acquired a base from where they could meet the needs of drug manufacturing units. However, in most developing countries the chemical industry or the packaging and engineering industries have not reached a stage of development when they could feed the pharmaceutical sector with many of its requirements. The pharmaceutical industry in developing countries will have to undertake manufacture of many of its requirements adding to the dimensions of the chemical industry in particular and accelerating the pace of industrialization in general. Progressively the organic chemical industry with corresponding developments taking place in other allied sectors, like dyes, plastics, synthetic fibres, textile auxiliaries and rubber chemicals has to orient its production to meet the needs by bulking the requirements of these industries. Also the engineering industries will have to meet the demands of machinery and the packaging industries to meet the requirements of packaging material. There is therefore need to regulate the development of all these industries to bring about a close integration of their activities to make production progressively more and more self-sustaining.

111. Expansions in the industry should be based from as basic a stage as possible and whenever such production is being undertaken from later stages they should under time-bound programmes be made to switch over to more basic stages. Production plans of organic chemicals and intermediates should also be oriented to coordinate and make available the basic starting materials at the appropriate stage.

Regulation and Technical Collaboration Agreements

112. Technology development in any industry has to be comprehensive and has to be aimed at achieving specific goals. There can be no rigid and fast rules and each case will have to be decided on merits weighing the advantages with the disadvantages.

113. There are two broad areas where flow of technology is important in the field of pharmaceuticals for developing countries. The first is with regard to existing drugs, to produce the essential items in quantities adequate to meet the increasing requirements and maximise production from available resources and manufacturing facilities if they are already established. Secondly, there are areas where existing drugs are not really very effective or have lost their effectiveness or where no curative drugs exist for certain diseases in the country. In this case technology has to deal with the introduction of better and more efficacious remedies for treatment, based on research. It is natural that the first part takes comparatively shorter time than the second which involves introduction of new drugs based on discoveries.

114. There are different ways in which technology can be obtained by developing countries:

(i) By outright purchase by making a lump sum payment for an existing technology. For this to be succesful it is necessary for the importing country to have some technical base to make a proper evaluation and to adapt the technology for local conditions and R and D facilities to update it. Moreover, in highly specialised fields or where the new technology is confined to one or two sources it may not be always possible to purchase the knowhow by this method. It has to be borne in mind that by this method of purchase there is no continuing access to improvements in technology which are taking place all the time and might result in repetitive purchase of technology whereafter a time, it becomes outdated and it is difficult for the R and D efforts to keep pace.

(ii). By payment of royalty on production. In this case the firm supplying the technology has some interest in the production really reaching the optimum capacity and keeping the production going. There is also a possibility of access to improvements as the supplier of technology does not desire the firm to go out of production in the face of competition by firms using better technology.

(iii). By equity participation with or without royalty payment. In such an arrangement there is a definite access to improved technology obtained by R and D efforts carried out elsewhere. The supplier of technology has a greater stake as his investment is involved and his earnings as dividends on capital invested depends on the successful operation of the company based both on progressive improvement of, technology and management.

115. Transfer of technology is not confined only from developed countries to developing countries. There are many instances where the developing countries can obtain technology from other developing countries where technology has developed. Such technology has an advantage as it has already been adapted to conditions prevailing in developing countries and is very suitable specially in cases where the industry is still in the earlier stages of development. It also helps developing countries which have reached more or less the same stage of development to exchange information and bring about a two way flow of technology. But this has its limitations where more sophisticated technology or production of newer products are concerned.

116. It will be seen from the above that there can be no rigid procedure which can be followed for technology transfer and each case will have to be treated on merits However, there can be certain guidelines which every country can draw up depending on the stage of its technological development for permitting import of technology and the types of association of foreign capital or otherwise, and payments for the same. As the country progresses these guidelines can be modified to ensure that local initiative in the field is given encouragement and the country becomes less and less dependant on imported technology. Most important step in this direction is to make sure that when any technology is brought in the available R and D resources are associated with the same so that further improvements can be made within the country and the need for repetitive import of technology is avoided in the same field as far as possible.

117. When the local R and D resources are limited and the field is highly sophisticated there will be need for the association in some form or other of the firm supplying the technology to ensure that new developments become available. Such fields can be spelt out in the guide lines so that the local firms as well as those outside supplying the technology know exactly where such association is permitted and do not waste their time or effort but restrict such negotiations to only these fields. Here as well the stage from which production can be undertaken as also the necessity to progressively switch over to raw materials that will become locally available with the development of the chemical and other industries in the country should be insisted. With expansions taking place the method of dilution of foreign equity, if involved, should be indicated as further investments for such expansion become necessary.

118. In fields where the country has already acquired a good technical base and where only a particular new development in process or a new strain for an antibiotic production is necessary to improve the yields, this should be acquired by lump sum payment or royalty arrangements depending on the foreign exchange position or other factors.

ANNEX A

LIST OF ESSENTIAL DRUGS USED IN INDIA

Sl. No. (1)	Name of Bulk Drug (2)	Dosage Form (3)
	ANTIBIOTICS	
1.	Penicillin	Vials
2.	Streptomycin	Vials
3.	Chloramphenicol Palmitate/Powder Powder Palmitate Succinate Stearate	Capsules Pediatric Drops
4.	Tetracycline HCL. (includes Chlor-tetracycline and Demethyl Chlortetracycline)	Capsules ointments
5.	Oxy-tetracycline	
6.	Ampicillin and other semi synthetic penicillin	Tabs
7.	Erythromycin	Vials
	SULPHAS	
8.	Sulphadimidine (6 sulphas; 320 T to five sulphas)	Tabs
9.	Sulphadiazine	Tabs
10.	Sulphacetamide and Salts	Tabs
11.	Phthalyl Sulphatiazole	Tabs
12.	Sulphasomidine (includes sulphamoxole)	Tabs
13.	Sulphamoxole	Tabs
14.	Sulphaguanidine	Tabs
15.	Sulphanilamide	
16.	Sulphamethaxazole Sulphaphenazole	
	ANTI-AMOEBIC AND ANTI-DYSENTRY	
17.	Iodochlorohydroxy quinoline	Tabs
18.	Di-iodo-hydoxy-quinoline	Tabs
19.	Metronidazole	Tabs
20.	Emetine (including di-hydroemetine	Tabs and injection

Sl. No. (1)	Name of Rule Item (2)	Dosage Form (3)
21.	Diloxamide furoate	Tabs
	ANTI-INFECTIOUS, ANTI BACTERIAL	
22.	Nitrofurantoin	Tabs, Ointments
23.	Nitrofurazone	
24.	Furazolidone	
	ANTI-HISTAMINIC	
25.	Chlorpheniramine maleate	Tabs
26.	Chlorpromazine Hcl.	Tabs
	VITAMINS	
27.	Vitamin A	Tabs
28.	Vitamin B-1	Tabs and injection
29.	Vitamin B-2	Tabs and injection
30.	Vitamin B-6	Injection
31.	Vitamin B-12 Vit. B(complex)	Injection and Tabs Tabs
32.	Vitamin C	Tabs and injection
33.	Vitamin D-2 D-3	Tabs
34.	Folic Acid	Tabs
35.	Calcium Pantothenate (includes Panthenols, Pantothenates)	Tabs
36.	Nicotinamide	Tabs
37.	Folic Acid	Tabs
	CARDIAC	
37.	Digoxin	Tabs
38.	Adrenaline	Injection
39.	Glyceryl Trinitrate	Tabs
	ANTHELMINTICS	
40.	Piperazine and its salts Piperazine Adipate	Tabs
41.	Tetrachloro ethylene	Liquid
	ANTI-DIABETICS	
42.	Insulin	injection

Sl. No. (1)	Name of Bulk Drug (2)	Dosage Form (3)
43.	Tolbutamide (also glybiaclamide)	Tabs
44.	Chlorpropamide	Tabs
45.	Phenformin	Tabs
	ANTI-TB	
46.	INH	Tabs
47.	PAS	Tabs
48.	Thiacetazone	Tabs
49.	Ethambutol	Tabs
50.	Rifampicin	Caps.
51.	Pyrzinamide	Tabs
52.	Morphazinamide Hydrochloride	Tabs
	ANTI-LEPROTIC	
53.	D.D.S. and its	Tabs
	ANTI-MALARIAL	
54.	Chloroquin Phosphate (includes chloroquin Sulphate)	Tabs
55.	Amodiaquin	Tabs
56.	Primaquin Phosphate	Tabs
57.	Quinine Salts	Tabs
	ANTI-FILARIAL	
58.	Diethyl Carbamazine Citrate	Tabs
	ANALGESICS ANTI-PYRETICS AND SEDATIVES AND ANAESTHETICS	
59.	Aspirin	Tabs
60.	Phenacetin	Tabs
61.	Paracetamol	Tabs
62.	Analgin	Tabs
63.	Salicylic Acid	Ointment
64.	Methyl Salicylate	Ointment Balms
65.	Phenobarbitone	Tabs
66.	Pethidine	Tabs and Injections
67.	Morphine Sulphate	Injection
68.	Procaine HCL.	Injection
69.	Xylocaine/Lignocaine	Injection

Sl. No. (1)	Name of Bulk Drug (2)	Dosage Form (3)
70.	Diethyl Ether	liquid
71.	Ethyl Chloride	spray
72.	Phenyl Butazone	Tabs
73.	Oxyphenylbutazone	Tabs
	HORMONES AND STEROIDS	
74.	Prednisolone	Tabs
75.	Norgestrel	Tabs
76.	Ethinyl Oestradiol	Tabs
77.	Norethisterone Acetate	Tabs
	DIURETICS	
78.	Furesemide	Tabs
79.	Hydrochlorthiazide	Tabs
	OTHERS	
80.	Theophylline	Tabs and injection
81.	Aminophylline	Tabs
82.	Ephdrine Hcl.	liquid
83.	Succinyl Choline Chloride	Tabs
84.	Caffeine	Tabs (along with other analgesics)
	ANTITOXINS, SERA, . VACCINES	
85.	Tetanus Antitoxin	injection
86.	Diphtheria Antitoxin	injection
87.	Anti-Venum Serum	injection
88.	Diphtheria Pertusis Tetanus,(Triple antigen)	injection
89.	Polio I, II and III Type	injection
90.	Tetanus Toxoid	injection
91.	Diphtheria Toxoid	injection
92.	T.A.B.C.	injection
	ANTIHYPERTENSION	
93.	Reserpine	Tabs
94.	Methyldopa (aldoment)	Tabs

Sl. No. (1)	Name of Bulk Drug (2)	Dosage Form (3)
95.	Dihydroergocrystine	Tabs
	TRANQUILISERS	
96.	Chlordiazopoxide	Tabs
97.	Diazepam	Tabs

B; 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) Moisture-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 wads.	(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.	—
		2. 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 Wraps.	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 & pisto ..	(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.

B. (cont'd). 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 pyrolidone
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

ANNEXURE 'C'

Requirement of Raw Materials for the Manufacture of Antibiotics

Penicillin

Streptomycin

Tetracyclines

Neomycin

Raw Materials:-

Carbohydrates

Strach

Dextrin

Dextrose

Cane Sugar

Protein Sources

Soya 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/Hyflos percel

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

D: 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 dichlo o 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%
Phenylhydrazin
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

E: CLASSIFICATION BY DRUG END-PRODUCT OF INTERMEDIATES, BASIC CHEMICALS AND OTHER RAW MATERIALS REQUIRED FOR THE MANUFACTURE OF DRUGS.

MAIN RAW MATERIALS REQUIRED FOR THE MANUFACTURE OF ALL DRUGS (Grouped Drugwise)

65.

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
1.	Acetanilide	Sulpha Drugs
2.	Acetaldehyde	Sulpha Drugs Indomethacin
3.	Acetic Acid	Phenacetin Chloroquin Sulpha Drugs
4.	Acetic Anhydride	Chloramphenicol Sulphacetamide, Paracetamol, Acetazolamide Thiacetazone Aspirin Vitamin B1 Phenacetin

66.

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
5.	Acetoacetic Ester	Amidopyrin Novalgin 4-Diethylamine-1-methyl butylamine
6.	Acetonitrile	Sulfas
7.	Acetone	Vitamin A, B6, Vitamin C, Ephedrine Amodiaquin
8.	Acetophenone	Para-nitro-acetophenone
9.	Acetone Semicarbazone	Nitrofurazone
10.	Acetoin	Sulphamoxazole
11.	Acetyl Acetone	Sulphadimidine
12.	Acet. Butyro Lactone	—
13.	Acetylaminophenol or Paracetamol	Amodiaquin
14.	Acetyl Chloride	Vitamin A
15.	Activated Carbon	All Drugs
16.	Acrolein	Folic Acid

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
17.	Acrylonitrile	Vitamin B_{12} Sulphas
18.	Adipic Acid	Iodipamide
19.	Alcohol (absolute)	All drugs
20.	Aluminium (metal)	Chloramphenicol
21.	Allyl bromide	Secoberbitol
22.	Aluminium Chloride (Anhydrous)	Chloramphenicol Prenylamine
23.	Amino-chloro-benzophenone	Chlordiazepoxide Diazepam
24.	d-2-Aminobutanol	Ethambutol
25.	4-Amino-2-6-dimethyl-pyrimidine	Sulphasomidine
26.	Aminohydantoin Sulphate	Nitrofurantoin
27.	O-Aminophenol	Di-Iodohydroxyquinoline
28.	M-Aminophenol	PAS & Esters
29.	P-Aminophenol	Paracetamol (P-Acetylaminophenol No. Dioxanide
30.	2-Aminopyridine	Mepyramine
31.	2-Aminopyrimidine	Sulphadiazine Sulphadimidine
32.	2-Aminothiazole	Sulphathiazole derivatives

67.

68.

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used
33.	Ammonium Thiocyanate	Acetazolamide Thiacetazone Vitamin B_1
34.	Ammonia gas	All drugs
35.	Ammonium sulfate	Antibiotics
36.	dl Alanine	Vitamin B_6
37.	Aniline	Acetanilide
38.	p-anisidine	Indomethacin
39.	Anthranilic Acid	Methaqualone Hcl.
40.	Anisaldehyde	Mepyramine
41.	Arquad 16 (c) (Quaternary Ammonium Compounds)	Tetracyclines
42.	Beet Molasses	Vitamin B_{12}
43.	Benzene	Vitamins Analgesics Sulfas Thiacetazone
44.	Benzaldehyde	Chloramphenicol Analgin
45.	Benzoic Acid and salts	Diazepam Chlordiazephoxide
46.	Bromine	Chloramphenicol Diphenhydramine

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
47.	Benzyl Chloride	Chloramphenicol Bephenium Hydroxy-Naphthoate Benzyl Cyanide Phenobarbitone
48.	Benzyl Cyanide	Pethidine Phenobarbitone Phenylacetic acid Phentermin
49.	2-Benzyl pyridine	Pheniramine maleate
50.	Boric Acid	Anti-dysentry drugs
51.	2-Bromopentane	Barbiturates
52.	Butyl acetate	Penicillin
53.	n-Butyl alcohol	Penicillin Tetracycline Vitamin B_{12}, B_2
54.	t-Butyl alcohol	Hydrochlorothiazide
55.	n-Butylamine	Tolbutamide, Methyldopa
56.	2-butene 1,4 diol.	Vitamin B_6
57.	Butyl-malonic-Diethyl Ester	Phenylbutazone
58.	Butyl oxide	Ephedrine

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
59.	n-butyl bromide	Phenylbutazone Oxyphenyl butazone
60.	Calcium cyanamide	Sulfamoxazole
61.	Calcium oxide	Antibiotics
62.	Calcium carbonate	Antibiotics
63.	Capryl Alcohol	Vitamin B_{12}
64.	Carbon di-sulphide	Tolbutamide
65.	Cetrimide (Quaternary Ammonium Compound)	Penicillin & Other antibiotics.
66.	Cellosolve (Ethyl Cellosolve)	Tetracyclines
67.	m-chloraniline	Amodiaquin Chloroquine Hydrochlorothiazide
68.	Chloral hydrate	Diloxanide
69.	Chloracetyl chloride	Xylocaine
70.	P-chlorobenzoic acid	Analgesics Indomethacin
71.	P-chlorobenzene sulphonamide	Chlorpropamide
72.	2-chloro-ethanol	Metronidazole

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
73.	1-chloro-2-dimethylamino-ethane	Chlorpheniramine maleate
74.	Chlorofurethane	Phenacetin DDS Paracetamol
75.	Chlorofurethane	Halothane
76.	2-chlorophenothiazine	Chlorpromazine
77.	P-chlorophenol	Clofibrate
78.	2-chloropropyl-dimethylamine hydrochloride	Chlorpromazine
79.	Chlorosulphonic acid	Sulfa drugs, DDS, Hydrochlorothiazide Furosemide Chlorpropamide
80	Chloropropionic acid	
81.	5-chloro 2,4-disulphonamido-aniline	Chlorothiazides
82.	Cholesterol	Ethisterone Spironolactone
83.	Citric Acid	Tetracycline Citrates
84.	Cinnamaldehyde	Prenylamine Lactate
85.	Cobalt nitrate	Vitamin B12
86.	Corn Steep Liquor	Antibiotics

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
87.	Copper Powder	Chlorpromazine
88.	Cotton Seed Flour (vegetable protein source)	Amphotericin Tetracyclines
89.	m-cresol	—
90.	Cyanoacetic acid	Theophilline
91.	Cyanacetic ester	Folic Acid Sulphamethoxazine
92.	Cyanacetamide	Ethionamide
93.	Dextrin	Antibiotics
94.	7-Dehydrocholestrol	Vitamin D
95.	Dibutyl Ether	Ephedrine
96.	2-4 Dichlorobenzoic acid	Furosemide
97.	Dichloromethyl acetate	Chloramphenicol
98.	4-7 Dichloroquinoline	Amodiaquin
99.	2-5 Dichloronitrobenzene	Chlorpromazine
100.	Dicyandiamide	Sulphaguanidine Sulphadimidine Phenobarbitone Phenformin
101.	Diethylamine	Diethylcarbamazine Xylocaine Amodiaquin Nikethamide Diethylamino-ethanol

	Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
73.	102.	Diethanolamine	Pethidine
	103.	2-Diethylamino-ethanol	Procaine Hcl. 4-Diethylamine-1-methyl butylamine
	104.	4-Diethylamino-1-methyl-butylamine	Chloroquin
	105.	Diethyl carbonate	Furazolidone
	106.	Diethyl ethoxymethylene malonic ester	Chloroquin Amodiaquin
	107.	Diethyl Malonate	Phenyl butazone Diethylethoxy methylene malonic ester. Vitamin B2
	108.	Diethylmethylamine	Pethidine Ethionamide
	109.	Diethyl oxalate	Phenobarbitone Vitamin B2 Ethionamide
	110.	Dimethylamine 100%	Chloramphenicol Bephenium hydroxy-napthoate
	111.	3-4 dimethylaniline	Anti-hystamines
	112.	2-6 dimethylaniline	Anti-hystemines Sulphadimethoxazine
	113.	Dimethyl chlorosilane	—

	Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
74.	114.	Dimethylamino-chloroethane hydrochloride	Mepyramine
	115.	Dimethyl formamide	Antibiotics, Steroids.
	116.	1-Dimethylamino-2-chlor-propane hydrochloride.	Promethazine & -salts.
	117.	Dimethyl polysiloxane	—
	118.	3-Dimethyl aminopropyl chloride	—
	119.	Dimethyl sulphate	Vitamin B, Novalgin Amidopyrin Diloxanide
	120.	Dimethyl sulfoxide	Vitamin A Diloxanide
	121.	Dinitrobenzal chloride	Vitamin D
	122.	Diphenyl oxide	Chloroquin Amodiaquin
	123.	Diphenylamine	
	124.	Diosgenin	Steroids
	125.	Ergosterol	Vitamin D
	126.	Epichlorhydrin	Xanthinol nicotinate
	127.	Ether (solvent)	Vitamins & Analgesics

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
128.	Ethyl acetate	Vitamins
129.	Ethyl Bromide	Phenobarbitone Vitamin A Ethambutol
130.	Ethylene Dichloride	Chloramphenicol INH Diethylcarbamazine Bephenium Hydroxy-napthoate Chloroquin Amodiaquin
131.	Ethylene diemine	EDTA Caffeine and Thiophylline
132.	Ethylene diamine tetracetic acid.	Antibiotics
133.	2-ethyl hexanol	Antibiotics
134	Ethyl orthoformate	Diethyl ethoxy-methylene malonate
135.	Ethyl chloroformate	Vitamin B.
136.	Ethylene Oxide	Chloramphenicol 4-Diethylamino-1-methyl butylamine Furazolidone Vitamin B.
137.	Ethylene chlorohydroin	Diethylamino ethanol
138.	Ethyl Palmitate	Vitamin A
139.	Ethyl Isopropyl-malonate	Amylobarbitone

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used
140.	Ethyl Methyl Ketone	Ethionamide Vitamins
141.	Filter Aid (Hyflosupercel and Dicalite)	All Drugs
142.	Formamide	Hydrochlorothiazide and other chlorothiazides.
143.	Formaldehyde 30%	Streptomycin Chloramphenicol Amodiaquin Tetracycline INH
144.	Formic Acid	PAS & Esters. Diethylcarbamazine Vitamin B1 Hydrochlorothiazide
145.	Fumaric Acid	—
146.	Fumaronitrile	Vitamin B6
147.	Furfurylamine	Furesemide
148.	Gelatine (Pharmaceutical grade)	Vitamin A Gelatine capsules
149.	Glucose (Dextrose)	Vitamin C Ca. gluconate Antibiotics.
150.	L-Glutamic Acid hydrochloride	Folic acid

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
151.	Guanidine Nitrate	Folic acid
152.	Guanidine carbonate	Sulfas
153.	Hexamethylene-Tetramine	Chloramphenicol
154.	Hydrazine Hydrate	INH Thiacetazone Nitrofurantoin
155.	Hydrazine Sulphate	Acetazolamide and others.
156.	Hydrobromic Acid	Methyl Dopa
157.	Hydrogen peroxide 30%.	Tolbutamide
158.	Hydroxyethylhydrazine	Furazolidone
159.	p-Hydroxy-napthoic acid.	Bephenium Hydroxy napthoate.
160.	3-Hydroxymethyl pyridazine	Pyrazinamide
161.	Hydroxylamine-hydrochloride	Hydroxy urea Sulfadimethazine
162.	8-Hydroxyquinoline	Halogenated Oxyquinolines
163.	Hydroquinone	Vitamin A
164.	Hexane	Soya flour vitamins
165.	Iodine	Iodochloro and Dichlorohydroxyquinoline

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
166.	Isoamyl Formate	Imipramine
167.	Isopropyl alcohol	Chloramphenicol Tetracyclines, etc.
168.	Isopropyl Ether	Vitamins
169.	Isophytol	Vitamin E
170.	Ketozectol	Vitamin A
171.	Lard Oil	Antibiotics
172.	Lithium Metal	Vitamin A
173.	Lactic acid	Calcium Lactate Calcium sodium Lactate
174.	Levulinic acid	Indomethacin
175.	Maleic Acid	Pheniramine } malectes Chlorpheniramine }
176.	Magnesium Metal	Vitamin A
177.	Malonic ester	Riboflavin Amylobarbitone and other barbiturates
178.	Methoxy Pyridoxin	Vitamin B.
179.	Methyl Alcohol	Streptomycin Chloramphenicol Vitamin A Vitamin C Ephedrine Pethidine Vitamin D Chloroquin

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used
180.	Methylamine 40%	Ephedrine Caffeine Theophylline
181.	N-Methylalanine	Vitamin A
182.	Methylbenzene sulphonate	Amidopyrin Novalgin
183.	2-Methylimidazole	Metronidazole
184.	Methyldichloroacetate	Chloramphenicol Vitamin A
185.	Methyl acrolein	Sulfomerazine
186.	Methyl Aminophenol	PAS & Salts
187.	B-Methyl amino ethanol	Xanthinol Nicotinate
188.	Methylene chloride	Vitamin A
189.	Methylethyl pyridine	Vitamin A
190.	Methyl formate	Chloramphenicol
191.	Methyl isobutyl Ketone	Tetracycline PAS & Esters Tolbutamide Chlorpromamide
192.	Methylaminochloroacetate	Vitamin A
193.	Methyl cyanoacetate	Sulfadimethoxazine
194.	Methylene dichloride	Antibiotics
195.	Methyl ethyl ketone	Vitamins Ethionamide

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
196.	B-Methyl Naphthalene	Vitamin K
197.	2-Methyl-1-3-propanediol	Meprobamate
198.	Monochlorobenzene	Chloramphenicol
199.	Monochloroacetic acid	Analgesics Vasodilators Xylocaine
200.	Monoethyl amine	
201.	Monoethanolamine	Piperazine salts
202.	Nickel catalyst	Vitamin C 4-Diethylamino-1-methylbutylamine
203.	Nickel alloy (Raney nickel)	Several synthetic drugs.
204.	p-nitroacetophenone	Chloramphenicol
205.	Nitrobenzene	Phenyl butazone
206.	p-nitrobenzoylchloride	Folic Acid
207.	5-Nitrofurfuryl Diacetate	Furazolidone Nitrofurazone.
208.	Nitromethane	Anti-hypertensives
209.	Nitroethane	Methyl Dopa

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
210.	Nitropropane	Methyl Dopa
211.	Nitrogen gas	Methyl Dopa
212.	O-Nitrophenol	Iodo-chloro & Diiodo-hydroxyquinoline
213.	p-Nitrotoluene	Thiacetazone Procain Hcl. Imipramine
214.	p-nitrobenzoic acid.	Procaine Hcl.
215.	m-nitrobenzoic acid.	Iodipamide
216.	Novaldiamine	Chloroquin Phosphate
217.	Oxalic Acid	Vitamin B_2 Diethyloxalate Tetracyclines.
218.	Oils (Maize, Peanut or Soya)	Antibiotics
219.	Palladized Charcoal	Vitamin A
220.	Palladium Chloride	Chloramphenicol etc.
221.	Palmitoyl Chloride	Vitamin A
222.	Pancreas (Animal gland)	Insulin
223.	Paraformaldehyde	Vitamin A Vitamin B_6
224.	Paraldehyde	Vitamins
225.	Phenol	Paracetamol Salicylic acid Iodo-chloro & Di-iodohydroxyquinoline Bephenium-Hydroxynaphthoate Chloroquin
226.	Phenothiazine	Promethiazine and salts.
227.	Phenoxyacetic acid.	Penicillin V
228.	Phenylacetyl carbinol	Ephedrine
229.	Phenylacetamide	Penicillin
230.	O-phenylene diamine	Thiobendazole
231.	Phenylacetic acid and its pot. salt.	Penicillin
232.	D-Phenylglycine	Ampicillin
233.	B-Phenylethylamine	Phenformin Diethylcarbamazine
234.	Phosgene	Phenobarbitone
235.	Phosphoric acid.	Antimalarials
236.	Phosphorous oxychloride	Chloroquin

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
237.	Phosphorous pentasulphide	Vitamin B1
238.	Phosphorous Pentoxide	Nikethamide Ethionamide
239.	Phosphorous Trichloride	Methaqualone Hcl.
240.	Phosphorous Pentachloride	Ethionamide
241.	Phytyl bromide	Vitamin E
242.	Phenyl acetone	Prenylamine
243.	Phenylhydrazine	Sulfas
244.	B-Picoline	Nicotinic acid/amide Nikethamide
245.	G. Picoline	I.N.H.
246.	Piperazine Hexahydrate	Diethylcarbamazine Piperazine salts
247.	Pipyridine	Ethionamide
248.	Potassium Acetate	Antibiotics Ethionamide
249.	Potassium Borohydride	Vitamin A Chloramphenicol
250.	Potassium Hydroxide	Antibiotics Vitamin B_{12} Synthetics
251.	Potassium Carbonate	PAS & Esters Penicillin

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
252.	Potassium dihydrogen phosphate	Antibiotics
253.	Potassium Permanganate	Pyrazinamide Nicotinic acid
254.	Potassium Cyanate	Tolbutamide Chlorpropamide
255.	Potassium Cyanide	Vitamin B_{12}
256.	Potassium Thiocyanate	Tolbutamide Chlorpropamide
257.	Potassium Ferricyanide	Antibiotics
258.	Procaine HCL	Penicillin
259.	Propargyl Bromide	Vitamin A
260.	N-propylamine	Chlorpropamide Probenecid
261.	Pyridine	Sulfa Drugs
262.	Pyrazine mono carboxylic acid	Pyrazinamide
263.	Quinoline	Hydroxyquinolines
264.	Resins IR-45 or Equivalent IR-124 or Equivalent IRC-50 or Equivalent IRA-402/410	Streptomycin and other antibiotics
265.	Salicylic acid	Aspirin Sod. Salicylate

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
85. 268.	Silicones	Antibiotics
267.	Sodamide	Pethidine
268.	Sodium borohydride	Vitamins
269.	Sodium Benzoate	Vitamin A
270.	Sodium Bromide	Analgesics
271.	Sodium Citrate	Antibiotics
272.	Sodium Acetate	Chloramphenicol
273.	Sodium cyanide	Phenobarbitone Vitamin B_{12} Phenylbutazone Diloxanide
274.	Sod. Diethyldithio-carbamate	Vitamin A
275.	Sod. Ferrocyanide	Tetracycline
276.	Sodium hydrosulfite	Antibiotics
277.	Sodium Metal	Metamizol Folic acid Phenobarbitone Vitamin B_1 4 Diethylamino-1-Methyl Butylamine Amidopyrin
278.	Sodium Methoxide	Vitamin A Phenylbutazone Sulfas Analgesics.
279.	Sodium sulphide	Analgesics.

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
86. 280.	Sodium metabisulphite	Vitamins
281.	Sorbitol	Vitamin C
282.	Sodium hydroxide (tech.)	All drugs.
283.	Sodium carbonate	All drugs.
284.	Sodium Nitrate	Vitamin B_{12} Folic Acid
285.	Sodium Nitrite	Chloramphenicol Phenacetin Analgin
286.	Sodium Phosphate	Antibiotics
287.	Soyaflour (edible)	Antibiotics
288.	Sulfuric acid	All drugs
289.	Sugar (cane.)	Antibiotics
290.	Stearyl alcohol	Vitamin C and other drugs
291.	Stannic chloride	Analgesics
292.	Sulphur	Anti.T.B.drugs
293.	Tartaric Acid	Chloramphenicol
294.	Thiosemicarbazide	Sulfas Anti TB drugs.

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
295.	Toluene	Analgesics
296.	O.Toluidine	Methaquolone
297.	Trichloroethylene	Chloramphenicol Emetine Bechenium Hydroxynaphthoate Phenylbutazone.
298.	P-Toluensulphonamide	Tolbutamide
299.	Trimethylquinol	Vitamin E
300.	Thionyl chloride	Procaine Hcl. Pethidine Hydrochlorthiazide 4-Diethylamino-1-methyl-butylamine
301.	Thiazole-4-carboximide	Thiobendazole
302.	Triethylamine	Tetracycline Vitamin B_6
303.	L-Tyrosine	Anti-convulsents (L-Dopa)
304.	Ucon (defoamer)	Antibiotics
305.	Urea	Chloramphenicol Vitamin B_2
306.	Urethane	Meprobamate

87.

88.

Sr. No.	Name of the Raw Material	Name of the drug or intermediate for which it is used.
307.	Vanillin	Methyl Dopa Anti-hypertensives.
308.	Wax Emulsion (Mobilpar S)	Antibiotics
309.	O-Xylene	Chloramphenicol Vitamin B_2 Phenylbutazone
310.	m-xylidine	Xylocaine
311.	Zinc Dust.	Phenylbutazone Chloramphenicol
312.	Zinc chloride	Vitamins

F: LIST OF MACHINARY 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.**

F (cont'd) 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 libre 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 delonisation, softening and effluent treatment plants.
15. Electrolytic cells to produce hydrogen etc.

(F. cont'd)

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. Single 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 sensors and controllers.
12. Automatic process cycle controllers (both electric and and electronic)
13. Temperature compensated totalizers and rate indicators.
14. Long distance transmission and control signals.
15. Mini computers for process control.

G. LIST OF EQUIPMENT FOR CONTROL OF QUALITY

D. 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) Heraeous Semi-Microcombustion Unit.

f) Conco Moisture balance

g) Leybold lab. 2 stage vacuum pumps.

h) Labline universal penetrometer.

i) Special Sterio Microscopes

j) Dialyzers, with accessories.

k) Impaciograph

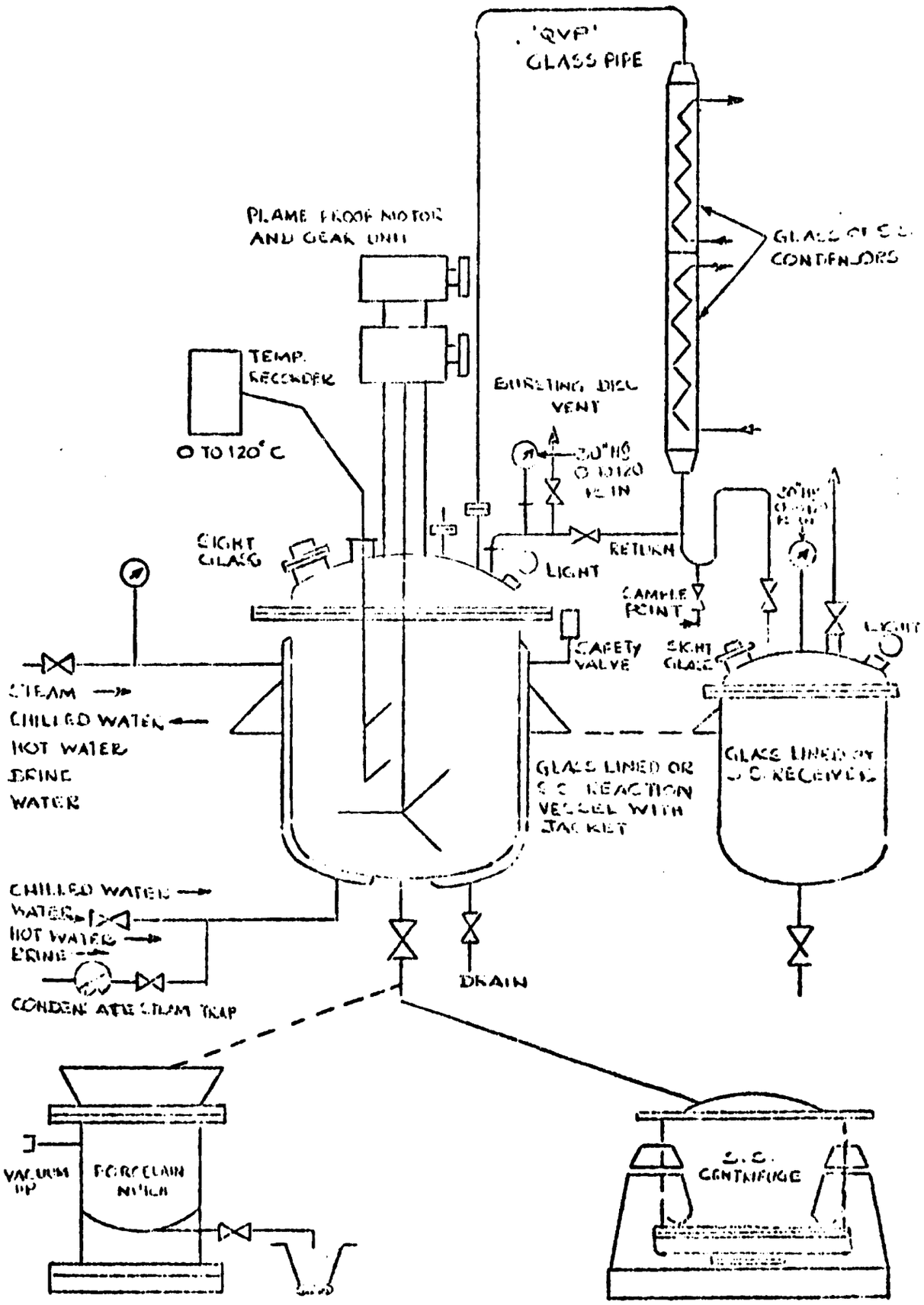
l) Aerosol Lab equipment

m) Apparatus for testing timed release of tablets.

n) Electrophoretic Apparatus.

o) Tensiometer

H. DIAGRAM OF MULTIPURPOSE PLANT TO PRODUCE DRUGS FROM INTERMEDIATES/



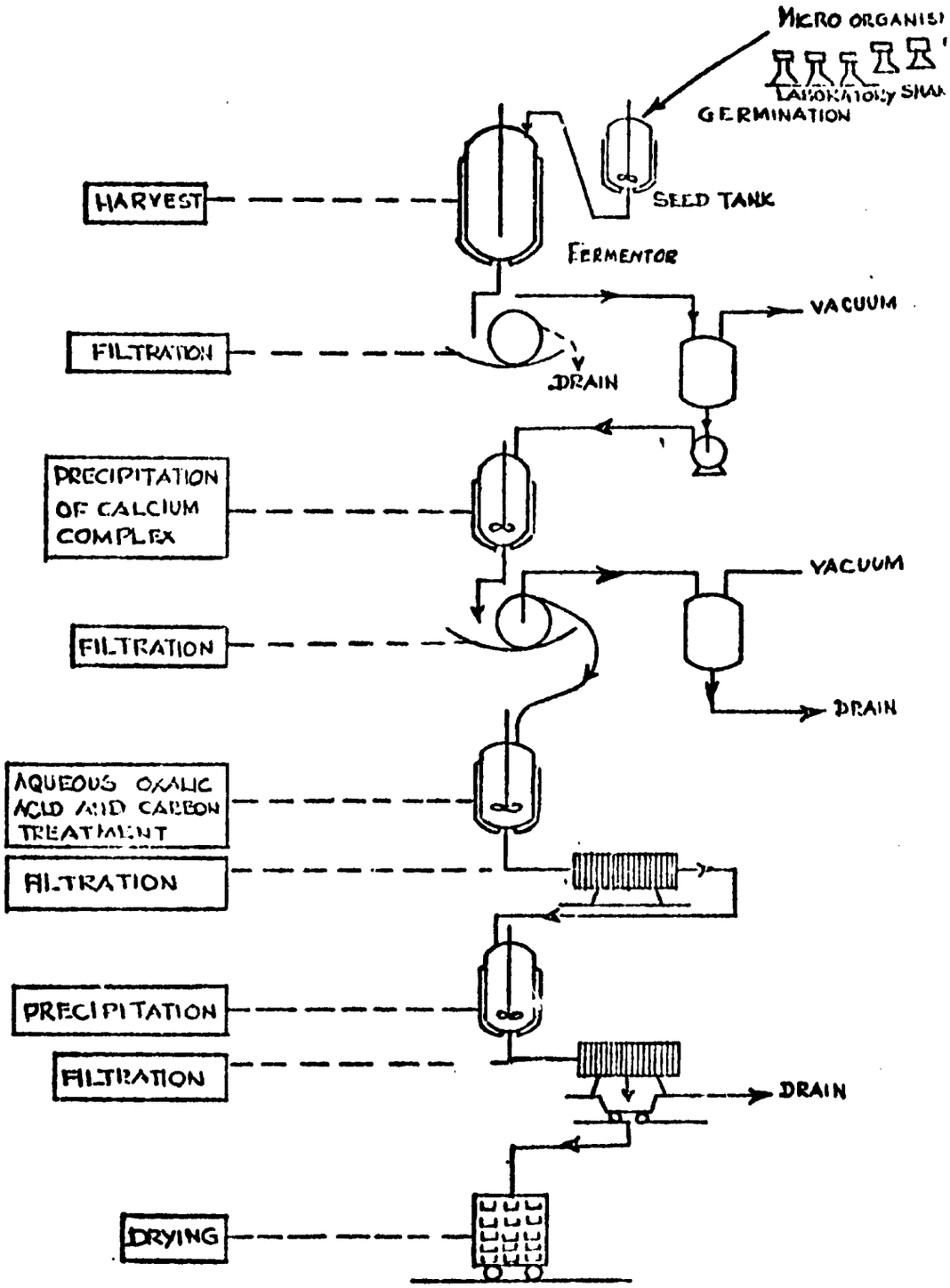
MULTIPURPOSE REACTION AND DISTILLATION UNIT

I. STATEMENT INDICATING QUANTITIES OF CANALISED DRUGS IMPORTED THROUGH CANALISING AGENCY AND INDIGENOUS PRODUCTION DURING THREE YEARS IN INDIA.

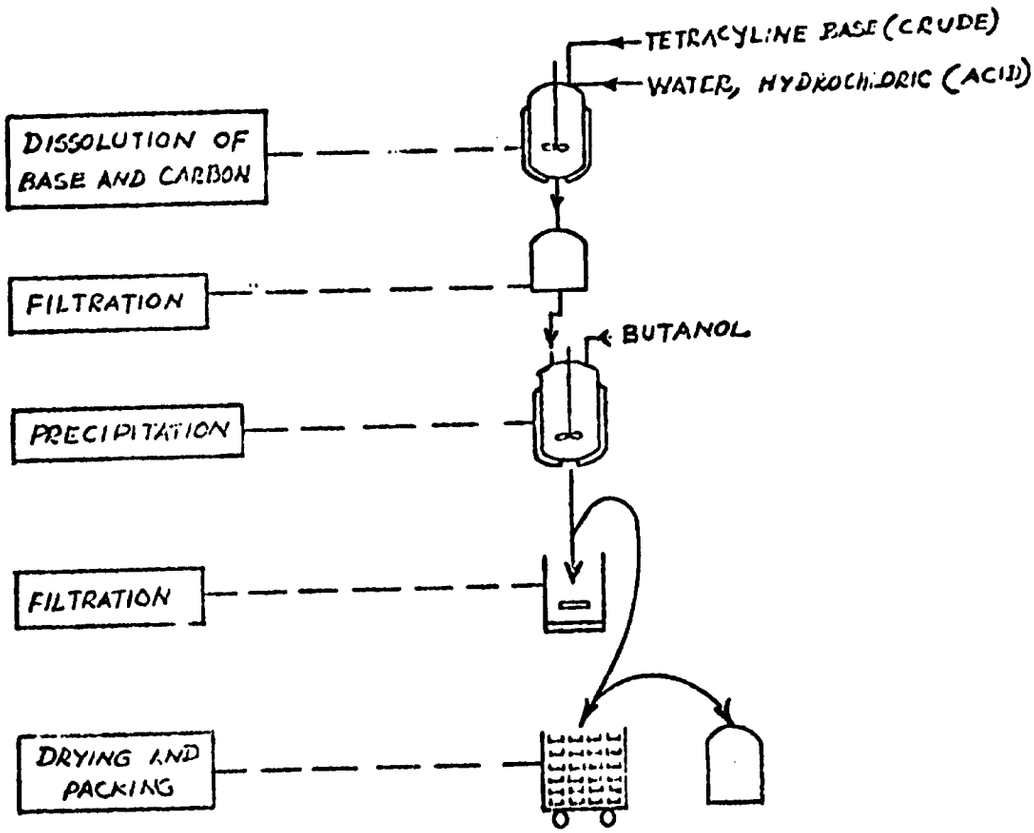
Name of the item	Availability 1975-76			Availability (Estimated) 1976-77			Availability (Planned) 1977-78		
	Imports	Ind. production	Total	Imports Planned	Ind. Prodn.	Total	Imports	Ind. prodn.	Total
(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
DISTRIBUTED THROUGH STATE CHEMICALS & PHARMACEUTICAL CORPORATION						Figures in tonnes			
Ampicillin Anhydrous	1	-nil-	1	4.5	1.8	6.3	4	5	9
Ampicillin Trihydrate	17	—	17	30	—	30	32	4	36
Ampicillin Sodium	2	—	2	1.5	—	1.5	2.5	—	2.5
Chloroquin Phosphate	200	20	220	250	28	278	325	36	351
Chloroquin Sulphate	15	—	15	15	—	15	15	—	15
Mebendazole				32	3.2	35.2	10	47	57
Metronidazole (Kgs)				350	850	1200	500	1000	1500
Nitrofurantoin	13	—	13	20	—	20	22	—	22
Nitrofurazone	1	—	1	2	.750	2.75	1	4	5
Oxytetracycline Ethyl Succinate	1.5	—	1.5	2	—	2	2	—	2
Oxytetracycline Stearate	11	—	11	4	8	12	3	9	12
Sulphamethoxy pyridazine	5	—	5	15	—	15	15	—	15
Chloramphenicol Palmitate	45	—	45	17	—	17	10	25	35
Chloramphenicol Powder	45	50	95	20	115*	135	5	165	170
Chloramphenicol Succinate	—	—	—	2.5	—	2.5	3	—	3
L—Dopa	25	—	25	80	—	80	100	—	100
Pyrazinamide	1.5	—	1.5	3.5	2.4	5.9	3	3.3	6.3
Calcium D Pantothenate	17	—	17	20	—	20	22	—	22
D Panthenol	1	—	1	3	—	3	3.5	—	3.5
Sodium Pantothenate	0.8	—	0.8	0.7	—	0.7	0.5	—	0.5
Erythromycin Lactobionate	0.9	—	0.9	0.5	1.2	1.7	1.25	1600	1.25
Folic Acid	300			850	700	1550	As per demand		
Folinic Acid	200	—	200	292	—	292	As per demand		
Inosine				95	—	95	-do-		
Nicotinic Acid	20	—	20	30	—	30	-do-	—	35
Vitamin B-6							35		
DISTRIBUTED THROUGH INDIAN DRUGS & PHARMACEUTICALS LIMITED									
Tetracycline	50	70	120	65	132	197	30	195	225
Streptomycin	20			17	235	252	20	280	300
Vitamin B-1 Amp. Grade	Nil	—	Stocks were available against earlier imports	13	—	12	15	—	15
Vitamin B-2	5			11.25	6	17.25	15	6.5	21.5
Chloramphenicol	18	11	29	18	13.5	31.5	20	21	41
Ampicillin	100	162	262	130	280	410	100	300	400
Ampicillin	55	—	55	40	5	45	55	10	65
Ampicillin Trihydrate	100	—	100	60	50	110	100	130	230
Phenyl Sulphathiazole				10	—	10	25	23	48

*Including production from imported L-base.

J: FERMENTATION, RECOVERY OF TETRACYCLINE BASE (CRUDE) FROM FERMENTOR LIQUOR.

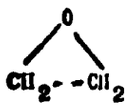


'(J. cont'd) PREPARATION OF TETRACYCLINE HYDROCHLORIDE FROM TETRACYCLINE BASE (CRUDE)



K: OUTLINE OF CHLORAMPHENICOL SYNTHESIS

Ethylene oxide



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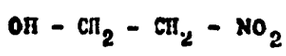
B-Nitro Ethanol



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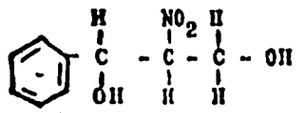
DL-threo-1-phenyl-2-nitro-propanediol-1,3



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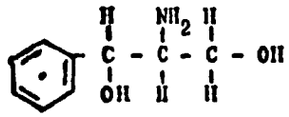
D(-)-threo-1-phenyl-2-amino-propanediol-1,3



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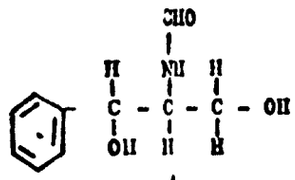
D(-)-threo-1-phenyl-2-formylamido-propanediol-1,3



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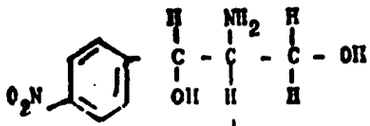
D(-)-threo-1-p-nitrophenyl-2-amino-propanediol-1,3



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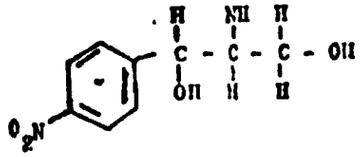
D(-)-threo-1-p-nitrophenyl-2-dichloroacetamido-propanediol-1,3



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