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APPROPRIATE TECHNOLOGY FOR THE MANUFACTURE OF DRUGS AND PHARMACEUTICALS

PROVISION OF DRUGS BY APPROPRIATE TECHNOLOGY

Background Paper

PROVISION OF DRUGS BY APPROPRIATE TECHNOLOGY

by

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* This paper was prepared by P. Dunnill on behalf of ITDG.

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SUMMARY OF TECHNICAL MATTERS

Technical action towards better provision of drugs must include the establishment of local chemical and pharmaceutical industries. However this will be a slow process in many countries and can be complemented by the encouragement of local compounding of bulk purchased pharmaceuticals. An ITDG project to assist this is described and its relationship to the role of the rural pharmaceutical auxiliary is discussed. (See CURRENT ITDG OBJECTIVES ON DRUG PROVISION.)

SUMMARY OF POSSIBLE RELATED GOVERNMENT ACTIONS

Effective technical assistance in providing drugs is particularly dependent upon government action. ITDG would welcome collaboration on pilot studies of local compounding and the training of pharmaceutical auxiliaries (see CURRENT ITDG OBJECTIVES ON DRUG PROVISION). More generally government action on bulk purchase and efficient importing of appropriate starting materials is important as is co-operative but firm liaison with industry and the medical and pharmaceutical professions.

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INTRODUCTION

1 The attainment of good health is perhaps the most basic requirement of any population. Many factors affect it such as the supply of adequate food and shelter and the provision of efficient water and drainage systems. History suggests that sanitation and vaccination should be given the highest priority in achieving good health for the greatest number of people at the lowest cost. However, there are situations where only the use of drugs can be effective.

2 Food, water, shelter and drainage can generally be provided by local, simple and small-scale operations given the vital input of proper information but many key pharmaceuticals are the products of intrinsically complex processes. Therefore finding ways by which communities other than fully developed ones can be better provided for is particularly difficult. Because of this the exploratory study for ITDG did not make the initial assumption that small scale operation was likely to be advantageous. It gave equal emphasis to conventional industrial production and to smaller scale projects.

3 The first part of the report outlines the technical considerations which lead ITDG to develop its current policy. The objectives of a current project are then described.

With no other products are the technical decisions so influenced by powerful commercial, ethical and social pressures as with drugs. For this reason a brief analysis is given of the ways in which government policies influence the provision of drugs, particularly to poor rural communities.

TECHNICAL FACTORS SHAPING ITDG POLICY

4 For the present purpose drugs may be divided into two classes. First, the traditional local remedies many of which are complex mixtures of plant origin. Second, the modern, 'Western' drugs which are mostly well defined chemicals derived from the petrochemical or fermentation industries. A few traditional materials have in a refined form become important drugs in all countries, for example, quinine, caffeine and ergot. Some of the remaining traditional remedies are comparable to say 'Western' cough and indigestion mixtures in giving comfort but are

not life saving. Greater claims are made for others but their effects, which may depend on the method of administration, are unproven. Without discounting the eventual emergence of further key drugs from traditional local remedies, present needs can only be met with the aid of a small number of modern drugs. The desire to utilize local resources does sometimes seem to be so great that it is put before sound medicine.

The Problem of Supply

5 The problem of providing modern drugs to a local community, often an isolated rural one, in a developing country will be considered in three parts,

1) Provision of chemicals from which the drugs are compounded at the lowest possible cost.

2) Compounding of the drug as a tablet, capsule, injectable, etc. from the chemicals at the lowest possible cost.

3) The provision of the drug to an individual patient with the maximum regard to local circumstances.

Production of Basic Chemicals

6 Few developing countries yet have the ability to produce the range of basic chemicals needed for their key drug requirements. Some like India are approaching this capability. The best that many others can expect in the next decade is the ability to manufacture selected basic chemicals from local raw materials. Coal and oil are obviously being used in this way but the production of solvents by fermentation in countries rich in sugar and starch resources is also important and is saving foreign currency even if it is not strictly economic.

7 Where imports are essential it is evident that only by being better technically and economically informed about world chemical supplies and by exerting a greater degree of central government control will developing countries obtain imported chemicals at the lowest possible cost.

8 All countries will progress when possible from the purchase of the chemicals which constitute the active ingredients of drugs to the purchase of simpler, cheaper, chemicals from which the ingredients can be made. Their sources of information to do this are local subsidiaries

of foreign companies, international agencies such as UNIDO and independent consultants. Organizations like ITDG have a role in providing information about the use of local raw materials and small scale production of basic chemicals.

9 Countries such as Egypt which have progressed some considerable way in the production of basic chemicals have experienced difficulty in preparing materials of the exceptional quality needed for pharmaceuticals and this will be a general problem. Quality control of the chemical steps by which the active ingredients of a drug are prepared is crucial and the requirement for expensive analytical equipment cannot be evaded.

Drugs from Microbial Sources

10 Drugs produced by fermentation, especially the antibiotics, are at first sight attractive for local production in developing countries since the principal starting material may be any number of low cost carbohydrates such as molasses or corn steep liquor. However even here the quality needs to be raised in some instances. Much greater problems are presented by the sophistication of the production process and by the need to obtain special strains of micro-organisms which produce high yields of product. Government involvement may be essential in negotiating for these strains or initiating strain selection in local research institutes and in being prepared to underwrite an unprofitable phase of production. Independent organizations such as ITDG and individuals can help by collecting together basic process design information which will aid countries either in setting up their own plant or more likely in negotiating from a position of greater knowledge for foreign plants and know-how.

11 Given that a government restricts advertising and promotion so that these overheads are cut it seems quite possible that antibiotic production on a smaller scale than is now practised in developed countries would be profitable. However the technology cannot be simplified beyond a certain level and regional rather than local production seems appropriate.

12 If antibiotic fermentation is technically too advanced, a carbohydrate rich country could begin by producing food yeast with technology closely allied to that of brewing to provide B vitamins. One ambitious

programme to combat vitamin deficiency by this means failed on the grounds of consumer resistance to a product of low appeal but a modest local programme closely linked with health clinics where a yeast product would be given with conviction and authority could be better accepted.

Drug Compounding

13 The compounding of drugs in appropriate forms is a field where much more radical change could occur. This step is generally done in large factories in the commercial companies of developed countries. Even small local companies would commonly process say a million tablets a year. However there is ample evidence that factory scale operation is not essential. Hospital preparation of drugs is still practised in a surprisingly large number of institutions. For example even in the USA in the late 1960s some 41% of hospitals surveyed operated a "manufacturing programme". Though drug compounding in the local pharmacy has lost its place in many developed countries, the procedures for sound practice are recorded in the literature and the approach is still used in developing countries with respect to simple remedies.

14 There appear to be no insuperable technical reasons why hand or very small machine compounding of drugs should not be the means of reducing costs and shifting the centre of gravity of manufacturing towards the local community. Quality control at this level would entail maintenance of clean mechanical handling in regulated conditions with regular checking of chemical quality by a regional regulatory laboratory.

15 Quality control is clearly a very sensitive issue on which doctors, conventionally trained pharmacists and industrial producers have strong views and it is an area where government involvement is essential. International agencies can also have a role if they adopt a strictly practical approach. Inter-government co-operation may also reduce costs but this development demands particularly close and harmonious relations.

The Pharmaceutical Auxiliary

16 The third requirement in providing drugs is a suitable method of transfer to the patient. It is increasingly accepted that rural communities most at risk will not have access to fully trained doctors in

the foreseeable future and that local people must be trained as medical auxiliaries to diagnose the more obvious local diseases referring only intractable cases to regional hospitals. It therefore seems sensible to consider making the compounding of drugs from bulk ingredients the responsibility of local people as well. The intention would be to train them locally to avoid the inevitable tendency of people trained in urban centres to gravitate back to them.

17 Pharmaceutical auxiliaries will need training and operation manuals in local languages, and guidance on small scale equipment, some of it hand operated including tablet punches and counters, blenders, mixers and dryers. At present neither suitable manuals nor consumer guides specifically on small equipment are available.

18 The training of pharmaceutical auxiliaries to compound, package, label, and prescribe a very limited number of drugs appears to be the only means of bringing modern life-saving drugs to rural communities. Even in India which has over 2000 drug manufacturing companies, with less then half the market foreign controlled, the population cannot be effectively served by conventional means. The country does require their larger firms to provide a proportion of drug ingredients which they manufacture to small companies for formulation. By analogy governments can elect to ensure supply of even smaller quanitites of material to rural centres for manual or very small-scale mechanical manufacture.

19 The provision of drugs at a rural level seems less likely to compete with powerful commercial interests than is the case in urban areas since the rural market is commercially less attractive. It is fragmented and its inhabitants are unable to afford drugs in the normal way. From the experience of missionary and similar hospitals, patients do not show the resistance to non-brand name drugs which is a problem in commercial pharmacies.

Other technologies needed for drug supply

20 The adequate handling of drugs by rural centres requires a number of other appropriate technologies. The assumption that chemical and biological quality is maintained after despatch of ingredients from a central store depends not only on good stock recycling but also on adequate, low-cost, cool or cold storage. Adequate packaging of drugs

is of great importance especially in tropical conditions. Organizations in developing countries often find, for example, that a lack of suitable local glass bottles restricts preparation of even simple formulations. While strip packaging of individual tablets or capsules is expensive, the preparation of sachets of numbers of tablets by hand-sealing of plastic sheet is already used and refinement of this method to make it more reliable and convenient would be valuable. ITDG and others have operated pilot schemes examining the use of pictorial labels to aid the correct self-administration of drugs since misuse is a major problem.

CURRENT ITDG OBJECTIVES ON DRUG PROVISION

21 Having concluded that small-scale compounding could make a contribution and that pharmaceutical auxiliaries could provide a means of delivery, ITDG is seeking to assist such developments. The UK Ministry of Overseas Development has recently provided funding for a project to survey small-scale pharmaceutical equipment together with a survey of the literature on how such equipment is or has been used. ITDG is also exploring with AHRTAG (Appropriate Health Resources and Technologies Action Group) the issues involved in training pharmaceutical auxiliaries.

22 It is hoped that the resulting catalogue of equipment and bibiography of uses will be of wide interest but ITDG is particularly concerned to see a specific practical outcome. It is therefore interested to collaborate with individual governments or local organizations who are prepared to establish pilot projects. With such pilot projects many of the problems of supply of bulk materials to the rural centre can be circumvented by special measures so that the central issue of local compounding can be tested. The total investment in such pilot studies will be very small so that modification after initial experience should not be a great problem as it can be with major capital investments.

GOVERNMENT ACTIONS INFLUENCING THE PROVISION OF DRUGS

23 Very many reports have been published concerning the ways in which the provision of drugs are influenced by social and political factors. A number of these reports are listed in an accompanying bibliography and this subject will not be re-worked yet again. However a single page (Table 1) is devoted to listing some of these factors simply to emphasise the complexity of the subject. Several ways in which governments can affect strictly technical developments have been outlined in earlier sections.

24 The present section will deal only with those aspects of government policy which relate directly to the local compounding of drugs from constituents imported in bulk and with the employment of rural pharmaceutical auxiliaries.

25 The objective of government policy in this case will be to obtain bulk materials at the lowest cost possible and to transfer them in smaller unit amounts to rural centres with miminal loss of drug activity. At these centres they will provide guidance on compounding, some equipment and regulatory checks on the use of material supplied.

26 The bulk purchase of drugs by non-profit agencies, governments and even groups of governments is becoming well established. Similar approaches are applicable to raw drug components and containers.

27 The efficient importatior of bulk drug components is crucial. Delays in customs clearance and transit will lead to deterioration much more rapidly than for many other commodities.

28 Special warehousing and careful stock recycling are imperative and a central facility for re-packaging into smaller units is required. The technology required is conventional but the organizational problems can be formidable.

29 Delivery to rural areas is often difficult and the work initiated by ITDG/AHRTAG and others, which is supported by WHO, on vaccine transportation has relevance here.

30 It is hoped that the current projects of ITDG on small-scale equipment and ITDG with AHRTAG on pharmaceutical auxiliaries will help to provide a basis for advice to local rural health centres.

31 Close cooperation with government will be essential to ensure that this information is made available in a useful form and in the local language. Therefore ITDG would welcome collaboration with individual governments and local organizations.

TABLE 1 SOME SOCIAL, POLITICAL AND ECONOMIC FACTORS INFLUENCING THE PROVISION OF BASIC DRUGS

1 Need to coordinate national chemical or drug buying to obtain favourable bulk purchase terms.

2 Desirability of persuading companies to produce and package basic but low-profit drugs while allowing them to manufacture some trivial but high-profit drugs and cosmetics.

3 Need to rely heavily on foreign company technical expertise while seeking to change the balance of drug production and packaging.

4 Shortage of servicing facilities for equipment and analytical instruments used in drug production and compounding.

5 Migration of entrepreneurs and skilled persons away from rural areas.

6 Need to persuade doctors to prescribe from limited lists mostly of generic drugs.

7 Resistance of conventionally trained doctors and pharmacists and of local "folk" doctors to the introduction of rural health auxiliaries.

8 The existence of powerful fashions in medicines, for example, the use of multivitamins.

9 Lack of experience in the use of potent synthetic drugs by rural communities and problems of prescribing to largely illiterate communities.

10 Tendency of universities and medical and pharmacy schools to reinforce conventional approaches.

11 Conflict of interest of middle-class urban patients and poor rural ones in terms of drug imports, packaging and health care.

APPENDIX

TECHNOLOGY APPROPRIATE TO DIFFERENT TYPES OF COUNTRIES - BACKGROUND INFORMATION

A common feature of many developing countries is that they are limited in their supply of capital for investment and that they have an under-employed population. It is these features, among others, which have suggested in many fields that small, local, and labour-intensive organizations are more appropriate than very large, capital-intensive and highly automated ones. However, the manufacture of pharmaceuticals provides a very severe test of this viewpoint.

Many of the most useful drugs, such as the antibiotics, are complex chemicals produced by methods which require very precise control. They are potent in action, may have to be taken by injection, and their quality control requires a degree of sophistication which is not easily attained. Pharmaceuticals must be available in stock for rapid prescription and medication may have to proceed for extended periods, so that the product must also remain in an essentially unchanged state for a relatively long time after production.

Governments may accept locally produced buildings of rather limited quality rather than have none for their communities; they may even accept for the treatment of illness the use of rather crude local remedies which have been long established. However, they are not likely to accept modern pharmaceuticals of a quality lower than those known to be produced in the most advanced facilities.

On occasions even a high grade pharmaceutical may be withdrawn because it is perceived to be inferior. One developing country banned the use of an imported vaccine against a common disease which was frequently fatal there. In the country of production the vaccine had been withdrawn because it very occasionally caused encephalitis (brain damage) and the disease was mild.* A government will naturally feel that what is not good enough for a so-called developed country is not good enough for its own community.

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*Most examples are of a sensitive description and have been made deliberately non-attributable. Instead, for countries cited in examples a UNIDO classification of the countries by pharmaceutical capability has been adopted here, together with a broad indication of the geographical region.

Concerning the degree of under-employment in developing countries, it is necessary to ask first whether an abundance of labour is of value in the controlled production of complex substances such as pharmaceuticals. The answer is that it probably is not. Professor A.E. Humphrey of the University of Pennsylvania has encouraged the development of fermenters even more highly instrumented than those used in current antibiotics production because in his experience the employment of operators of limited training or motivation to measure and control important parameters leads to serious errors. These errors, if anything, grow with the number of personnel committed to control. Taken in isolation, this argues for large centralized production facilities with highly trained staff and fairly sophisticated instrumentation. Most of the pharmaceuticals manufactured in developing countries are indeed produced in this way in foreign-owned companies. The past record suggests that this approach has not provided adequate amounts of pharmaceuticals for those sectors of the community most in need.

OPTIONS OPEN TO DEVELOPING COUNTRIES

In assessing the options open it is necessary to define the general state of a particular country with respect to the provision of pharmaceuticals. A UNIDO report of 1972 (UNIDO document ITD 82) accomplished this.

The United Nations Industrial Development Organization (UNIDO) prefaced its report by an analysis of trends in the pharmaceutical industries in industrialized countries. Here the processing of natural products (5% of total) has been largely superseded by the large-scale manufacture of highly complex chemical (55%) and biological (40%) compounds made to exact specifications. Research and development expenditure by pharmaceutical companies in the developed market economies is quoted as $500 million in 1963, $750 million in 1972 and probably $2000 million by 1980. While about half the important drugs are still protected by patent, the patents of many most likely to be of interest to developing countries have lapsed or will shortly expire.

Promotional expenditures on new drugs is quoted as typically 15% of turnover. The growth in exports from developed countries from 1955 to

1972 averaged 153% with a maximum of 435% by the Federal Republic of Germany. A medium sized firm in an industrialized country is estimated to have a turnover of £50-100 million, employing upwards of 2000 people, and a sales to investment ratio of 3 to 4. It is suggested that only some smaller firms producing, say $300,000-400,000 of materials per year, employing only about 50 people and with a sales to investment ratio of around 2 may survive. This will be due to the wide variety of demand for drugs and to the fact that economies of scale are not particularly marked in drug production (although they are in research and marketing).

A Stanford Research Institute study quoted gives the 1967 production of pharmaceuticals at manufacturers' prices (in millions of dollars) as:

USA and Canada	5,050	(33.2% of total)
Latin America	860	(5.6% ")
Japan	2,290	(10.3% ")
Other Asian	730	(4.8% ")
Western Europe	4,760	(31.3% ")
Eastern Europe	2,015	(13.3% ")
Africa	75	(0.5% ")
Oceania	150	(1.0% ")

The proportions are not expected to change greatly by 1980 though world production is predicted to rise from $15,200 million to $45,000 million. At present the industrialized countries are estimated to account for 88% of the world's production of pharmaceuticals and about 85% of the consumption and again the general position is not expected to change radically during the 1970s.

With respect to the developing countries it is estimated that three-quarters of the total drug manufacturing operations in developing countries takes place in 12 countries and the vast majority of others have either few or no drug manufacturing facilities. Following from this 4 categories of country are suggested for the discussion of production of pharmaceuticals.

CATEGORY I. Countries with no manufacture of pharmaceutical products. This includes 20-30 small countries, mostly engaged in traditional agriculture with a sizeable subsistence or non-market sector and a GNP probably under $1000 million and under $100 per capita. This included in 1972 Botswana, Chad, Dahomey, Guinea, Haiti, Laos, Niger, Western Samoa, and Yemen. With a ratio of doctor to population of less than 1 to 10,000

there is a relatively small demand for drugs, probably under $10.50 per capita or $1 million total per annum. UNIDO believes this renders modern manufacturing activities uneconomical and this situation is expected to be maintained during the 1970s. In view of this conclusion, a number of proposals are made to improve the supply of pharmaceuticals. These include collection of data on therapeutic needs, establishment of a control laboratory or licensing system to control the quality of imports, training schemes for pharmacists, bulk purchase by government and local formulation.

CATEGORY II. Some 30-40 countries in this category have reached the earliest stages of developing their own pharmaceutical industries. They included in 1972 Ceylon, Nigeria, Ivory Coast, Senegal, Thailand, with possibly 1 doctor per 4-5000 people and a drug demand of about $5 million per annum. Some 10-50% of the drugs will be formulated and/or packaged in the country in small workshops or factories built with public funds or foreign capital. Suggested actions for the 1970s include: collection of data to permit restricting the proliferation of equivalent brands, increased repackaging of bulk imports, planning for increased local production, consideration of vaccine production, encouragement of foreign company collaboration and a search for cooperation with neighbouring countries such as has been studied by UNIDO in the East African Community.

CATEGORY III. The GNP per capita in this category will usually be $200-300 with a total GNP of $5000-10,000 million. They have underdeveloped rural areas but considerable infrastructure, and urban areas with a good deal of industry. They included in 1972, Chile, Colombia, Iran, Republic of Korea, Malaysia, Peru, Philippines, Singapore and Venezuela. The doctor-to-population ratio may be as low as 1 to 2000 although most are concentrated in towns. Total pharmaceutical demand ranges from $5 million to $70 million with a per capita consumption from less than $1 to nearly $6. Because of large populations the total demand may support a wide range of pharmaceutical sectors, mostly final processing of bulk imports.

In a single country study, UNIDO has recommended that dispersed tabletting and formulating facilities should be concentrated in one modern installation. A typical plant capable of producing annually 200 million coated or uncoated tablets with facilities for liquid manufacture and

possible expansion into ointments would cost $600-700,000 (1972). This includes air conditioning, 700 sq. metre warehouse, 600 sq. metre laboratory and office. Working capital was estimated to require perhaps another $250,000.

The report suggests that most basic active ingredients, for example synthetic organic chemicals and antibiotics, can be stored for long periods and a small multi-purpose plant may permit economic operation. A typical plant making a total of about 250 tons per annum of various intermediates such as sulfa drugs, analgesics and sedatives was estimated to cost about $1 million (1972) plus $0.5 million working capital.

Other suggestions include reduced/patent protection to companies. The report notes that two category IV countries in recent years have proposed to reduce protection, e.g. by cutting the life of a patent and allowing materials for government requirement to be manufactured irrespective of patent.

CATEGORY IV. These countries are stated to be able to produce drugs comparable to those on the/world market and have the means of effectively distributing their products. They include the A.R.E., Argentina, Brazil, India and Mexico. It is the relatively large size of their total national market for ethical pharmaceutical products, $60 - 200 million, rather than uniformly high average levels of per capita consumption which are taken to place the countries in this category. Most domestic requirements are stated to be satisfied by local manufacture, although specialities representing 10-20% of consumption may still be imported.

Recommendations for the 1970s include increasing the size and scope of research with a view to developing original drugs particularly suited to the country's needs, regrouping with a view to increasing efficiency and reducing production costs with the aim of creating units able to stand up to international competition.

MANUFACTURE OF PHARMACEUTICAL RAW MATERIALS

The precursors of many modern drugs are fine chemicals which are converted in pharmaceutical processing into tablets, capsules, injectables and other preparations suitable for administration in therapy. The variety of fine chemicals required is very great and clearly their quality must be as high as the quality of the preparations into which they are to be formulated. In these circumstances few developing countries will be in a position to manufacture the necessary range of fine chemicals. For example, a recent official report from a Category II country in Asia states: "We do not envisage the setting up of fine chemical industry for many years to come as this requires a sophisticated chemical industry which does not exist".

The production of drugs directly from local natural products has been the subject of considerable interest in both the developing and developed countries. The United Nations Industrial Development Organization (UNIDO) has as one of its five pharmaceutical programmes the "Production of raw materials for pharmaceuticals", i.e. extracts from medicinal plants and utilization of slaughterhouse wastes.

The production of drugs from local natural products is one of the most difficult aspects of pharmaceuticals supply to assess. Aside from a few well known natural drugs and precursors which have been examined in detail in developed countries, there are a vast number of natural materials for which healing properties are claimed, but on which little controlled study has been done. The extraordinary range of curative properties claimed for some materials might seem unrealistic in the light of currently accepted Western practice, but it must be admitted that the natural materials are complex mixtures unlike most modern drugs. In addition, where no modern drugs have been available, the use of local natural materials with long historical and often religious associations is likely to involve an element of healing by faith. Modern drug trials show this to be a powerful element in the treatment of at least some physical conditions.

The increased production of those natural drugs and precursors of defined value and their complete processing in the country of origin is certainly to be encouraged. Complete processing will avoid loss of foreign exchange in re-purchasing the final more expensive product from a foreign manufacturing country. It may even provide a source of high-cost pharma-

ceutical exports. The controlled testing of curative properties of local traditional drugs is perhaps desirable in view of their widely established use. However, the task is one of great expense. It seems likely that, in most instances at least, the chances of a successful outcome in producing drugs with clear "physical" curative value will be small. The advanced pharmaceutical companies of the world do not lightly dismiss promising sources of important new drugs. While again the complexity and variability of the natural materials could account for some failure to recognise important materials, this only further emphasizes the difficulty and expense in assessing their potential. It would, however, be hypocritical to suggest that people of other countries should abandon the use of natural materials of "unproven" value in view of the equivalent use, for example, of digestive aids in Western countries.

It would be useful to have local assessments of those natural materials which, though not as accepted as caffeine, ergot, quinine or senna, do seem to have fairly definite benefits. At present there appears to be a tendency to produce very large lists of natural materials with no such classification of the confidence in their efficacy.

The studies of medicinal plants in India and Pakistan serve to illustrate some of the points made above (Baquar and Tasnif, 1967; Zaman and Khan, 1970; Zaman, Khan and Ahmed, 1971). Kempanna (1974) has recently surveyed the prospects for medicinal plants in India. In 1970-71, India exported drugs valued at Rs 48 million ($5,720,000, 1975 conversion). To this export, psyllium- and senna-based products alone contributed Rs 33 million ($3,960,000). In the same year, crude drugs, alkaloids and other derivatives from vegetables worth Rs 14 million ($1,661,000) were imported. This indicates the extent to which imports might be substituted for. Kempanna cites the rejuvenation of cinchona plantations (for quinine) through improved planting systems, better management practices, optimising extraction techniques, etc. as the kind of approach that is applicable to sources of drugs of proven value. He notes that of 200 tonnes of caffeine available from the country's 8000 tonnes of tea wastes per annum, only 80 tonnes are produced. Huge quantities of tea waste are apparently burned as a measure of waste disposal. The demand for diosgenin as a precursor of steroid hormones has led to the finding of several Dioscorea species rich in this material. The annual turnover on pharmaceuticals in India was Rs 2000 million ($237,600,000) in 1972, but only 1.6% of this was spent on research. About 98% of

research expenditure was on chemistry and clinical aspects of pharmaceuticals, with only 2% for studies of the cultivation of suitable plants. However, since then a coordinated national programme has begun to isolate improved plants and preserve collections as forests and jungles disappear. Kempanna concludes by arguing the need for careful planning to integrate the growing of medicinal plants with other food crops, better marketing to eliminate the speculative trade, and better quality control. Agricultural polytechnics (the proposed Krishi Vigyan Kendras) represent local agencies for spreading the necessary technical knowledge.

The preparation of vaccines and the production of antibiotics from microorganisms by fermentation will be considered here as the biological equivalent of fine chemicals manufacture. The technology demanded, particularly for vaccine preparation, is even more advanced than that for fine chemicals. In developed countries the preparation of vaccines does not involve very large-scale operation but the degree of expertise and the exceptional quality control requirements would seem to make this field too difficult to approach by any but the most advanced technology. In one Category II country in Central Asia a vaccine and sera institute is already functioning under the financial auspices of a public health institute. An enlarged, independent institute is under construction with an estimated capital development cost of about $3.3 million. This is relatively a very large project for the country concerned.

Fermentation is operated on an extremely large scale (up to 500 m^3). There is therefore ample scope for scale reduction. However, while the fermentative stage does not present the hazards of live virus handling faced in some vaccine operations, the technology is still very demanding. For example, in penicillin fermentation if the culture is contaminated at any point over a 6-8 day period, not only may the contaminating organism utilise nutrient and synthesize unacceptable substances, but enzymes may be produced which totally degrade the penicillin. In these 8 days with a vessel of 120 m^3, a volume of sterile air of 1,380,000 m^3 will be required for growth and power totalling 43,000 kw/hr will be required for agitation. The surface finish and sealing of the whole fermenter and ancillary fittings must be such that effective sterilization can be achieved and maintained during the same prolonged period. Construction is normally of stainless steel, requiring specialist fabrication, but recently a 3000 litre plastic

fermenter vessel has been tested (for other applications) where the agitation as well as the aeration for respiration is brought about by compressed air. Following this work, a 20,000 litre vessel of plastic-glass fibre inside standard concrete pipe sections is planned.

The production and extraction of some other antibiotics produced by fermentation is not quite as difficult. However, given that for all antibiotics production some very well trained and experienced staff are required, there is little incentive to operate a small-scale facility. The question of how small a scale is technically worthwhile will require a detailed analysis. The assessment of economic feasibility will be unique to each case. Nevertheless, the developing countries currently face great difficulty in ensuring adequate supplies. A doctor working in a Category II country in Africa states that antibiotics account for up to 30% of the annual budget. Perlman (1974), reviewing the fermentation industries, notes that penicillin G wholesale prices rose 50% in 1973-74. In these circumstances countries with adequate capital resources may be expected to set up medium-sized fermentation and production facilities.

MANUFACTURE OF PHARMACEUTICALS FROM RAW MATERIALS

The manufacture of pharmaceuticals from fine chemicals and the formulation of the final drug represent an area where greater use could be made of local industry. The scales of manufacture which are in operation in different developing countries range from very small with less than 10 staff to the full industrial level. Some problems such as quality control are common to all scales, but the manufacturing problems are rather different. Very small-scale manufacture may in the limit involve just the operations of compounding of a kind which are undertaken in hospital pharmacies. The latter will be dealt with in the next section since it can be undertaken in establishments which are not strictly manufacturers.

Table A1 summarises the facilities of a modest non-governmental facility in a Category I country in Africa. It processes imported materials to produce the 39 preparations listed in Table A2. "The facility processes about one 40-litre batch of liquids per working day. The tablet machine works all day most days. About one million capsules are produced annually. One trained worker from Europe and one university trained African pharmacist control operations and two dependable and experienced secondary-level local men do most of the manufacturing work. Others assist in packaging, cleaning, etc. The plant is in fact under-utilized and production could be greatly increased with little or no additional outlay for plant." The organization is limited politically to supplying its own hospitals and clinics.

The majority of full industrial-scale plants in developing countries are foreign-owned and are not the subject of this technical section. The establishment of equivalent plants locally owned, probably by governments, is likely to be achieved by licensing know-how. It seems probable that potential purchasers of plant and process know-how would be placed in a more reasonable negotiating position by the possession of basic design information provided by international agencies or ITDG. Plant manufacturers in developed countries also have an interest in providing general process data in so far as confidentiality agreements allow.

COMPOUNDING OF PHARMACEUTICALS

It was noted in the previous section that the borderline between small-

scale manufacture and the compounding of pharmaceuticals in what are not primarily manufacturing establishments is ill-defined. The potential importance of compounding in hospitals, clinics and pharmacies is, however, so important that is is worthwhile examining what can be done to encourage and improve it. Two extreme examples illustrate this.

The section of a report dealing with availability of drugs in a Category II country in Central Asia notes that: "The pharmacy network of about 600 outlets, together with the bazaar merchants and others who sell drugs, represents a major, under-utilized group of health workers already active in every community of any size. The Ministry of Health, by exercising simple regulatory authority, may well be able to improve the availability and quality of health care through simplification of drugs sold generically."

In the USA, statistical data on manufacturing or bulk compounding in hospitals (Francke et al., 1966) revealed that approximately 41% of 1853 hospital pharmacies operate a manufacturing programme. The survey further demonstrated that 78% of the sample group prepared galenical pharmaceuticals; 74% products not commercially available; 42% sterile solutions for topical use; 33% sterile pharmaceuticals such as collyria, ointments, etc.; and 30% small volume injectable solutions. In addition, the same survey showed that hospital pharmacists were also active in the preparation of sterile products such as surgical irrigating fluids, large volume injectable solutions, and special sterile products for investigational use. This volume of hospital manufacturing may seem surprising, particularly when viewed in the light of the size of the American pharmaceutical industry. It probably reflects a desire to use skills otherwise wasted rather than economic advantage.

PACKAGING OF PHARMACEUTICALS

Concern with packaging and storage methods for pharmaceuticals affects all distributors of pharmaceuticals of whatever level of development.

In the case of drug supply from a developed country or local manufacture in an advanced plant, concern will be centred upon the suitability of the packaging in severe climatic conditions with the possibility of poor handling. Most foreign companies producing drugs for tropical countries are aware of this problem. Small manufacturing facilities and hospital pharmacies must devise their own appropriate packaging systems which not only satisfy local conditions but are cheap and simple to operate. A variety of approaches are used.

A voluntary agency worker in a Category II country in Africa noted in 1973 that: "Working on a limited budget, conventional packaging materials for dispensing medicine are normally too costly. Envelopes or paper cartons are not adequate protection for drugs in a tropical climate. A relatively cheap alternative used for packing tablets and capsules is plastic sheeting, made into sachets using a heat sealing machine. For solutions and mixtures, plastic bottles are used. Storage trials under tropical conditions need to be carried out to find the most acceptable. There may be possible reactions between the drug and the plastic. Medical staff are asked if possible to prescribe pre-packs which usually are a complete course of treatment or a month's supply. Pre-packing of tablets is at present done by hand using one person nearly full-time and three of the hospital outpatient interpreters on the non-clinic days. This job is very tedious and there is much scope for design of a simple mechanically operated tablet-counting machine".

A similar comment from a relief agency in a Category I country in Far East Asia notes that, "because of the high humidity, rain and mode of life we found that it was not sufficient protection to place the tablets and capsules especially in envelopes." Re-cleaned plastic vials from American church organizations were satisfactory but were subject to customs requirements on the used plastic material. "Plastic happens to be quite an industry but they have not yet produced medical vials. All in all, though, this method proved to be the most satisfactory since it

protects the patient's medicine after the first dose, which we felt the plastic bag did not."

Another worker in a Category I country in Africa remarks that: "There are no locally made screw cap glass bottles. We used locally made beverage type bottles in the 200 ml to 1 litre range. The local plastics industry could produce containers for us, but we lack the sophistication for testing such containers with our products and we doubt that the plastic product would be of consistent quality. We package capsules and tablets mostly in bulk in sealed bags of 1000's and pack them in tins. We are not presently filling ointment tubes as the cost is high. Most of our products are dispensed from these bulk packages into paper or plastic containers for the patient at the time of use." A 1974 report of a non-profit organization suggests a supply from UNICEF of 20,000 1-litre bottles at an approximate cost of $10 - 20,000 with shipping.

Rather in contrast to these comments is a report (Djerassi, 1974) that "in China - - which is probably producing enough oral contraceptives for 20 million people - - one form of the 'pill' is a small package of perforated paper strips on which the chemicals have been deposited. The monthly sheet contains 22 squares, each about one-third the size of a postage stamp. The woman just tears off one of the bits of water-soluble paper and chews it for her daily dose. This 'paper pill' has great advantages, particularly on a mass scale. It saves pills, bottles, and the machinery for making them."

A field worker in a Category II African country has reported on the problems of adequate labelling: "A sample survey in the outpatients' department showed that over 50% of returning patients had taken one or more of their drugs wrongly. This perhaps is not surprising, as a large proportion of the patients are illiterate and only able to speak one or two of the many tribal languages."

STORAGE OF PHARMACEUTICALS

The problems of storage of pharmaceuticals apply to all types, whether imported or locally produced. The following examples will illustrate how critical is correct storage. In a central Asian Category II country, a report notes: "The typical (drugs) warehouse is a dank, decrepit

room kept locked and sealed by a storekeeper who has assumed personal liability for the material entrusted to him in return for his salary. This arrangement has several shortcomings: since the storekeeper is never on the premises, he must first be located. If he is sick or on leave, no material can be taken out. Long delays are not uncommon. The storekeepers have very little experience or familiarity with the proper identification, storage or handling of medical and technical supplies. Due to general disorganization of its warehouses the government incurs substantial losses due to spoilage of medicines and food, damaged equipment, and materials which simply cannot be found."

A southern Asian Category II government report on a visit to the government medical stores notes that a "deplorable state of affairs" was found, "resulting in near breakdown of their procedures - - indenting, receiving, storing, record keeping and supply of drugs to institutions." Several reports remark on the lack of stock cycling and its consequences. Problems with small local establishments are different but considerable. A field worker in West Africa reports that "the air conditioned store is kept at a mean temperature of 70-75°F. Although a worthwhile investment, air conditioning is still an expensive item. Other pharmacists from West Africa have found this less important." Another pharmacist processing pharmaceuticals in Northern Africa deals with the storage problem as best he can by the use of conservative expiration dates.

QUALITY CONTROL

Among the technologies needed by developing countries, the requirements of pharmaceutical products for stringent quality control are probably uniquely demanding.

The World Health Organization has been very active in establishing internationally recognized standards of quality for pharmaceuticals and especially vaccines (Matthews, 1972). It has laid down desirable standards with respect to manufacturing personnel, premises, equipment, sanitation, manufacturing operations, labelling, packaging and quality control.

Unfortunately in many instances it is the difficulty of achieving these

standards rather than ignorance of what is desirable that is the central problem. For example, the leader of a small African processing unit notes that: "Problems of quality control are primarily due to lack of skilled workers. We would try to up-grade facilities if we had the expertise. Also our operation is small for supporting a good quality control facility." The latter feature is common to all instrumental facilities associated with production plants. The instrument costs, for example, on a small fermenter may be much greater than the cost of the vessel but will be fairly insignificant in relation to a 400,000-litre vessel for which they will provide the same precise control. Regional rather than local quality control laboratories may represent the most desirable goal, although once again this will frequently be a political and not a technical problem.

The same leader of a non-governmental African facility describes his own situation thus: "We are building up our range of equipment for the quality control laboratory (which is humidity controlled) but, even so, it will be a very modest laboratory for the foreseeable future. We plan to do aqueous and non-aqueous titrations, pH readings, other ordinary chemical and gravimetric tests, etc. Our range of capabilities will stop short of spectrophotometric determinations, bio-assays, most chromatographic determinations, and all kinds of animal tests."

A muchmore developed Category II Asian country stated in a recent official report that: "This aspect (quality control) has been most neglected. Although private and public drugs are said to be tested for quality before they are shipped it is not known whether the drugs actually conform to standards when they arrive in the country. It is also not known whether the drugs retain their quality six months and one year after they have been stored under the conditions of temperature and humidity prevailing in private and government drug stores.... The establishment of a quality control laboratory for testing pharmaceuticals in this country is urgent and essential." In commenting on the type of controls needed, the report notes that: "In quality testing of drugs 70% is chemical analysis 20% is microbiological analysis and 10% is pharmacological. The quality control laboratory (under construction) will restrict itself to chemical testing for some years."

The field of quality control is one where labour intensive methods could

be used in place of expensive automation but, since this activity is the guarantee of standards of operation throughout manufacture and distribution, quite high technical proficiency and motivation are important.

LARGE-SCALE VERSUS SMALL-SCALE PRODUCTION - THE WRONG QUESTION

Industrial producers in developed countries must be governed by strict commercial interests, so the greatest and fastest gains will often be made by assisting these industries to see profit in new modes of operation or business which happen to lead to cheaper drug supply. Much has been made of the undoubted differential between the costs of proprietary medicines and their exact generic equivalents. It may be that, with the increasing identification and general recognition of the few most basic drugs and the vast market represented by those who cannot afford proprietary drugs, companies will increasingly use the economies of very large-scale operation to supply their proprietary products at generic prices, or to supply generic drugs very cheaply. They are likely to find that this policy will only work if a single "premier" product is marketed to all. The concept of separate cheap medicine for the poor is, as in the food field, likely to provoke a customer resistance that would prevent the opening up of a total market more profitable than the present one which is limited to the comparatively rich. The initial marketing effort may be more laborious with a narrower profit margin and may require the use of new types of local pharmaceutical auxiliaries. Here, however, is an instance where the surplus of modestly educated people in many of the developing countries, if simply but adequately trained, could represent an asset not available elsewhere. Appropriate technology studies have a role in provoking discussion of such questions and the economies involved as much as in seeking small-scale production.

With respect to small-scale local production of generic medicines as alternatives to proprietary equivalents or mass-produced foreign generic products, it must certainly be borne in mind that a switch in multi-national company policy of the kind mentioned above could destroy the commercial viability of a small-scale plant which was,

in any case, profitable only in the artificial sense of saving foreign exchange.

In an introductory paper to the Delhi meeting for ITDG, "Appropriate Industrial Technology: An Integrated Approach", Frost has stressed the need to relate appropriate small-scale ventures to large-scale ones. This is certainly valid for drugs. If countries have centralized facilities these can be asked to devote part of their activity to the packaging of drug components into lots which are suitable for despatch and local compounding. The gradual development of centralized facilities of increasing complexity is not to be regarded as excluding local small-scale compounding, or vice versa. In the provision of drugs, appropriate technology means giving equal weight to centralized large-scale and localized small-scale operations.

TABLE A1 A SMALL NON-GOVERNMENTAL PROCESSING FACILITY IN AFRICA

1 None of the equipment is large so the rooms are small. The rooms, according to function, are as follows:

(a) quarantine storage for incoming raw materials and batch samples
(b) raw material storage
(c) weighing and batching
(d) mixing, granulating, drying
(e) compressing (tabletting)
(f) packaging
(g) capsuling
(h) ointment and suppository processing
(i) liquids processing
(j) washing-up facilities
(k) quality control laboratory
(l) office

2 For equipment the following are used:

(a) Stainless steel kettles for liquids with batch capacity up to 40 litres. There are now kettles of about 100 litre capacity and a motor-driven filter. Small, propeller-type electric powered stirrers are used. Various types of small restaurant-type electric mixers are employed for making pastes for suspensions. For bottling, there is a hand-operated self-metering filler and a hand-operated capping machine.

(b) The wet and dry granulation and direct compression techniques are used for tabletting. For powder blending it is hoped to acquire a drum-type blender. Also expected soon is a small oscillating granulator. At present large stainless steel sieves are used and the material is processed by hand. Drying of granules is accomplished in a home-made cabinet with a capacity of about 25 kg. Compression is by a single punch machine.

(c) For ointments either the ingredients are stirred in after melting the base or, where milling is required, a small Erweka mill is used.

(d) A small capsule-filling device was recently purchased. The capsules or materials for this operation had not yet been received. This device is reputed to have an output of about 12,000 to 15,000 capsules per shift with one operator.

3 In four rooms of the new facility there will be humidity control.

4 Spares are a problem. Both foresight and capital are needed to stock sufficient spares.

TABLE A2 PHARMACEUTICALS PROCESSED IN THE FACILITY SUMMARIZED IN TABLE A1

1 Antist tablets 4 mgm (chlorpheniramine maleate)
2 Whitfield's ointment
3 Baby aspirin 75 mgm tablets
4 Carbarsone tablets 250 mgm
5 Chlorpromazine 25 mgm tablets
6 Calcium gluconate tablets
7 Diazepam 5 mgm and 10 mgm tablets
8 Sulfanilamide ointment
9 Diethylcarbamazine 50 mgm tablets (hetrazine)
10 Folic acid 5 mgm tablets
11 DDS tablets 5 mgm, 10 mgm, 25 mgm, 1.25 mgm
12 Prednisolone-di-iodoquine cream
13 Cherry cough syrup
14 Neomycin wound powder
15 Paracetamol tablets 500 mgm
16 Promethazine tablets 25 mgm (Daraprim)
17 Phenobarbital and atropine tablets
18 Streptoguanine tablets
19 Streptoguanine powder
20 Sim San (benzalkonium chloride)
21 Benzyl benzoate application
22 Chloramphenicol syrup
23 Chloroquine syrup
24 Citrazine syrup (piperazine citrate syrup)
25 Codeine cough syrup - adult use
26 Codeine cough mixture - children's use
27 Diphenhydramine expectorant
28 Elixir terpin hydrate with codeine
29 Gripe water
30 Kaolin and pectin
31 Paracetamol elixir
32 Phenobarbital elixir
33 Promethazine syrup
34 Sulfa dur suspension (sulfamethoxy pyridazine suspension)
35 Triple sulfa suspension
36 Vitamul syrup (multiple vitamin syrup)
37 Scabex ointment (gamma benzene hexachloride)
38 Icthyol ointment
39 Analgesic balm ointment

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