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Effective Collaboration between Industry and Research Laboratories for Developing Indigenous Know-how, Import Substitution and Process & Product Technology

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In view of the critical situation demanding utmost self-reliance and rapid replacement of imports by indigenous sources, whether it is finished products, intermediates, raw materials, know-how or equipment, it is imperative that a very close collaboration be brought about between industry and research laboratories of the country. Unfortunately the Indian industry is not sufficiently equipped for undertaking developmental problems or studies on import substitution and would benefit immensely by the help, guidance and investigations if carried out on their behalf by the National, Regional, State, University and other laboratories. To make such collaboration possible first of all it is necessary to gather, classify and make freely available the following information in as much detail as possible.

First of all it will be necessary to know which are the items at present imported for which local production will have to be taken up or suitable substitutes evolved. Secondly, while investigating the possible routes of manufacture, it would be necessary to have ready the detailed information about the chemicals (inorganic and organic), intermediates and drugs at present manufactured in the country, their output, whether surplus quantities of these would be available for new projects under investigation or whether the present output is already inadequate even for present demands, possibilities of stepping up the production of these raw materials to meet the anticipated demands, cost structure, location of factories manufacturing these raw materials etc. While collecting this information it would be necessary to see whether any of these items itself depends on imported components so that in case of cut in imports that item will not become scarce.

To the industrialists or intending entrepreneurs it would be necessary to provide sufficient information about the different laboratories, their facilities in terms of trained research workers and their experience in the different fields, equipment available etc. and the willingness to render help in the form of guidance, advice, providing know-how if already available or to take up the problems for collecting the required know-how.

It is equally important to have ready information about the manufacturers of industrial, pilot plant or laboratory equipment, instruments and machinery with particulars of their specialities, range of products manufactured by them routinely and additional facilities available for taking up of newer types or range of production.

It is therefore suggested that CSIR and the industries should jointly collect the above categories of information in full detail and make it available to all concerned and furthermore keep it revised and up-to-date by issuing periodic supplements or revisions. This information could be disseminated by joint (CSIR-Industry) regional liaison offices in major industrial centres and helped by scientists or technologists having a very wide background of different fields and conversant with the facilities available in the different laboratories in the country and who could effectively bring about the necessary collaboration between the industry and the research workers. This could be achieved by referring the problems simultaneously to all the likely laboratories or research workers and inviting suggestions or offers of taking up the problem so that in case a ready solution is already available, duplication of taking up the problem afresh could be avoided. Thereby the industry could hope to get the results in the quickest possible time.

While trying to work out as above it will be found that even the best equipped laboratories may not be sufficiently provided with all the possible equipment, funds for extra chemicals, additional space or staff to take up the investigation. Small items will come in the way of expeditious solution. Such problems of nonavailability of funds for extra equipment, additional staff, services etc. required for any particular problem which a laboratory or investigator can otherwise take up should be met by making available funds for the project by the Industrialists entrusting the problem or by means of a pool of fund created jointly by the industry and CSIR.

Similarly, to create incentives for the investigators to take up additional problems and to tackle them successfully in the shortest time possible, they may be permitted to be engaged as consultants or to accept honoraria, irrespective of whether the investigator is borne on National, Regional, State, University or other organization. This system has worked very well in other countries and instead of normal work suffering, as might be feared, it has given much greater impetus to the advancement of research and technology. From our own country the example of the Department of Chemical Technology of Bombay University whose Dyes and Intermediates Department research workers acting as consultants has brought about tremendous progress and advancement not only for the development of indigenous know-how and large scale industry but also in the advancement of the department and its increased stature.

Sometimes the processes, know-how or facilities required for drug industry not readily available within its own field may be already available and a common practice in quite another industry such as the dyestuff and intermediates industry and therefore active collaboration for these facilities could be and must be sought between different industries rather than trying to work out these know-how afresh. Such inter-industrial collaboration often produces much quicker results and benefits both. Indeed we can go one step further and say that even among a group of manufacturers of the same items or class of items, instead of considering themselves rivals or competitors, if they can pool their information, know-how, technology etc. we can minimize the losses, make the products most economically with minimum of imported ingredients and jointly share the expenditure of investigations of import substitution.

In the matter of getting locally fabricated intricate or specialized equipment, machinery and plant it is suggested that the facilities of inspection, understanding of special features and working principles, making of drawings, lay-outs, circuit diagrams of such imported equipment at present

not made in this country may be given by those who are in possession of such items of plant, machinery, equipment etc. This will very rapidly increase the industrial potential of indigenous manufacture and has worked very well in our experience. During the emergency created by the Chinese attack we had to get immediately additional capacity for preparing freeze-dried plasma. The Haffkine Institute made available the facilities of inspection, working principles, drawing and other details to interested private manufacturers and to the Atomic Energy Establishment and as a result of this collaboration it was possible to get locally fabricated new equipment in a very short time.

While taking up the projects of import substitution in drugs and pharmaceutical industry, it will have to be borne in mind that Hindustan Organic Chemicals at Panvel plans to produce certain basic intermediates required in large quantities by the pharmaceuticals industry in the near future and it would be worthwhile to decide whether efforts should be made to create know-how for those items or efforts should be made to expedite this project with the top priority so that in the field of basic requirements of the industry a good foundation is laid.

It is felt that by taking the steps suggested above it would be possible to make rapid progress for successful cooperation between industry and the laboratories of the country for the creation of indigenous know-how as a step towards self-sufficiency.

Some Technological Problems in the Production of Drugs

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In the drug and pharmaceutical industry, synthetic drugs occupy a significant place. In the synthesis of a compound to be used as a drug, proper selection of raw materials and their processing through diverse unit operations are needed. A number of essential drugs are now being produced in India and this indicates the development of the technology of drugs manufacture. But, in spite of this achievement it has been noticed that in many cases the raw materials or intermediates used are imported. Though, however, production technology of some of the raw materials or intermediates has been developed, still many are yet to be taken up, and their chemical kinetics are to be studied. This paper presents some problems which stand in the way of economic production of some drugs.

The alkyl pyridines on oxidation afford pyridine carboxylic acids like nicotinic acid and isonicotinic acid, and the conventional process of oxidation is followed in India for their production as intermediates in the drugs manufacture. The use of modern technique of catalytic vapour phase and pressure oxidation, yet to be developed commercially, is expected to be more economical and offer a more elegant process.

The high pressure reductive amination technique will solve many problems. This process will facilitate the reduction of carbonyl and oximino groups to amino group and cyanogen group to aminomethyl group. In the synthesis of drugs or intermediates for drugs similar conversions are often necessary. For example, acetamidomalonic ester, an intermediate for the commercial synthesis of various amino acids, both essential and non-essential, is prepared by the reduction of oximinomalonic esters, and this reduction can be effected economically by high pressure technique.

Another intermediate, 4-diethylamino-1-methyl butylamine (Novol diamine) required for the synthesis of antimalarials like chloroquin is best prepared by reductive amination of the corresponding ketone, 5-diethylamino-2-pentanone. Amphetamine and its analogues can also be prepared in the similar way from the corresponding ketones.

Beta-phenylethylamine, an intermediate in the manufacture of the hypoglycemic agent, phenformin, is another example of formation by this technique from benzyl cyanide which can be obtained from toluene through benzyl chloride. Substituted beta-phenylethylamines can also be prepared in this way commercially. Some of these amines have medicinal value and these amines can be utilized in the synthesis of drugs like papaverine and its chemical congeners which belong to the isoquinoline group.

Intermolecular condensation under different conditions is of immense importance in drug chemistry and techniques of such condensation on large

scale are yet to take shape in India. The formation of diethylethoxymethylene malonate, an intermediate for 4, 7-dichloroquinoline, which is the penultimate stage in the synthesis of chloroquin and amodiaquin, from ethyl orthoformate and diethyl malonate may be cited as examples.

The drug quinidine is now having a great demand as an export item and consequently a commercial process for the stereoisomeric conversion of quinine to quinidine needs immediate development in view of the fact that India produces quinine in large quantity.

The examples cited are some of the technological problems of manufacture of drugs in India. Compilation of such data from different units will give an assessment of the nature and the diversity of the problems. The research organizations in the public and private sectors may come forward to help the country towards self-sufficiency by solving the problems.

The problems may then be taken up by units specializing in the development of analogous chemicals or unit processes.

Raw Materials for Pharmaceutical Industry

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The raw materials for the pharmaceutical industry offer several special problems. Most of these are the finished products of chemical and allied basic industries; even where no large scale industry is concerned, some intermediate agency has to look after the collection, storage and transport of these raw materials before these are delivered to the pharmaceutical manufacturer. Secondly, the quantum of consumption by the pharmaceutical industry varies widely, in most cases from a few kg. to several tons; considered from the output of the producing industry, this offtake is frequently low. Thirdly, the manufacture of drugs imposes very rigid standards on the quality of raw materials. All these, with the acute shortage of all manufactured products in general, combine together resulting in the needs of the pharmaceutical industry being, more often than not, ignored.

Depending on the position of supply from indigenous sources or by imports, the raw materials may be classified into three broad groups:

(i) Raw materials, previously imported, now indigenously manufactured, partly or wholly

(ii) Raw materials, now imported, which have possibility of indigenous manufacture in the near future

(iii) Raw materials, now imported, which do not offer any immediate prospect of indigenous manufacture

Indigenously manufactured raw materials. Since the last war, a large number of raw materials, which were previously imported, are being manufactured within the country. These include inorganic chemicals like acids and alkalis, calcium and magnesium compounds, ammonium sulphate, barium salts, boron compounds; benzene, toluene, alcohol; formaldehyde; dextrose; starch; calcium gluconate and lactobionate; mineral products like kaolin, talc, fullers' earth; charcoal; vitamins; alkaloids etc. Such raw materials are listed in Table 1. In most of these cases, but not in all, the basic raw materials from which these are made are available in the country; sulphuric acid is a notable exception, and there are others where one or more basic ingredients still continue to be imported. In spite of this, the general tendency has been to start manufacture from more and more basic stages. Many of these products are still not past the stage of early teething troubles, and suffer for a variety of causes. As such the output is frequently low, in others the installed capacity is not fully utilized. In the face of low output, the main emphasis has been on the quantum of production rather than on quality, a trend which affects the pharmaceutical industry very severely. A few typical cases may be discussed.

Table 1 — Some raw materials, previously imported, now available indigenously

Acid, Citric	Ephedrine hydrochloride	Papain
Acid, Cresylic	Formalin	Phosphorus oxychloride
Acid, Chlorosulphonic	Fullers' earth	Procain hydrochloride
Acid, Phosphoric	Hexamine	Phenolphthalein
Acetic anhydride	Insulin crystals	P.A.S.
Acetyl salicylic acid	Kaolin	Phenacetin
Activated charcoal	Liquid paraffin	Reserpin
Adrenalin	Magnesium carbonate	Sodium chloride
Borax	Methyl salicylate	Sodium bicarbonate
Bromine	Metachloroaniline	Sodium glycerophosphate
Calcium gluconate	Menthol	Sodium ascorbate
Calcium carbonate	Methyl *p*-hydroxy	Sodium lauryl sulphate
Calcium lactobionate	benzoate	Strychnine hydrochloride
Caustic soda sticks	Nicotinamide	Sulphadiazine
Casein	Nicotinic acid	Salicylamide
Chlorobutol	Nikethamide	Sodium sulphide
Chloral hydrate	Potassium iodide	Starch
Caffeine	Potassium glycerophosphate	Vitamin A
Dextrose	Potassium permanganate	Vitamin C
Diethyl carbamazine citrate	Piperazine citrate	Vitamin B_{12}
Ethylene dichloride	Peptone, Protcose	Yeast powder

Kaolin. Although there are extensive deposits in India, a grade suitable for pharmacopoeial use is not available. Pharmacopoeial kaolin, apart from being free from adventitious impurities, must satisfy a suitable particle size requirement. Now it is possible to fractionate Indian kaolin by washing and classifying, and sort out a grade suitable for pharmaceuticals. This is a point which it is very difficult to impress on kaolin producers; and the result is that either we accept what is offered by them or do the processing ourselves. Actually such a process was in operation in our works for some time, but had to be discontinued because of high overhead cost. Moreover, kaolin is not the only material which requires such upgrading, and if the process has to be followed by the pharmaceutical industry in half the cases where such improvement is called for, the face of the industry will soon be changed beyond recognition.

Talc. Although India exports a good quantity of talc, and also consumes a large amount in the cosmetic industry, pharmacopoeial grade talc is not easily available. The available grades suffer in that the acid-soluble matter is a little too high, a drawback which can be remedied by a little extra processing. Moreover, such improvement in its quality would have earned a better price for the exported grade.

Fullers' earth. Groundnut oil, used in pharmaceuticals, should have a low F.F.A., peroxide value and good stability. Now the position of the supply of edible oils is too well known, where the special needs of the pharmaceutical industry can hardly make an impression. It was therefore decided that the quantity we require should be processed by us, beginning from crushing, so that rigid controls may be observed over all stages. The fullers' earth used in bleaching was previously imported, but as soon as

local production was taken up, the imported material was substituted by an indigenous grade, although in doing so, we had to compromise some of our requirements. Recently, when fresh supply was needed, we were told the particular grade was no more in production due to shortage of sulphuric acid. Our predicament can now be visualized; the processing of oil was undertaken so that we could be assured of its quality, in spite of the added cost involved. Now it appears we should also undertake the processing of fullers' earth. But as stated before, the problem will not end there, since similar questions will come up with the case of charcoal also.

Charcoal. The industry consumes several special grades, having low ash content and soluble matter, and high decolorizing power. Several grades are now manufactured in the country, and have been used where such use can be permitted. Now the compatibility of the charcoal with pharmaceuticals, particularly injectable solutions, involves many complex considerations, which require prolonged study. A good deal of work on this and on the activation of charcoal has been done in our laboratory, and the results clearly indicate that the local products will have to be considerably improved, in their range of adsorption characteristics and stability, before the needs of the pharmaceutical industry can be adequately met.

Lime and precipitated calcium carbonate. For a pure quality lime, having very low acid insoluble matter and low magnesia, we used to burn a selected grade marble stone. This could continue so long as the requirement was low; on a larger scale, the intermittent lime burning proved to be too costly and bothersome.

A search throughout India resulted in the location of several producers who used the lime for their own manufacture of precipitated calcium carbonate. With great difficulty, we have induced some of them to spare a part of the pure lime for us; we have yet to succeed in making them stick to a particular specification.

There is a potential demand for pure grades of precipitated calcium and magnesium carbonates, which apart from satisfying pharmacopoeial specification, should have a low bulk density and offer a clear solution in acid, without any opalescence or turbidity. Several grades that have come up are being used for some applications but are not yet suitable for others.

Ammonium sulphate. A special grade of ammonium sulphate having a very low iron content is needed for the manufacture of serum, but in spite of our best efforts, it has so far not been possible to procure it. Curiously, the material we need is there in our fertilizer factories, and no extra effort is required except to collect the material separately for us. What is lacking is a little bit of understanding of each other's viewpoint. The result is that we have to redissolve and recrystallize the material, which obviously requires a good deal of labour and causes some wastage.

Sodium sulphide nonahydrate, crystalline, iron free. This is an essential raw material in the production of the anti T. B. drug — Thiacetazone. Sodium sulphide (fused) which is produced in considerable quantities in India does not meet the requirement for this purpose. Some manufacturers of sodium sulphide have been approached and their cooperation enlisted in obtaining the required variety. Although the quality is still not of the required standard it is expected to improve gradually as experience grows more and more.

Dextrose. The manufacture of this material has recently been started, but the grade required for injectable purpose should satisfy special standards such as for clarity of solution, etc., which we have tried hard to impress upon the producer. The material which is produced satisfies the specification needed for confectioneries and other pharmacopoeial uses, but hardly meets the demand. The special requirement for the injectable grade therefore goes by default, although this is an essential material.

Calcium gluconate. The oral grade has long been in production in the country, and the injectable grade has also recently been started. The quality is satisfactory, but the availability is limited, due probably to limited supply of glucose.

Glass container and rubber closures. Although no import is involved here, it is useful to recount some of the steps we took with regard to their quality and supply, which produced quite satisfactory results. Fortunately here, our competitive position as a consumer entitled as a serious and patient hearing from the suppliers. Now the pharmaceutical industry consumes different qualities of glass, the specification of which was laid down by us before these were incorporated by the pharmacopoeias. Having done this we sorted out the available supplies and took up the matter in right earnest with the glass manufacturers. Although there was a good deal of hesitation on the part of many of these manufacturers to modify their composition, we succeeded in enlisting the cooperation of a few progressive manufacturers. Thereafter, the story is one of a period of fruitful cooperation between the producer and the consumer and within a few years the quality was fully within control. The manufacturer now has developed his process so as to suit our requirements, and we are also assured of our containers. Once the value of such cooperation has been demonstrated, other manufacturers also followed suit, with the result, that the question of resistant glass having clearly defined limits of neutrality is no longer a novelty with the producers. The problem of resistant rubber closures, which has not yet been finally solved has also developed along similar lines, with frequent discussion with the producer, experimentation and testing, and some improvement in the quality of the goods has already been achieved.

The few cases mentioned above will suffice to illustrate the problems of raw materials of the pharmaceutical industry. Fourtunately in many of the cases cited, the main problem is not one of import or foreign exchange. A little extra processing, a little extra effort, and most important of all, a little more understanding are necessary so that the different branches of industry which together can ensure a smooth and balanced growth, can pool their resources together and solve the problems which arise in the process. There is a feeling in some quarters that once the production of a new item has been taken up, any deficiency with respect to quality or quantity will ultimately be made up as a matter of course. This view may be correct in some cases, but the fact remains that no difficulty will solve itself unless there is some positive effort behind it. Therefore there should not be any complacence with respect even to the indigenous materials. A raw material does not become important simply by its bulk or value. A few kg. of one material may be much more important and essential than several hundred tons of another.

While dealing with our raw material problems, it will be improper to imagine that the manufacture of these raw materials has no problems of their own. Some of these industries are pretty old and suffer from

outmoded methods of production; some are quite new and are not yet past the stage of early teething troubles. They also have their full quota of difficulties with regard to the supply of basic materials, equipments, spares, *lack of proper facilities of testing, standardization, research and development. The difficulties however can be broadly classified into two groups; the first is the shortage of output resulting from irregular or inadequate* supply of basic ingredients, equipments etc. With all-round scarcity of goods and services, there is no easy way out of this. But so far as the difficulty relates to poor or inadequate quality of the output (which frequently is the case with pharmaceutical raw materials), the responsibility of solving the same is clearly their own. The more prosperous sections of the industry concerned can undertake their own testing, research and development; even for them as well as for the weaker sections, there are the chain of national laboratories whose resources they should be encouraged to draw upon. As consumers, we can also render great help, which in the past we did to a number of industries — such as glycerin, oil, glass and other industry, with mutual benefit to both the parties, and can pledge our readiness to do so in the future in our own interest and in the interest of the nation in general.

Imported raw materials. This group includes those which are at present imported, but for the production of which the basic raw materials are available, and some advance planning has already been done and in several cases licences issued. Many of these products are such as phenol and aniline, required in bulk of which the pharmaceutical industry consumes a small part, although by no means small compared with other pharmaceutical raw materials. Here the problem is of large scale production technology, and clearly the problem is beyond the grasp of the pharmaceutical industry. A list of these materials is given in Table 2, and include some which were selected for state owned enterprise. For one reason or

Table 2 — Raw materials now imported, but having prospect of manufacture indigenously in the near future

Acid, Benzoic	Diethyl oxalate
Acid, Carbolic	Magnesium oxide
Acid, Folic	Monochloro acetic acid
Acetarsol	Mepyramine maleate
Atropine sulphate	Piperazine hydrate
N_4-acetyl sulphanilamide	Paranitrotoluene
Benzyl alcohol	Paranitrochlorobenzene
Benzoyl chloride	Phthalic anhydride
Benzaldehyde	Phenyl hydrazine
Calcium pantothenate	Phenyl acetic acid
Calcium hypophosphite	Sodium phenobarbitone
Chloroform	Sulphanilamide
Diphenyl oxide	Sulphamerazine
Dimethyl sulphate	Thiamine mononitrate
Ethyl acetoacetate	Theophylline
Ethyl chloroacetate	Terpin hydrate
Gamma-picoline	Testosterone propionate
Hydrazine and salts	Vitamin B_1
8-Hydroxyquinoline	Vitamin B_2
Isopropyl alcohol	

other, the implementation of these projects has been delayed to the detriment of many other consumer industries. These materials are in many cases the starting material for several important intermediates, some of which are used exclusively by the pharmaceutical industry; once the availability of the former is assured, the manufacture of these intermediates could be left to the care of the pharmaceutical industry.

In cases where the basic materials are available within the country, it is urgently necessary that the technology should be developed. The manufacture of pyridine bases from coke oven by-products is a case in point. The pharmaceutical industry is the main consumer; the production of isoniazide, the main armament in our antitubercular campaign, depends on the availability of gamma-picoline. A good deal of exploratory work have already been done on the characteristics of coke oven by-products and on the methods of recovery of gamma-picoline as well as pyridine and its other analogues. It is now necessary to take some concrete steps in this direction, so that the raw material for this vital drug may be ensured.

***o*-Cresol.** Coal tar is a potential source of cresols. The *o*-isomer which is wholly imported is an intermediate for the muscle relaxant drug, Mephenesin. The organizations dealing with coal tar may undertake the separation of the *o*-isomer for utilization by the pharmaceutical industry.

***p*-Nitrotoluene.** Mixed nitrotoluenes are produced in quantity by ordnance factories. The separation of the isomers require elaborate fractionation units and as such the work is not suitable for the pharmaceutical units. This work may be carried out by some units having suitable facilities for large scale fractionation. The *p*-isomer may then be utilized by the pharmaceutical industry. The *o*-isomer can be used up by the already expanding dyestuff industry.

Imported raw materials having no immediate prospect of local manufacture

The raw materials of the pharmaceutical industry are so varied in nature that no one country can be fully self-sufficient with all of them. Even developed countries have to import many of their raw materials, and it is therefore no wonder that even when our indigenous resources have been more fully developed, there still will remain a large number of chemicals which will have to be imported. A list of such materials is given in Table 3. It will therefore serve no useful purpose to consider their availability except by import; the question of their production can be taken up at a later date when the basic chemical industry has reached a broader base in its range and quantum of production.

Therefore in these cases, the question of import substitution assumes added importance. For instance, there was a suggestion once that dichlorooxyquinoline can substitute the iodo compound as an antidysentery drug. Since iodine is not available in the country, and will remain so in the immediate future, such possibilities, if any, should be fully explored with urgency and speed. It is useful to mention in this connection that our exploitation of marine resources has so far been insignificant. A number of highly useful products is obtained from the sea, such as iodine, alginic acid and its derivatives, diatomaceous earth and these are required not only by the pharmaceutical industry alone. Search for location of suitable sources of these products should be intensified, and this is an area where the Central Salt & Marine Chemicals Research Institute can take a lead.

Table 3 — Imported raw materials having no immediate prospect of indigenous manufacture

Acid, Tannic	Methylene blue
Acid, Glutamic	Mercury
Acid, Alginic	Mercuric oxide yellow
Amiophylline	Oil pipermint
Acetyl methionine	Ostradiol monobenzoate
Corpus luteam extract	Oil cinnamon
Cinnamic aldehyde	Potassium antimony tartarate
Creosote beechwood	Potassium guaicol sulphonate
Cetyl alcohol	Parachlorometacresol
Chlorophenyramine maleate	Parachlorometaxylenol
Diamine	Pepsin
Diethyl ethoxymethylene malonate	Pituitary posterior lobe
Sulphur	powder
DL-Methionine	Polyvinyl pyrolidone
Ethylene diaminehydrate	Propylene glycol
Iron pyrophosphate	Piperidine
Gum tragacanth	Riboflavin-5-phosphate sodium
Hyflo	Papaverine hydrochloride
Hyoscine hydrobromide	Sodium cacodylate
Iodine	Sodium metal
Dicyandiamide	Rutin
Choline theophylinate	Tween 60, 80
Lactose	Urethane
Lanette wax	Vitamin E
L-Cystin hydrochloride	Digitalin
Maltose	Ergometrine maleate

Export promotion

Any move for export promotion must be based on products derived from indigenous raw materials. The number and output of such materials which may lead to exportable finished products are by no means small. It will be useful to recount here the efforts that have been made in this regard and the difficulties we have faced.

Bile products. Ox-bile gives a number of useful products for the pharmaceutical industry, such as ox-bile extract, cholic acid, dehydrocholic acid, taurocholic acid etc. The technology of converting bile to these products was developed in our laboratory long ago, and during the last war, large supplies of some of these were made to the defence department. In the course of this work, valuable knowledge has been gained on the quality of Indian ox-bile, the availability from different localities in different parts of the year, the relation between quality and the age of the kill, the method of storage for transport from one place to another, and any change in them during storage.

There is a good demand for these products in India, and there is an equally good prospect for their export. Although we are equipped to process large quantities of bile, we really do a fraction of it to meet part of the internal demand, due to poor availability of bile.

India has a vast cattle population, and the number of kills in different slaughter-houses and those of private kills is quite large. Unfortunately the systematic collection of bile has been a very big problem. This is an area where municipal authorities who supervise slaughter-houses can be of great help, but so far our efforts to interest them in this task have been fruitless. The result is that a good amount of valuable material is wasted, and bile salts cannot be exported in quantity.

Peptone. This is another product having good internal demand and export possibilities. The technology has been developed indigenously, and the product has been well received by the reputed biological standardization laboratories. Actual production has, however, been irregular, due to irregular supply of meat. The production of standard grade of peptone requires a good quality meat, which should be from young and healthy animals. The animals which go to our slaughter-houses are almost always old and emaciated. As such we have to allow for a large amount of rejection from the meat we get, and this reduces output and increases cost.

Once again, this is an area where municipal authorities could render help and again, we have not been successful in impressing upon them the special needs of the industry.

Antacids. Two products of the highest standard have been developed by us: one is magnesium trisilicate, a pharmacopoeial antacid, and the other is magnesium aluminium silicate, a new buffer antacid. The raw materials are all available in the country, and as such if bulk production can be undertaken at internationally competitive prices, there is a good export possibility.

Now although sodium silicate, which is a raw material for the antacids, is available in the country and is consumed in large quantities by the soap and foundry industries, the quality is not sufficiently pure for its use in pharmaceutical manufacture. However by repeated representations to the producers, we have been able to induce them to undertake production of a special grade suitable for us. Their production is however dependent on the availability of soda ash. Secondly the bulk production of magnesium trisilicate will require mechanization of the unit, so that cost may be reduced. This needs high speed filters which are again dependent on imports. All these have delayed our programme; we are continuing the efforts to overcome the foreign exchange difficulty and step up production as far as possible with indigenous resources.

Import rationalization

With the object of developing indigenous technology and reducing our dependence on imports, the production of several basic drugs has been undertaken by us, partly to meet our formulation needs, and partly to supply the needs of other pharmaceutical manufacturers.

This includes chloroquin, phenformin and radio-opaque substances like diodone. The manufacture of chloroquin is based on two imported raw materials, novol diamine and ethoxy methylene malonate (EMME). Although the need for imports is not wholly ruled out, this has enabled a great saving of foreign exchange.

In this process 4:7 dichloroquinoline (DCQ) is produced as an intermediate; actually the synthesis of DCQ involves almost 75 per cent of the labour involved in the production of chloroquin. From the manufacturing

point of view, it was therefore easier to import DCQ and then proceed to chloroquin. Instead, the longer route from novol diamine and EMME was selected with a view to reduce foreign exchange load. This has resulted in the production cost of chloroquin being higher than the cost of the imported drug.

Once this technology was fully mastered, we proposed to undertake the manufacture of DCQ so as to meet our own requirement, as well as to meet the requirement of others who might select this direct shortcut route to chloroquin. This proposal has been turned down by the licencing authority on the ground that the production cost of DCQ is higher than the cost of the imported material. Now if this argument is extended to its logical conclusion, the manufacture of any chemical can be prohibited since in India, raw material cost, equipment cost and scale of operation do not permit production at international price right from the start. We firmly believe that in refusing us the licence for the manufacture of DCQ which we developed at great cost, the case for indigenous technology has been ignored.

To make matters worse, imported chloroquin has been exempted from part of the customs duty, which makes the comparison between costs of imported and indigenous products still more unfavourable. On the other hand if the custom duty levied on the raw materials for DCQ be removed, the cost would come down by about 15 per cent.

Conclusion

These indicate the vast and complex nature of the problems of the Indian pharmaceutical industry with respect to raw materials. Surprisingly, the present problem is not wholly technological; actually its solution would have been simpler if it were so. In many cases, administrative deficiency and the lack of a sense of priority in the allocation of resources, play a big part, and these are very difficult to counteract.

Secondly, although the present emergency has brought the problem of import substitution and rationalization sharply into focus, which will call forth a good deal of improvisation in our selection of processes, equipments and raw materials, this should not divert onr attention too much from the problem of long range basic research and development. This may need an orientation in our schemes for research and investigation. More basic research that would help in enhancement of our knowledge and more technological study including chemical kinetics would continue to remain essential more than ever before.

Self-sufficiency in Raw Materials for Antibiotics Production

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The raw materials required for the Antibiotics Plant can be classified broadly under three categories :

(i) Agricultural raw materials
(ii) Chemicals
(iii) Auxiliary materials including packing materials

In all, about 80 different types of raw materials amounting to over 25,000 tons are required annually. A survey was undertaken during 1963 to find out the sources of different types of raw materials conforming to our specifications. The survey revealed that about 81 per cent, by weight of all raw materials required, are produced indigenously while the remaining 19 per cent have to be imported. Constant efforts are being made to locate indigenous sources as well as indigenous substitutes for the imported raw materials.

Agricultural raw materials

These raw materials are used exclusively in the fermentation process. Fermentation being a biological process, it is not possible to define these materials precisely on the basis of specifications alone as in the case of chemicals and it is necessary to carry out biological tests as well. For biological testing to have any significance, it should be carried out with the same antibiotic producing commercial strains as are used in the regular plant. This is particularly so since these commercial strains are highly sophisticated in their nutritional requirements. Besides, any toxic substances even when present in minute traces are very likely to inhibit the growth of antibiotic producing micro-organism. There is also the possibility of these substances getting extracted along with the antibiotics during the recovery process resulting in deterioration of the quality of the antibiotics. Special emphasis has, therefore, to be placed on the raw materials in question not only fulfilling the nutritional needs of the micro-organism concerned but ensuring freedom from even minute traces of undesirable substances. This makes any substitution of imported raw materials by indigenous ones rather difficult.

Soyabean products required for antibiotics production are, by and large, imported at present. We have located some sources of soyabean grown in the hill districts of Western U. P. and sent the samples abroad for testing with the commercial strains proposed to be used in our plant. The results are quite encouraging and it is expected that we shall be able

to substitute in phases all our requirements of imported soyabean by indigenously grown produce.

Chemicals

The position with regard to chemicals required for fermentation as well as purification is simpler. The chemicals required can be defined by a set of specifications precisely. However, there are number of chemicals such as ion exchange resins and special type of activated carbons which are necessarily to be imported. Recently we were able to locate indigenous sources for major solvent such as methanol and chemicals such as Captex (rubber vulcanization accelerator), calcium stearate, carboxymethyl cellulose. As far as procaine hydrochloride is concerned, this material is being manufactured in India, but the capacity is not adequate to cope up with our requirements. In case the existing capacity is not increased, we have to import this material. Regarding sulphonated carbon, the indigenously produced variety is suitable for boiler feed water only. However, the quality required for producing demineralized water for pharmaceutical use is not available and this has to be imported. It is hoped that in due course, this type also will be available indigenously.

Different types of activated carbons are required in the process. Efforts are being made to get the indigenous manufacturers to get interested in producing the types that are currently not manufactured in India to meet our requirements. A bulk sample has been received and this will be tested in our Pilot Plant soon.

Auxiliary materials including packing materials

We have procured fully automatic plant for filling sterile antibiotic powders. This will obviate manual handling to a large extent, thus eliminating the chances of contaminating the sterile powders in addition to resulting in economy. These machines naturally require glass vials, rubber stoppers and aluminium seals of close tolerances. A thorough survey has been made all over India and we were able to locate sources for the supply of these auxiliary materials conforming to our specifications. These samples have been sent abroad for testing on the machines on order and the results are encouraging. We hope that it should be possible to depend entirely on indigenous manufacturers for these materials. We have intimated our requirements to existing manufacturers as well as entrepreneurs and it is gratifying to note that some industrial units for manufacturing these items are being set up in the vicinity of our plant. The aluminium foil required for making seals is being imported from abroad. We have sent samples of indigeuously manufactured foil abroad and the results again are enccuraging. It should be possible to replace in stages the imported foil by indigenous supply. Similar is the case with aluminium foil required for strip packing as well as cellulose film needed for wrapping. Similarly, survey has been conducted with respect to hard gelatine capsules required for filling antibiotic powders. The indigenous samples have been sent abroad for testing on Encapsulation Machinery on order and the results are satisfactory. In this case also it is hoped that we should be able to rely on indigenous sources of supply. As regards capacity, the firms have been intimated about our requirements and it is hoped that the required capacity will be forthcoming when we need it.

From above, it can be seen that we have been surveying all available indigenous sources for meeting our various requirements and it is gratifying

to note that 81 per cent of our requirements of agricultural raw materials and chemicals can be met from indigenous production while almost all the auxiliary materials including packing materials should be available indigenously. And 19 per cent of our requirements of the former category have still to be imported and the search for indigenous substitutes will continue. Our pilot plant, which has been commissioned will also help in this process. Similarly, when our Research and Quality Control Laboratories are ready, this task will be facilitated to a great extent. However, organization like Council of Scientific & Industrial Research with a string of well-equipped research institutes in various fields as well as the Research and Development Establishments of the Industries can render valuable assistance in this regard. Similarly, the existing industrial units as well as entrepreneurs can take up the manufacture of the items yet to be imported and save valuable foreign exchange.

Organic Constituents of Coke Oven By-products and their Potential as a Raw Material Base for the Pharmaceutical Industry in India

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As part of a continuing programme the composition of coke oven by-products, i.e. tar, benzole, liquor, acid sludge and gas from the major industrial coke ovens of the country are being studied in this laboratory. In a study involving more than 25 man-years of work and several thousand infrared and ultraviolet spectra and v.p.c. analyses and several hundred fractionations, the constituents of the by-products from the major industrial coke ovens have been identified compoundwise, estimated and catalogued. In the context of the increasing interest in low temperature carbonization for the production of smokeless fuels, and the increased yield of tar from this source, the l.t.c. by-products have been given the same attention as h.t.c., and their composition too largely determined. Of the more than 300 compounds identified and estimated in the different coke oven by-products, a few are of direct interest from the standpoint of the production of pharmaceuticals, drugs, vitamins and food nutrients and their significance in providing an indigenous raw material base for the pharmaceutical industry is discussed here.

Although in terms of per cent concentration, many of the constituents are present only in small quantities, the recovery potential is actually large. This follows from the consideration that about 10 million tons of coal per annum are at present carbonized in the country in the steel plants alone, apart from another 2 million tons in the merchant ovens, and the quantity would be larger still in the next plan period. Assuming a yield of about 8 gal. of tar per ton of coal carbonized, the recovery potential of a compound occurring in a concentration of 100 parts per million works out to about 80,000 lb. per annum.

Broadly speaking, from the standpoint of the pharmaceutical industry, the raw materials which the by-products of the coal carbonization industry can provide can be divided into two categories. First, intermediates for which there are no substitutes or ready methods of synthesis and which are imported at present. In this category fall the nitrogen heterocycles. And secondly, organic chemicals for which there are alternate sources available within the country, e.g. from petrochemical manufacturers.

To enumerate some typical requirements, the current consumption of the tuberculostat, isonicotinic hydrazide, has been estimated at more than 50 tons per annum and that of *p*-aminosalicylic acid, 300 tons. The consumption of sulfa drugs (sulfadiazine, sulfadiamidine, sulfapyridine and others) is believed to be as large as 1000 tons. The two major analgesics,

Table 1 — Individual bases in Rourkela tar

Sl. No.	Compound	Percentage in the total* tar bases	p.p.m. in tar
1.	Pyridine	1·10	216·7
2.	Alpha-picoline	1·11	218·7
3.	Beta-picoline	0·50	98·5
4.	Gamma-picoline	0·80	157·6
5.	2, 6-Lutidine	0·47	92·6
6.	2, 4, Lutidine	2·23	439·3
7.	2, 4, 6-Collidine	0·77	151·7
8.	Aniline	3·12	614·8
9.	N : N-Dimethylaniline	** Minor component	—
10.	N-Methyl-2-methylaniline		
11.	2-Ethylaniline		
12.	3-Methylaniline	Minor componennt	—
13.	Quinoline	19·35	3813
14.	Isoquinoline	4·50	886·5
15.	2-Methylquinoline	Minor component	—
16.	4-Methylquinoline	** Major component	—
17.	2, 4-Dimethylquinoline		
18.	2, 7-Dimethylquinoline		
19.	2, 8-Dimethylquinoline	Major component	—
20.	2, 6-Dimethylquinoline		
21.	7-Methylquinoline		
22.	6-Methylquinoline		
23.	5, 6-Benzoquinoline	Major component	—
24.	Phenanthridine		
25.	Acridine	2·99	589.1
26.	7, 8-Benzoquinoline	Major component	—

* Total base content in Rourkela tar = 1·97 per cent

** Where the percentage concentration is likely to be more than 5, the compound has been classified as major component, and where the concentration is believed to be less than 5 per cent, the compound has been rated as a minor component.

phenacetin and aspirin, account for between them sales of over 1000 tons per annum, while that of the antibiotic chloromycetin is about 10 tons. The current imports of beta-picoline, which on oxidation yields nicotinic acid, is about 30 tons per annum and that of pyridine 75 tons. The requirements of some other intermediates are as follows: Sulfanilamide, 450 tons; toluene sulfonamide, 12 tons; chloronitrobenzene, 250 tons; *m*-aminophenol 320 tons; *o*-aminophenol, 10 tons; *p*-aminophenol, 3 tons; toluenesulfonamide 12 tons and phenol, 136 tons.

In this paper, an attempt is made to show how most of the raw materials in the quantities that are required for the drug industry, can be obtained by processing the products of coal carbonization. The importance of an integrated approach is also brought out, as in order to render the processes economical, it would be necessary to find outlets for most of the major constituents in coal carbonization by-products, and many of these would be for end-products outside the pharmaceutical industry in such diverse fields as synthetic fibres, plastics, resins, automotive chemicals, detergents, cosmetics, dyes and solvents.

Table 1 details the nitrogen heterocycles found in a typical high temperature industrial tar*, (Rourkela Steel Plant Coke Ovens) and Table 2 that in low temperature tar. Table 3 gives the comparative yields of some aromatic hydrocarbons in high temperature and low temperature tar. Table 4 gives the composition of a typical* benzole and Table 5 reports on the composition of tar acids as found in Bhilai tar*.

*Data on other industrial tars and by-products are available and can be furnished on request.

Table 2 — Individual bases in low temperature tar

(Quantity expressed as wt per cent of total tar bases, i.e. bases obtained from all oils, b.p., I.B.P. — 360°)

Sl. No.	Compound	Quantity present in the			p.p.m. in tar
		Oils b.p. up to 270°C.	Oils b.p. 270 to 360°C.	Total oils	
1.	Piperidine	traces	—	traces	—
2.	Pyridine	0·24	0·10	0·34	79
3.	Alpha-picoline	0·70	0 21	0·91	212
4.	Beta-picoline	0·22	0·16	0·38	89
5.	Gamma-picoline	0·50	0·14	0·64	149
6.	2, 6-Lutidine	1·94	0·49	2·43	566
7.	2, 4-Lutidine	major	major	major	—
8.	3, 5-Lutidine	traces	traces	traces	—
9.	2, 3-Lutidine	traces?	traces?	traces?	—
10.	2, 4, 6-Collidine	3·23	0·80	4·03	939
11.	4-Isopropylpyridine	traces	—	traces	—
12.	4-Ethyl-2-methylpyridine	minor	traces	minor	—
13.	2, 6-Dimethyl-4-ethylpridine	do	do	do	—
14.	5-Ethyl-2-methylpyridine	do	do	do	—
15. 16.	3, 4-Diethylpyridine and/or 3-Ethyl-4-methylpyridine	do	do	do	—
17.	Aniline	0·65	0·20	0·85	198
18.	3-Methylaniline	minor	minor	minor	—
19.	2, 3, 4, 6-Tetramethylpyridine	traces	traces	traces	—
20.	2, 3-Cyclopentanopyridine	do	do	do	—
21.	Quinoline	0.69	1·27	1·96	457
22.	Isoquinoline	major	major	major	—
23.	2-Methylquinoline	do	do	do	—
24.	4-Methylquinoline	do	do	do	—
25.	8-Methylquinoline	minor	major	do	—
26.	2, 4-Dimethylquinoline	major	do	do	—
27.	2-Phenylpyridine	do	do	do	—
28.	2, 4, 6-Trimethylquinoline	do	do	do	—
29.	2, 7-Dimethylquinoline?	minor	minor	minor	—
	Total base content of the tar (i.e. bases recoverable from the tar oils I.B.P. — 360° expressed as wt per cent of dry tar)	2·53%			

*Where the percentage concentration is expected to be near about 5 or even more the compound has been classified as a major constituent, and where the conc. is believed to be in the range 0·1–5 per cent the compound has been rated as a minor component. Concentrations below 0·1 per cent have been referred to as traces.

Table 3 — Comparative* yields of aromatic compounds identified in h.t.c. & l.t.c. tar

Sl. No.	Compound	Concentration expressed as wt per cent of tar in		Yield (lb./100 ton) of coal in	
		h.t.c. tar	l.t.c. tar	h.t.c.	l.t.c.
1.	Benzene	0·10	0·03	6·0	4·8
2.	Toluene	0·04	0·39	2·4	62·4
3.	*o*-Xylene	0·02	0·16	1·2	25·6
4.	*m*-Xylene	0·05	0·26	3·0	41·6
5.	*p*-Xylene	0·01	0·13	0·6	20·8
6.	Ethylbenzene	0·02	minor†	1·2	270
7.	1, 2, 3-Trimethylbenzene	minor	1·38	100	220·8
8.	1, 3, 5-Trimethylbenzene	do	0·30	100	48·0
9.	1, 2, 4-Trimethylbenzene	do	0·56	100	89·6
10.	1, 2-Diethylbenzene	do	minor	100	270
11.	Naphthalene	8·40	0·86	504·0	137·6
12.	1-Methylnaphthalene	0·43	0·30	25·8	48·0
13.	2-Methylnaphthalene	1·22	major	73·2	170
14.	Anthracene	0·97	0·20	58·2	32·0
15.	Fluorene	1·88	0·46	112·8	73·6
16.	Fluoranthene	3·76	0·59	225·6	94·4
17.	Pyrene	0·39	0·03	23·4	4·8
18.	Biphenyl	0·55	—	33·0	—
19.	Acenaphthene	1·59	—	95·4	—
20.	Carbazole	0·78	—	46·8†	—
21.	Diphenylene oxide	major	—	100	—
22.	Fluoranthene	do	—	100	—
23.	3-Methylanthracene	minor	—	100	—
24.	1, 2-Benzfluorene	do	—	100	—
25.	2, 3-Benzfluorene	do	—	100	—
26.	Chrysene	0·07	—	4·2	—
27.	1-Methyl-3-ethylbenzene	—	minor	—	270
28.	1-Methyl-4-ethylbenzene	—	do	—	270
29.	1-Methyl-2-ethylbenzene	—	do	—	270
30.	1-Methyl-4-isopropylbenzene	—	do	—	270
31.	1, 3-Dimethyl-4-isopropyl-benzene	—	do	—	270
32.	1, 3-Dimethyl-5-isopropyl-benzene	—	do	—	270
33.	1, 3-Dimethyl-4-ethylbenzene	—	do	—	270
34.	1, 2-Dimethyl-4-ethylbenzene	—	do	—	270
35.	1-Methyl-4-*tert*-butylbenzene	—	do	—	270
36.	*n*-Hexylbenzene	—	do	—	270
37.	1, 2, 3, 4-Tetramethylbenzene	—	0·43	—	68·8
38.	Tetralin	—	0·23	—	36·8
39.	2, 6-Dimethylnaphthalene	—	0·10	—	16·0
40.	1, 2-Dimethylnaphthalene	—	minor	—	270
41.	2-*n*-Butylbenzene	—	do	—	270
42.	1, 5-Dimethylnaphthalene	—	0·16	—	25·6

*Sample of h.t.c. tar from Bhilai Steel Plant and that of l.t.c. tar obtained on carbonizing coal at CFRI pilot plant were selected for the comparison. The yield of h.t.c. tar is assumed to be 6 gal. and that of l.t.c. tar 16 gal. per ton of coal carbonized.

†Major and minor indicate whether the concentration of the compound is more than or less than 1·7 respectively.

Table 4 — Composition of crude benzole (Rourkela Steel Plant)

Compound	Wt per cent	Compound	Wt per cent
Benzene	66·4	Pyridine bases	0·1
Toluene	22·8	Carbon disulphide	0·2
o-Xylene	0·6	Cyclopentadiene	0·3
m-Xylene	2·5	Dicyclopentadiene	0·8
p-Xylene	1·2	Butadiene (gas)	(3·5 ml./100 ml. of benzole)
Styrene	absent		
Naphthalene	1·6	Thiophene	not determined
Phenols	nil	Unidentified olefins	1·5

Table 5 — Compounds identified in Bhilai tar acids

(Quantity expressed as wt per cent of total tar acids, i.e. tar acids obtained from all oils, b.p., I.B.P. — 360°)

Sl. No.	Compound	Quantity present in the			Percentage in tar
		Oils b.p. up to 270°C.	Oils h.p. 270–360°C.	Total oils	
1.	Phenol	19·0	1·4	20·4	0·29
2.	*o*-Cresol	8·6	1·8	10 4	0·15
3.	*m*-Cresol	15·8	2·1	17·9	0·25
4.	*p*-Cresol	5·8	1·3	7·1	0·10
5.	2, 3-Xylenol	minor*	minor	minor	—
6.	2, 5-Xylenol	do	do	do	—
7.	2, 4-Xylenol	do	do	do	—
8.	2, 6-Xylenol	do	do	do	—
9.	3, 4-Xylenol	do	do	do	—
10.	3, 5-Xylenol	major	major	major	—
11.	*p*-Ethyl phenol	—	minor	minor	—
12.	*o*-Phenyl phenol and/or *o*-propenyl phenol	—	do	do	—
13.	Alpha-naphthol	—	0·40	0·40	0·006
14.	Beta-naphthol	—	0·30	0·31	0·004

*Where the concentration is likely to be more than 5 per cent, the compound has been rated as major. Concentrations of less than 5 per cent have been termed as minor.

The exhaustive data obtained in this laboratory on the composition of coal tar nitrogen heterocycles, of which a cross-section is given in Table 1, indicate that if the recovery of coal tar bases is effected in the major steel plant coke ovens, a quantity of pyridine, alkyl pyridines, quinolines and isoquinolines, adequate to provide the raw material base for the heterocyclic drug industry, would become available. The amount of gamma-picoline recoverable from a plant carbonizing 5000 tons of coal per day works out to about 10 tons per year and the existing carbonization capacity in the steel plants alone, should be more than adequate to cover the current annual requirement of 50 tons. Any process for the recovery of gamma-picoline would incidentally yield comparable quantities of beta-picoline, needed for the production of nicotinic acid (an ingredient of Vitamin B complex), nicotinamide and the analeptic, coramine. Apart from this, much larger quantities of pyridine and still larger quantities of quinolines and isoquinolines would become available. Since each of these has a ready outlet in the

pharmaceutical industry, their integrated economic exploitation should become feasible. Pyridine finds use in a wide range of medicinal products, such as antiseptics (cetyl and lauryl) pyridinium chlorides, bacteriostatic drugs, antihistamines such as pyribenzamine, urinary analgesics (e.g. 2, 6-diamino-3-phenylazopyridine hydrochloride), pyridine arsenals used in respiratory infections, pyridine-N-oxides etc. Quinoliue can be utilized for the production of nicotinic acid by oxidation to quinolinic acid followed by selective decarboxylation.

Both l.t.c. tar and h.t.c. tar contain substantial quantities of phenol which is the starting material for the production of salicylic acid, needed for making the analgesic aspirin, the anaesthetic benzocaine and several other therapeutic preparations. As phenol recovery is already being practised in the West Bengal Coke Ovens, Durgapur, and is available in tonnage quantities, it is no longer necessary to have to depend on synthetic phenol.

Ready availability, in tonnage quantities, of the basic hydrocarbons is also an essential pre-requisite for a drug industry. The simpler basic hydrocarbons are required not only as solvents for crystallization and purification purposes, but they also form the starting points for the synthesis of the key intermediates. Toluene forms the first stage in the synthesis of *m*-aminophenol from which the tuberculostat PAS is manufactured.

The synthesis of the anaesthetic procaine requires *p*-nitrobenzoyl chloride, and that of follic acid, *p*-nitrobenzoic acid, both of which are readily made from toluene. The production of aniline needed as an intermediate for a host of synthetic drugs, phenacetin, *p*-acetanilide sulphachloride (ASC), is dependent on the ready availability of benzene. 'Benzole', obtained at the rate of 2 to 3 gal. per ton of coal carbonized, can provide the pharmaceutical industry's requirements of benzene and its simpler alkyl homologues.

While the simpler hydrocarbons like alkyl benzenes can be just as readily obtained from the petrochemical industry, and to that extent the coke oven recovery units would face severe competition, in the case of some of the higher hydrocarbons, coal tar oils constitutc the only practical source. This is particularly true of the alkyl naphthalenes. Beta-methyl naphthalene which occurs in appreciable quantities in high temperature tar oils, and in still greater quantities in l.t.c. tar yields on oxidation in the liquid or vapour phase 2-methyl-1 : 4-naphthaquinone required for the production of vitamins K_3 and K.

Conclusion and recommendations

Coke oven by-products, i.e. tar, liquor, benzole and acid sludge, all contain many valuable constituents which if recovered by suitable processing, can help to meet many of the immediate requirements of the pharmaceutical industry in respect of reaction intermediates and raw materials. The recovery is likely to iuvolve only simple operations and may even result in incidental advantages to the main coke oven practice. The economics of recovery is likely to be facilitated by an integrated approach on the part of the pharmaceutical manufacturers with utilization of as wide a range of constituents as possible and the formation of a common pool of raw materials. The Rourkela Steel Coke Oven Plant which has an excellent by-product recovery and rectification unit would appear to be a suitable place to initiate recovery operations. Alternately, the West Bengal Coke Ovens, Durgapur, may also be able to provide the facilities required for processing.

Treatment of Waste Liquor from Low Temperature Carbonization by Biological Oxidation

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Low temperature carbonization possibilities of Indian coals are being tested over the last few years in two pilot experimental plants, one at Central Fuel Research Institute, Jealgora, and the other at Regional Research Laboratory, Hyderabad. A stage is now reached where it appears that in near future quite a good number of large scale plants will be coming up for the purpose of production of domestic coke and/or coke for low shaft furnace. As in the case of conventional high temperature carbonization, low temperature carbonization will also produce considerable quantity of liquor which, being even more harmful than the h.t.c liquor, must be treated before being discharged to the sewers, rivers, lakes, etc.

For treatment of h.t.c. liquor for a safe disposal, a number of processes are in use. These are based either on the recovery or destruction of its harmful constituents, e.g. phenols. Recovery of phenols is accomplished by any of the processes, like extraction with benzene and alkali, steam-recirculation process of Koppers, phenosolvan and phenoraffin processes of Lurgi, ion exchange and active carbon processes (the Corby process), etc. Of the various chemicals, physical and bacteriological processes available for destruction of phenols, the bacteriological process seems to be the least costly one, besides being reasonably effective, simple in nature and without any secondary complication like pollution of atmosphere, etc.

The recovery techniques constitute a separate important field by themselves and will not be dealt with here. The bacteriological destructive process consists firstly of a number of interconnected treatment tanks of suitable dimensions as to allow the required time of retention, fitted with aeration arrangements, sludge recirculation arrangement and froth controlling sprayers. The liquor to be treated with added inorganic nutrients is fed into the first tank and allowed to flow from one tank to the other. The tanks contain bacterial suspension from previous operations which destroy the phenols in the presence of oxygen supplied through aeration. The treated water from the last tank is allowed to settle. The clear liquid passes on, while the settled sludge is returned to the system, at least partly, often after separate activation, and the excess sludge is disposed off suitably by burning or otherwise. The treated liquor, if still needed, can again be trickled through percolation filters where same bacteriological oxidation process is continued by bacterial films developed in course of use on the filling medium.

While the recovery techniques, which are possibly more economical applicable to l.t.c. liquor, it is not known how the bacteriological process will fit in, as the nature and concentration of the harmful

constituents, especially the phenols, are different in this case. In the present study, therefore, an attempt has been made, at first, to establish the general nature of l.t.c. liquors and then the feasibility of bacteriological oxidation has been investigated.

Nature of low temperature carbonization liquor

A number of low temperature liquor samples collected from CFRI pilot plant during carbonization tests with different coals have been analysed. Table 1 shows the average analytical figures for six different liquor samples. In Table 1 are given the oxygen demand for complete oxidation and relative toxicity figures (with 4-hour permanganate value as unity) to indicate the relative harmful effects.

It may be seen that phenols are the most toxic constituents and they are also very high in their concentration. Moreover, phenols from l.t.c. liquors contain large quantities of polyhydroxy phenols 40–60 per cent (10-25 pe cent in case of phenols from h.t.c. liquor). This relationship is imprortant, as it indicates that phenols in l.t.c. liquor are more difficult to be treated than the same in h.t.c. liquor, even when the concentrations were brought to the same level. It is known that polyhydroxy phenols are less easily oxidized and in treated h.t.c. liquors it is this type of compounds that accounts for the residual permanganate value. Of the other constituents, ammonia is important because of its high oxygen demand. This constituent is present, at a relatively low concentration, in l.t.c. liquor. Sulphide has a high toxicity and a moderate oxygen demand but its concentration is not alarming. This is partially removed during aeration. Thiocyanate has a high oxygen demand, although it has no high toxicity. Their removal by bacteriological treatment poses the problem that so long as phenol concentration is not reduced to a low level removal of thiocyanate does not take place.

As regards the harmful effects due to the constituents other than phenols, and ammonia there is not much difference between l.t.c. and h.t.c.

Table 1 — Nature of liquor from low temperature carbonization pilot plant at CFRI

Specific gravity	Oxygen demand	Relative toxicity†	Range (av. of six samples)
Specific gravity	—	—	1·004–1·007
Evaporation residue	—	—	3·95–6·76 g./l.
Free ammonia as NH_3	3·76	2	2·13–5·83 „
Fixed ammonia as NH_3	—	—	0·60–2·85 „
Total ammonia as NH_3	—	—	3·03–6·63 „
Monophenols*	2·38	20	3·59–7·10 „
Total phenols*	—	—	6·30–12·64 „
Thiosulphate as $Na_2S_2O_3$	*1·30*	*1*	*868–1537* p.p.m.
Sulphide as H_2S	1·80	20	64–139 p.p.m.
C.O.D. (4 hr $KMnO_4$ value at 27°C.)	—	—	12,160 – 21,280‡ p.p.m.

*By the UV spectrophotometric method

†Based on 4 hr $KMnO_4$ value as unity

‡The same for h.t.c. liquor hardly exceeds 4000, a good average being 2000

liquors. The difference in O/A or permanganate value of the two liquors is, however, quite high — one shows about 10 times of O/A more than that of the other. High concentration of phenols is obviously the cause of this.

However, as the phenols are commercially very important and are present in very high concentration in l.t.c. liquor, recovery of phenols by solvents (e.g. butyl acetate in the phenosolvan process) should be considered an economic proposition and hence the final waste from l.t.c. liquors may not pose so staggering a problem.

Bacteriological oxidation of phenols in l.t.c. liquor

The bacteria required for the process was developed from a sample of soil collected from the drainage site of effluents from high and low temperature carbonization plants.

Preliminary conditions for treatment were fixed up by static studies in enamelled vats. Continuous runs were made in cement concrete tank, divided into three interconnected compartments of 13 litres volume and fitted with aeration and heating arrangements. Liquor, containing proper phenol concentration and *p*H is charged into the first compartment at a specified rate together with the nutrients. Retention time allowed in each compartment is about two days. After passing through these compartments the treated liquid passes through a level regulator to a settler where about 12 hr settling time is allowed. The sludge settling at the bottom is returned intermittently to the first tank by air lifting arrangement.

It was found that low temperature liquor whose phenol concentration even brought down to that of the high temperature liquor is more difficult to treat than the latter. For l.t.c. liquor about twice as much retention time is required as that for h.t.c. liquor. With fresh bacterial suspension an oxidation capacity of about 25–35 lb. phenol/1000 cu.ft/day could be obtained. Under the same conditions where the phenol concentration of h.t.c. liquor was reduced from about 600 p.p.m. to less than 10 p.p.m. in less than 24 hr the phenol concentration of l.t.c. liquor could be reduced from 500 p.p.m. to 30–60 p.p.m. in two days.

Experiments carried at a temp. 40–45°C. showed better results than at a temperature 30–41°C., but any further increase in temperature did not show any improvement in the phenol oxidation. C.O.D. removal which like phenols depends on load and is about 70 lb./1000 cu.ft/day at 40–45°C. This is higher at 50–55°C. Amount of air necessary for oxidation was also investigated and it was observed that 10–15 l./min. of air was essential for the three compartments for a daily feed rate of 6–7 litres of liquor of about 1000 p.p.m. phenol concentration. When the liquor contained foreign organic impurities, like butyl acetate in the phenosolvan process, it proved advantageous to use 20 l./min. of air for the same feed rate. This corresponds to an aeration rate of 22,000 cu.ft of air/1000 cu.ft of tank volume per hour (or 17,000 cu.ft/lb. of phenol removed or 8000 cu.ft/lb. of C.O.D. removed) which can possibly be reduced to a great extent if efficient aeration equipment like Kessener brushes are used in large scale experiments.

A phenol concentration of up to 750 p.p.m. in the oxidation bath was found to be harmless for the bacteria while a concentration up to 1000 p.p.m. did not perhaps kill them. In actual operation the phenol concentration was not allowed to rise above 500 p.p.m. in the treatment tanks.

Table 2 — Bacteriological oxidation of l.t.c. liquor

[Composition of l.t.c. liquor: Total phenols, 10 g./l.; C.O.D., 20,000 p.p.m.; Total ammonia (as NH_3), 7·35 g./l.; Thiocyanate (as NH_4CNS), 720 p.p.m.; Sulphide (as H_2S), 103 p.p.m.; Temp., 29-30°C.; Air rate, 15 l./min. (equally distributed between three compartments)]

Run No.	Loading in lb./1000 ft³/day* (first compartment)		Destruction in lb./1000 ft³/day* (first compartment)		Final effluent (from settler) composition	
	Phenol	C. O. D.	Phenol	C. O. D.		
	FEED: RAW LIQUOR DILUTED 1:9 WITH DISTILLED WATER					
1.	16	26	13	18		
2.	17	28	15	27		
3.	14	24	13	26		
	FEED: RAW LIQUOR DILUTED 1:9 WITH DISTILLED WATER					
1.	34	80	26	73	Phenol	10 p.p.m.
2.	33	79	28	70	Thiocyanate	nil
3.	34	80	30	70	Total ammonia	700 p.p.m.
4.	34	80	32	70	C.O.D. (O/A)	150 p.p.m.

*Capacity in the other compartment is much less due to much lower loading

A constant check of the phenol concentration in the tanks was thus very essential with l.t.c. liquor. This constant check is not required in the case of h.t.c. liquor as the phenol concentration is never very high.

Studies with butyl acetate extracted liquors showed that the oxidation efficiency in this case was lower than with diluted l.t.c. liquors. The efficiency of phenol removal was of the order of 20–28 lb. phenols/1000 cu.ft/day — the same for C.O.D. removal being of the order of 40–50 lb./1000 cu.ft/day (at 50–55°C., this increased to 80 lb./1000 cu.ft/day).

All the above results refer to the treatment in the first tank only. The quality of liquor, after the third tank (after 6 days aeration) and after settling was, in all cases very satisfactory. Phenol concentration generally did not exceed 30 p.p.m.; thiocyanates were reduced to nil. Ammonia was only slightly affected (some loss occurred due to aeration) and C.O.D. was reduced from about 20,000 p.p.m. to about 1000 p.p.m. with butyl acetate treated liquors and less than 150 p.p.m. with diluted liquors.

Sludge formation was never very disturbing, although frothing some times occurred. Intermittent recirculation of the sludge was high to maintain a smooth operation . For froth control no special chemical like tri-*n*-butyl phosphates or tri-*n*-butyl citrate was tried.

Results of the bacteriological oxidation of l.t.c. liquor are given in Table 2.

Conclusion

Investigation has been undertaken at CFRI to find out the chemical nature of the effluent liquor from low temperature carbonization and to examine the feasibility of its treatment by biological oxidation process.

L.t.c. liquor differs appreciably from h.t.c. liquor, the most important variation being the much higher concentration of total phenols and high proportion of polyhydroxy phenols in the former. Bacteriological oxidation of l.t.c. liquor phenols is feasible but it requires a longer time as compared to h.t.c. liquor and needs greater control. Oxidation efficiency is of the order of 25–35 lb./1000 cu.ft/day for phenols and 50–80 lb./1000 cu.ft/day for chemical oxygen demand. For effluents containing added solvents like butyl acetate, the efficiency is somewhat lower. If longer reaction time is allowed a very satisfactory effluent can be obtained as a result of bacteriological oxidation. As longer time means retention tanks of greater volumes, the treatment of l.t.c. liquor is expected to be more costly than the same for h.t.c. liquor.

Some Problems Facing Pharmaceutical Industry in Relation to Toxicological and Clinical Pharmacological Work in New Drug Research

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In the birth of a drug, thousands of compounds have to be conceived and prepared in the laboratory. For example nearly, 1,00,000 compounds were conceived for anticonvulsive studies during the last four decades, resulting in the preparation of nearly 20,000 compounds in the laboratory. Of these only about 1000 compounds could emerge out of the animal pharmacological screening work. When it came to the next hurdle, namely toxicological evaluation, barely 100 compounds could pass this stage for clinical pharmacology. Finally after the clinical pharmacology, only about 10 compounds have emerged for marketing all these decades. Today we have barely 10 compounds in the market with significant anticonvulsive potency.

From the above example we can state that in the birth of a drug we have the following stages:

1. The theoretical conception of compounds
2. Laboratory preparation
3. Pharmacodynamic screening in animals
4. Toxicology including metabolic studies
5. Clinical pharmacology in the human

Therefore if we are to wrest the initiative in pharmaceutical research from other countries, we must have facilities in this country for all these stages of research work. Let us now consider as to what facilities are there in this country for these various stages.

For the first two stages good organic chemistry laboratories are essential. We have various university chemistry departments, national laboratories etc. which can help in these two stages, but curiously enough, there is no co-ordinated effort on the part of these institutions and the industry to jointly tackle the needs of the Pharmaceutical Industry. Compounds are synthesized from purely organic chemistry point of view, the structure of these worked out, the thesis submitted for degree and there they end. Very rarely compounds from these institutions have been examined with a view of applications in medicinal chemistry.

In rare cases, we have gone one step more, namely to work out some preliminary pharmacological or bacteriological screening, as in the case of methaqualone and 5-nitro-8-hydroxyquinoline. Both these compounds

have been synthesized by Regional Research Laboratory at Hyderabad, but it was left to the continental workers to work out the next two important stages — the toxicology and clinical pharmacology — and establish them as valuable therapeutic agents. The same can be said of Hamycin of Hindustan Antibiotics, Pimpri. A valuable antibiotic has been isolated and all preliminary work done. Even 4 years after isolation, I do not think we have enough toxicological or clinical data on this drug. When compared with the quality and volume of data collected in the first 4 years of the discovery of similar antifungal agents like nystatin and amphotericin-B, we will realize the inadequacy of our work.

Let us now see as to the nature of the bottlenecks in relation to creating the facilities for these two stages, namely toxicology and clinical pharmacology in the birth of a drug.

Toxicological studies require a very well-equipped animal house, large numbers of pharmacologists, biochemists and pathologists. For screening one drug in terms of toxicology including teratogenicity, we require nearly 5000 rats and mice, 50 to 100 dogs or cats to be kept over 5 to 10 months, with the drugs administered in different doses. Sometimes even monkeys will be required to be maintained for long periods. This requirement, if it is projected in terms of total breeding capacity to be maintained and facilities for large kennel etc. and if we add to it the animal requirements for the routine pharmacodynamic screening, it will roughly come to creating facilities, involving a capital cost of nearly Rs 20 lakhs, with an operational expenditure of nearly Rs 22 lakhs a year. The animal house facilities available at two leading institutions in this country are quite big compared to other inctitutions but they can hardly cope up with the volume of toxicological work. No pharmaceutical company in this country is likely to invest such a heavy capital and recurring expenditure unless some extraordinary inventives are granted by the Government for units willing to set up such facilities.

The difficulty is not only in the lack of such facilities but also in getting personnel specially trained and oriented for such work. The pharmacy colleges in this country at present do not have training programmes oriented to meet the needs of the industry. As it is, the industry itself has to invest heavily in getting their personnel trained, which is an additional burden for them.

Regarding the facilities available for clinical pharmacology the position is still more hopeless. There are so many medical colleges, with facilities for taking up such work without difficulty. All the same, the position is like the man in the midseas, with water all around but dying for lack of drinking water. Let us analyse this paradoxical situation by taking up a hypothetical case.

Suppose we have a product which the laboratories have cleared as a safe drug against intestinal organisms. Now clinical evaluation is necessary and you to go the physician in a medical college. The medical college, being a Government institution, the clinician asks for permission from the Dean, who in turn goes for permission from the Director of Medical Services and after a lapse of nearly 5 to 6 months, you will get a letter stating that the scheme of work will be accepted, if the company can sign a letter stating that the work done is purely for the promotion of research and the results obtained on the completion of the work will be the property of the college and the data will not be used by the company for their advertisement,

literature or promotion work. The company must be willing to pay a heavy grant for a period not less than two years. Then out of disgust the company accepts the conditions and sends the grant and the material. After 6 more months when you go for the report, either the clinician has gone abroad or the post of the assistant for the scheme has been just advertised and the selection is pending. After one year when you go for the report again, the work has not been started because, the Pathology and Bacteriology Departments are not interested in cooperating, since it is a grant only for the clinician. Once again you start negotiating and after 6 more months the team consisting of the clinician, pathologist and bacteriologist commence work. After another year, when you ask for the report you may get a report consisting of data from 15 cases without any significant or relevant toxicological function studies and statistical evaluation of the data. No Drug Control Administration would accept such data for registering the drug. Therefore, three years after setting up the trials, you are just where you have started. This is a typical story. Reports are never received on time and even when they are received, they are often lacking in essential data. Unless the medical profession shoulders the responsibility in screening new drugs with greater zeal and sincerity, no new drug can emanate from Indian Pharmaceutical Industry. There are, of course, a few institutions who are really more helpful but they cannot meet the full needs of the industry.

To sum up, the Pharmaceutical Industry in developing new products face two major hurdles, (i) in toxicological evaluation of the new products and (ii) in getting clinical pharmacological data for new drug registration. Efforts must be made to get these facilities created as early as possible, if we are serious in contributing significantly in Drug Research.

Problems Facing Research Efforts in Pharmaceutical Industry in India

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Most of the research efforts in the pharmaceutical companies in this country, stop at the level of formulation research. That is to say, in getting marketable products with known therapeutic ingredients either imported or purchased locally from a few basic manufacturers. Very often the failure to develop basic manufacture and high prices of drugs are attributed to the Patent Act and a hue and cry is often raised demanding repeal of the Patent Act.

Now let us consider a few widely used pharmaceutical raw materials and see how far the patent laws are responsible for difficulties in their production. There are no patents today for the manufacture of Aspirin, procain HCl, vitamin C, most of the sulphonamides and sulphones, antitubercular compounds etc. Nobody prevents anyone to manufacture these, if they can develop their research know-how. Thus it will be seen, the bugbear of the Patent Act standing in the way of indigenous research efforts is more imaginary rather than real. Most of the important pharmaceutical agents were discovered during 1942–50. The patents on most of these have expired or are expiring in a year or so. Are we today capable of producing all these? The answer is no; because it is not the Patent Act that had stood in the way of our progress but it is because of various other factors.

One of the most important factors against indigenous basic manufacture or research is the high cost of the local production. A company which go into basic manufacture of a product will often find itself stuck with a high cost local product, while the competitors who are not making it, can import or purchase imported material at cheaper cost and earn greater profit. The import cannot be stopped unless the local production can meet the entire requirement of the country. Thus an indigenous producer is handicapped and there can be no incentive for local research effort. The local cost of production cannot be reduced, because of (1) high raw material cost, (2) high cost of power and transport, (3) high cost of refrigeration, (4) high cost of basic reagents like sulphuric acid, nitric acid, alkalies etc., (5) high cost of equipments particularly glass and rubber lined vessels, (6) high cost of solvents, and (7) above all a low volume of production, with a less efficient local know-how.

None of these causes can be eliminated as things stand today. One way by which many bigger firms solve the problem is by going in for more efficient foreign know-how and manufacturing the material on a larger and economic scale. This naturally reduces the role of indigenous research effort. From what I have stated above, it will be clear that a local research

effort is bound to be suicidal. This is one of the main reasons why many firms maintain Research and Development Units more for the name-sake than for real research efforts. The only method to get out of this vicious cycle is to have a Central trading body to import a material and also to purchase the local production at a profitable price for the local producer and market the entire product at an average price. For the local know-how and local production a special premium must be paid as an incentive for developing the Research and Development Departments.

A second important factor standing in the way of setting up big research units within the pharmaceutical industry is the high initial capital cost and recurring operational cost involved. An ideal research set up consisting of (a) Research and Development Section with pilot plant facilities, (b) Medical and Biological Division to carry out new drug screening and toxicological studies and clinical evaluation, with an optimal size animal house, and (c) a formulation research division to translate a new drug as a practical marketable product, will involve an initial capital investment of nearly one crore of rupees, with an operational expenditure of nearly 35 lakhs a year. Half-hearted piecemeal investments will not help. Unless very encouraging incentives are offered for the companies to set up such research units, the local research effort within the industry is going to be understandably insignificant. The type of incentives that can be offered are:

1. A complete income tax relief on capital and operational expenditure for the research set up.
2. Giving import licences outside the company's ceiling for the equipments, chemicals, spare parts etc. for the Research Unit.
3. Making use of the facilities available at the research set up by smaller companies etc. on a definite fee basis.
4. Offering incentives to foreign collaborators to come in with capital for research efforts locally and to develop research centres in this country as part of their international operation. For example, a significant tax relief can be given for foreign firms on their investment in the research units of their local collaborators.

Unless some bold and encouraging incentives are offered by the Government, the local research effort in this country is going to have only a crawling existence.

To sum up, the research efforts within pharmaceutical industry are facing two difficulties. A local production with indigenous know-how is very costly and cannot stand international competition. A proper method of compensating the local production against such competition is essential for encouraging indigenous research efforts. The second difficulty is in relation to the heavy investment required for pharmaceutical research units. Proper incentives for encouraging companies to invest in research efforts must be offered. In this even foreign collaborators can be made to invest by offering significant incentives to them.

Import Substitution : A Challenge to Industry and Government

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The present emergency has forced Indian scientists to plan for import substitution with available techniques by indigenous materials and also to develop indigenous substitutes for imported items. Amongst the Chemical Industries, Pharmaceutical Industry demands from its very nature, raw materials which have to pass very strict pharmacopoeal specifications and hence ask for specialized techniques. The problem, therefore, comes to (i) specialized equipment and (ii) specialized processes needing purification to the highest degree. Since it will be impossible to achieve everything immediately the work should be so planned that during the coming year or two, substantial forward steps would have been taken to achieve maximum self-sufficiency. This requires a clear cut planning of priorities, namely, (i) Listing of essential drugs for the country; (ii) Allocation of foreign exchange among the various units based on their existing plant capacities and also additional production they can achieve with installation of balancing equipment, mostly from indigenous sources; (iii) Allocation of critical and non-substitutable imported raw materials for these industries to achieve the maximum production; and (iv) Assistance to them by way of technical know-how, process development etc. to (a) improve the yields, (b) substitute as far as possible the imported raw materials or use alternative raw materials for production, and (c) permitting expansion and development wherever necessary to help these processes.

All these require close coordination between the Development Councils, National Research Laboratories as also the Universities with research facilities.

First of all a priority has to be drawn up as to the list of essential drugs required for the country and also quantities required during the next five years. Then, a review has to be made of (1) the present capacities of various manufacturing units; (2) processes employed by them; and (3) the imported raw material content of finished drugs produced by these units. Some of the units may be using very much lesser imported raw materials and these units should be encouraged to maximize their production. They should simultaneously also initiate work to further reduce the import content.

Then an assessment has to be made of the minimum foreign exchange required to import the necessary raw materials for manufacture of these drugs. It has to be remembered that no import of finished drugs which are being manufactured at present in India should be allowed in the country on any of the licensing procedures like 'barter' or 'National Defence Remittance Scheme' or 'Export Incentive Licences' etc. This will really

result in considerable outflow of foreign exchange since nearly with one-third to one-fifth of such foreign exchange we can import the raw materials for these drugs and these drugs can be manufactured in India itself. Strict ban will have to be enforced to avoid import of such finished drugs as can be manufactured indigenously. On the other hand, indigenous manufacturers should be encouraged to import raw materials required for increased local production by allocation of foreign exchange generated by 'barter', 'exports', etc. This can be done by means of close cooperation between Export Promotion Councils, Development Wing, S.T.C. and M.M.T.C. and the Industries.

Another aspect that has to be tackled is development of alternative raw materials and alternative processes to substitute imported raw materials. For example, it is possible to substitute dextrose (in antibiotic fermentation) production of which depends upon imported maize by tapioca starch or sugar which is indigenously available. It may also be possible to develop alternative nitrogen sources like groundnut meal, cotton seed meal etc. in place of the imported soyabean flour.

Pharmaceutical iudustries require very pure grade of activated carbon and the needs of the industry could be developed locally. Already, in this connection the Regional Research Laboratory, Hyderabad has been making efforts to produce carbon suitable for Pharmaceutical Industries and it is hoped that in the near future they will be able to obtain a satisfactory quality material. The product developed by the research laboratories should be translated on a larger scale by industrialists.

Even in importing raw materials for production of finished drugs a very careful analysis has to be made where the total import content can be reduced by using alternative raw materials and processes. Further, industries could be greatly helped to maintain the optimum production whenever possible by the expeditious issue of licences for Rupee payment imports when they are able to negotiate contracts with these countries.

Finally, it has to be mentioned that it is impossible to produce all the essential drugs needed by the country without any imports. Some of the items will have to be imported at least for the next 2/3 years before we can develop the necessary intermediates and basic chemicals locally. The new Petrochemical industries that are developing near Bombay and Baroda are expected to be in production by the next 2/3 years by which time it is possible that most of the solvents required like butanol, butyl acetate, MIBK, isopropyl alcohol, MEK etc. will be available locally. Even the indigenously available raw materials require to be allocated among the manufacturing units more equitably than at present. The allocations should be on the basis of production capacities and actual production during the preceding years. And allocations should be made on the basis of the recommendations of D.G.T.D. This applies to items like sugar, alcohol, dextrose, starch etc.

As regards the equipment for the Pharmaceutical Industries, the position is not at present very satisfactory. Although sufficient facilities exist for indigenous fabrication of various vessels and reactors it is necessary to import stainless steel which is not indigenously available, it is possible to replace in many cases, stainless steel vessels by rubberlined vessels. But this is not always possible. Requirement of stainless steel will have to be allocated in consultation with the various manufacturing units. This could be imported by a central agency and distributed on the basis of the

recommendations of the D.G.T.D. There is sufficient indigenous capacity for fabricating stainless steel vessels and other equipments. Certain chemical processes require glasslined reactors. It may take at least 12/18 months time before the glasslined vessels are made in India and until this time the immediate requirement of the industries has to be obtained by import. We understand that some glass lined vessels are available from rupee payment countries like Hungary and such sources can be utilized profitably.

Another aspect which also needs a very careful consideration is the import of maintenance spares. Since some equipments are of very specialized nature, it will be necessary to import the essential spares from the original manufactures of the equipments. Substitution of high precision spare parts may not be possible for the present. An assessment has to be made of the minimum essential requirement and each industry allocated certain quantum of foreign exchange for such imports. Wherever possible, the old and obsolete imported equipments should be scrapped instead of importing very costly spares for the same and substituted by indigenously available equipments.

To achieve these goals the industry will have to give a higher mark up for research, both basic and applied through its own laboratories as also through the various Government organizations. In other words, by pooling available tools and talents, attempts will have to be made to turn the corner.

All these programmes will, in the initial stages, mean substantially increased costs which will have to be borne by the consumers to some extent. After a couple of years it may be possible to achieve reduction in costs with the stabilization of production and also increased productivity.

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