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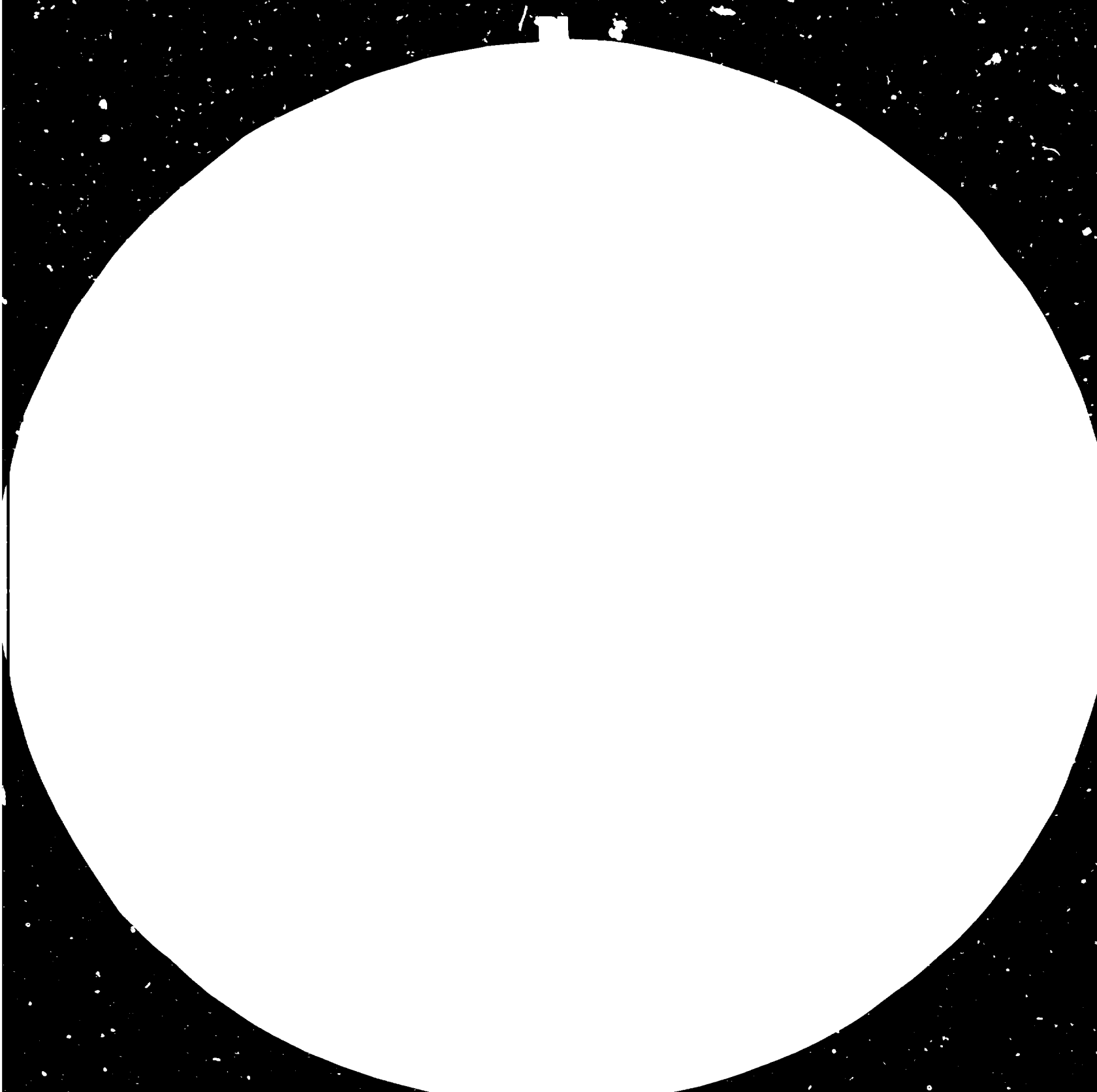
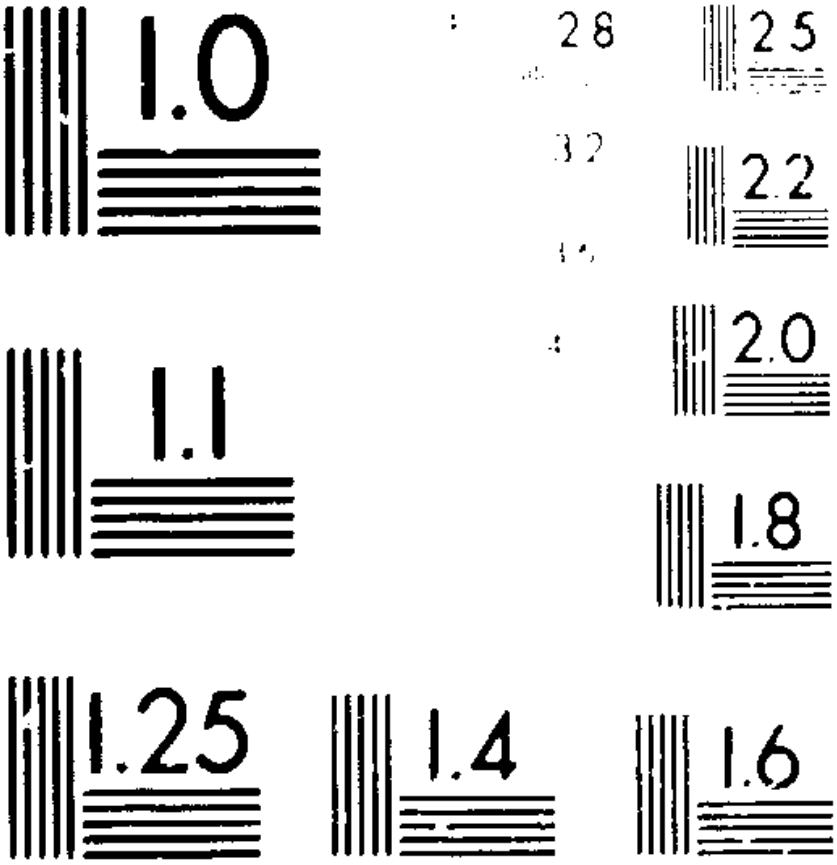
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org





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HOW TO ESTABLISH A PHARMACEUTICAL INDUSTRY IN DEVELOPING COUNTRIES*

prepared by

Pharmaceutical Industries Unit
Chemical Industries Branch
Division of Industrial Operations

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1. Introduction

Of the 124 million children born in 1981, it was predicted that 13 million would die before their first birthday. In Africa and Asia, a half million women die yearly due to child bearing and child delivery. An estimated 340 million people in the developing countries are disabled, or about 1 on 10 of the population. In developing countries, only 20 to 25 per cent of the population have access to health services.

In 1979, in developed country 8% of the GNP was spend on health care expenditure, while this figure in developing countries was 1 to 2%. In developed countries approximately 10% of the health budget goes on drugs, which figure in developing countries 50% or more (US$ 75 and 1.5 per capita) each year respectively.

Africa as a whole accounts for only 0.5% of the world pharmaceutical production, and 3% of consumption, but its population is about 10% of the world population.

From the above statistical data, one can clearly understand that even the insufficient medical care with low coverage of population absorbs a significant proportion of both government expenditure and family budgets. Governments of developing countries are actively seeking ways of controlling costs and increasing efficiency. The health economics has become attractive to them since it could help to improve the allocation of health resources and increase their efficiency. At the same time, the health status of a population can itself influence economic progress. Health programmes have, therefore, become a part of a comprehensive strategy aimed at improving the social and economic welfare of developing countries.

But how can the costs of health expenditure be controlled? How can the scarce foreign exchange be used more efficiently? What could be the first step of action? Since, proportionally the largest category of the health expenditure is the amount which is going on drugs, it seems obvious that by controlling the costs for drugs and ensuring their efficient and, at the same time, economic administration could be one of the alternatives to answer the above questions.

The development of pharmaceutical industry should not remain a desire, it is within the capability of almost all developing countries. Even the least developed countries and the Sub- Saharan African countries, which are especially far behind in developing their domestic pharmaceutical industry can turn bulk drugs into dosage forms and package them for the local market. The technology involved in the later stages of pharmaceutical production is relatively easy to obtain and absorb. Since the development of pharmaceutical industry is a realistic objective for developing countries. one should ask which are the benefits of such a development. The answer is convertible currency savings by the control of imports. Secondary factors are the notion of self-sufficiency, which may be attractiv for strategic reasons and the number of jobs provided by the industry.

Based on the experiences in developing countries, the prerequisites for the development of a pharmaceutical industry seem to be not only a sufficiently large national market (according to some estimates 3 million customers would be the minimum)nor the availability of skilled manpower. What is crucial is the government's political decision to promote the development of national pharmaceutical industry. This policy can be referred as pharmaceutical policy and it includes the drug policy and pharmaceutical industrial policy.

Based on the pharmaceutical policy, the strategy for the development of pharmaceutical industry can be established. At this stage a technical and economic feasibility study should be prepared to select the best alternative for the plan of action. (It should be noted that feasibility studies can also be carried out in advance of the policy making.) The plan of action gives the obligations and responsibilities of all parties concerned and the schedule of implementation. The engineering phase of the project can start according to the recommendations of the feasibility study. During the same period the training of local personnel should commence. Finally, after the completion of engineering phase, the manufacturing operations can start.

Here we are. How to establish pharmaceutical industry in developing countries? The aim of this paper is to give guidance from the pharmaceutical policy making through the period of the feasibility studies and engineering operations to start of manufacture, by highlighting some aspects which could have particular relevance to the developing countries to establish pharmaceutical industry.

2. Aspects considered in pharmaceutical policies for developing countries

Many developing countries are unable to secure the drugs they need at prices they can afford. Contrary to this, these countries often spend their scanty resources for useless, unnecessary and at times harmful drugs. The governments of many developing countries have no control over the price of pharmaceutical raw and packaging material which contribute generally more than 60% of the prices of the finished product and similarly they have no provision for regulating either technology transfer or licensing agreement with foreign companies.

To overcome the above and many other constraints, national pharmaceutical policies should be formulated in developing countries. Any pharmaceutical policy should serve as complex multidisciplinary approach to get and keep the present disorganized situation under control.

The two basic elements of a pharmaceutical policy are:

1. the drug policy based on an economic approach ofhealth programmes; and
2. the policy for pharmaceutical industry based on a techno-economic approach

Several developing countries, notably Bangladesh, Cuba, Egypt, India, Mozambique, Pakistan, Sri Lanka, etc. have formulated their own national pharmaceutical policies.

The principal elements of a drug policy have to be chosen to reduce or at least not to increase expenditure on drugs, while at the same time to increase their availability to those in greatest need: in other words to provide higher coverage of the population. The principal elements of a drug policy for developing countries can be as follows;

1. the control of drug procurement and/or importation
2. the control of drug distribution
3. promotion of basic and essential drugs and elimination of ineffective and inappropriate preparations
4. promition and use of generic rather than brand bames for drugs
5. promotion of preventive medicines against curative drugs
6. the control of drug pricing
7. creation or adaptation of institutions to promote pharmaceutical policy including dissemination of information about the correct use of drugs
8. the creation of national control authority and establishment of national control laboratory
9. the establishment of national pharmacopoeia or adoption of any well-known pharmacopoeia
10. the establishment of domestic pharmaceutical industry
11. the regulation of technology transfer and licensing agreement with foreign companies; and
12 research and development of drugs for local health care based on medicinal plants

It should be noted that the above list of principal elements of a drug policy is far from complete and the weight of the individual elements are different and it can change from country to country. It is obvious, therefore, that the ways in which these policies are implemented will vary greatly, according to the nature of each country's political structure, economic conditions and health services. However, the fundamental throughout the development of these policies is the stage of pharmaceutical production in each country and its proposed expansion.

With regard to the development and establishment of pharmaceutical industry in developing countries, the prerequisite is a technically and economically feasible production programme. It is optimal that the output of this production programme meets the market demand. In the case of over-capacity, the pharmaceutical products can be exported. At this stage of development, the domestic price of a product has to be compared with the international market price. It should be noted that for developing countries with small domestic market, the development of pharmaceutical industry on subregional or regional basis is recommended (TCDC and ECDC)

Some further aspects which have particular importance and relevance to the development of pharmaceutical are as follows:

a. The development of pharmaceutical industry in developing countries will be hardly feasible economically if the proposed production programme included only a group of essential drugs, since these drugs have a narrow margin of profit. In order to guarantee an economically feasible production, an industrial approach has to be applied, considering all the techno-economic factors leading to a more diverse production programme, the so-called "mixed product approach".

b. The direct comparison of the cost of domestic production in developing countries with the international market price is an inappropriate approach since the international market price is often a subsidized price and does not reflect the true production cost. Such direct comparison leads, therefore, to a false assumption on the production costs in developing countries.

c. The pharmaceutical industry in the developing countries is young and without traditions, and therefore cannot be compared directly with the well-established pharmaceutical industry of the developed countries.

Summmarizing the above, it should be emphasized that the aim of this presentation was to highlight a few principal elements which have, according to UNIDO, particular importance and relevance in the formulation of national pharmaceutical policies of developing countries. It should be mentioned that these policies will differ from country to country according to their stage of pharmaceutical industry. The actual stage of pharmaceutical industry of a developing countries may have a feed-back effect to the pharmaceutical policy, therefore the amendment of pharmaceutical policy may be a necessity if the development reaches a new stage. This fact also shows that the fundamental for the pharmaceutical policies is the stage of pharmaceutical production. The other parameters, however, are also important and they should be taken into account.

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3. Feasibility study

A feasibility study should arrive at definitive conclusions on all basic issues of a project after consideration of various alternatives. The feasibility study includes the project background and history with pre-investment studies and preparatory investigations; determines the plant capacity based on the market demand, projected sales and production programme; describes general availability of raw materials, auxiliary materials, factory supplies and utilities and lists annual supply requirements of material inputs; describes location and plant site; describes layout, technology finally selected, equipment selected and required civil engineering works, plant organization and overhead costs, manpower; gives implementation scheduling; gives financial and economic evaluation; and finally gives the conclusions and recommendations. The UNIDO "Manual for the Preparation of Industrial Feasibility Studies" gives a useful guideline how to prepare such a study.

Apart from special situations such as natural disasters, wars, etc. feasibility studies should be carried out as pre-requisites to find the technically and economically most advantageous alternative of any industrial investment decision. Since the feasibility studies in the different industrial sectors have special characteristics, this presentation is focused only on the pharmaceutical industry in the developing countries.

Production (Formulation of Pharmaceutical Dosage Forms)

1. In many developing countries, and especially in Africa, the pharmaceutical sector of the industry is far behind the other industrial sectors. In the least developed countries, not only the pharmaceutical industry but the health care system exist in a rudimentary form or, in other words, the public health care measures and drug supply cover only

a small portion of the population. For all of those countries which are just starting to establish their pharmaceutical industry a step-wise development is recommended.

2. In order to define production programmes first the market demand has to be estimated. The apparent consumption can be estimated from the local production and the import. Information on the quantity and quality of imported drugs can be collected from different sources such as IMS/International Medical Services/or Ministry of Health, (bill of entry), Customs Authorities (customs invoices), banks and from central purchasing units (tender forms). The IMS has processed data on imports but its services cover only a few developing countries, therefore one can mainly depend on local unprocessed data. The projected consumption data can be used as the estimate of future demand. Based on this demand products from the essential drug list are recommended to be selected for production along with specialities which have public health relevance in the country. This mixed product approach seems to be very important since economic feasibility can be hardly reached with the formulation of essential drugs only because there is usually a small profit margin on these products. To make the plant economically more viable it should be identified what type of other products could be manufactured within the same premises and/or what type of other services could be provided by this manufacturing establishment.

3. The sources of supply of essential bulk drugs, added substances and packaging materials have to be identified. A useful assistance for this would be the "Directory of Sources of Supply of 26 Essential Bulk Drugs, their Chemical Intermediates, and some Raw Materials", which has been recently prepared by the UNIDO Secretariat. The Directory of Sources of Supply will be extended for all essential drugs in the forthcoming years.

4. The technologies for the formulation of pharmaceutical dosage forms are available from different sources but to choose the most appropriate one, many factors have to be taken into consideration. The active substances have to be imported, but sources of supply for added substances could be identified in the local market. However, it should

be noted, that in most cases the purity of these added or auxiliary substances are not of a pharmacopoeial grade. To meet the specifications for the demand of pharmaceutical industry will be economically feasible only if there is a significant local market for these highly purified materials or they can be exported. The technologies should be selected to fit the actual climatic conditions and from this point of view the selection of packaging materials has particular relevance. It is obvious that the packaging materials will be different in the economy packs for clinical use and the small packs for retail pharmacies.

5. The manpower sufficient to carry out the production programme (staff and labour force) should be determined. The staff should receive a special training. During the training the personnel shall be not only provided with the necessary technical information and familiarized with the manufacturing techniques, but they shall be motivated to meet the special demands of the pharmaceutical manufacture such as high moral and professional standars. The duration of this training will differ from country to country depending on the stage of development of local pharmaceutical industry ,which should be considered in the feasibility study.

6. The location and site of the pharmaceutical plant have to be evaluated according to the topographical suitability, level of pollution, communications, expansion possibilities and availability of public utilies.

7. Since a step-wise implementation of the project is recommended, a one-storey building has the advantages that it is easy to extend at a later stage. The building shall meet the requirements of the GMP.

8. The feasibility study should be prepared for short ,- medium - and long - term objectives of the development. The patents of bulk

drugs as starting materials for formulation of products selected from the essential drug list had, in most cases, expired and the prices are low because of the competition of suppliers. If the construction work is not too ambitious and the products are carefully selected, the economic feasibility of the project can be easily achieved. To introduce a new stage is recommended only if the previous one is functioning well and shows viability. Duration of each stage can be determined by reaching of economic production. Starting from the formulation of pharmaceutical dosage forms such as tablets and syrups, one can introduce the formulation of injectables at a later stage.

Quality control

1. Many developing countries, especially those which have no pharmaceutical manufacturing facilities, do not have pharmaceutical quality control laboratories. Without these facilities there is no way to recognize the deteriorated or otherwise sub-standard drugs which can reach the consumer.

2. Drugs can be imported from numerous sources. Many sources are major manufacturers enjoying a high reputation for the quality of their products. However, there are also suppliers who are not well known and some of these appear not to be known to the purchaser. The standard of packing and/or poor physical appearance of drugs gives real cause for concern as to quality.

3. Quite apart from their quality, for medicines to be effective and for their potential harmful side effects to be minimized, it is essential that they be prescribed and used in rational manner. In the developing countries there is, however, much evidence of widespread uninformed carefree self-medication often involving the use of potent drugs. They are sometimes freely available from pharmacies and some even from street hawkers.

4. A pharmaceutical quality control laboratory can contribute to the upgrading of the quality of medicines only if it functions within an appropriate legal and administrative framework. The stage of activities of such a laboratory should cover the evaluation and licencing of medicines and their suppliers; inspection of all places where medicines are produce , sold or handled; laboratory testing of medicines and drug information services.

5. The establishment of a national pharmaceutical quality control laboratory under the auspices of the Ministry of Health is recommended. However such a project should be implemented in consecutive stages. At the first stage this laboratory would carry out its evaluation, licencing and inspection activities. In a second stage facilities for simple quality control testing of drugs such as weight and volume measurements, sterility and pyrogenicity tests, etc. should be established. In a final stage the overall quality control of drugs and drug information service should be implemented.

6. It should be noted that the national control laboratory should belong to the Ministry of Health while the quality control units of the production facilities are under the auspices of the Ministry of Industry. The costs of the national control can not be included in the price of drugs produced by the manufacturers in the governmental sector, therefore in the feasibility study two different approaches

have to be made. Either the national quality control laboratory can provide services for the local manufacturers or the quality control department of a local manufacturer can act as the national quality control laboratory but it is very important that by avoiding the duplication or multiplication of the investment costs, significant amount of funds can be sent.

Research and development

1. The research and development (R and D) activity has its role even in the earliest stage of development of pharmaceutical industry. Local sources of supply for packaging materials can be identified and tested to be in conformity with the climatic conditions.

2. In this stage of development the most appropriate formulation techniques should be selected to improve formulation and fit the manufacturing processes to the climatic and environmental conditions.

3. Finally, a pilot plant may be established to study how can any imported material needed for production be replaced by locally manufactured products.

Summary

Since establishing viable pharmaceutical industries would make a tremendous impact to meet the health needs of developing countries, the development of this industrial sector has also significant social and political consequences. The investment decision for the establishment of a pharmaceutical manufacturing plant should be based on a feasibility study in which the technically and economically most advantageous alternative for the investment has been determined.

It should be emphasized that the above presentation only highlighted a few characteristics of the feasibility study on the pharmaceutical industry. The governments of developing countries and the investors should take note of all aspects of the development of the pharmaceutical industry. The formulation of drug policy, pharmaceutical policy, contractual arrangements, licencing arrangements, etc. should go along with the feasibility study. This can be considered as the first phase of implementation of the pharmaceutical policy which links the construction and engineering phase of the establishment of a pharmaceutical manufacturing plant.

Apart from the specific technical and economic characteristics of the feasibility studies for the pharmaceutical industry, one should keep in mind that any development of public health care is a contribution not only to "Health for All by the Year 2000" but also to a healthy, socially and politically harmonized and balanced society

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4. How to start an engineering operation

Effective project management is essential for good planning, thorough design, completion on time and within budget. The efficiency in operation is also based on the effective project management. Some major elements to be considered when managing projects in the construction industry are as follows :

- Initial outline planning which may be presented by precedent networks, critical path diagrams or bar charts. Good planning at the start can reduce significantly the delays and cost increases which otherwise occur.

- Detailed planning follows the agreement of the initial plan. It contains the architectural, structural and civil engineering design but also the process engineering and plant design.

- Site layout and access should be carefully selected considering the wide variety of contractors and sub-contractors who will require access, together with plant delivery problems. Towards the completion of the project the plant management should provide safe access for the staff.

- The key factors of the temporary works are the cheapness and speed with which they can be prepared without safety hazard, and the speed and effectiveness of removal.

- Personnel requirements should include the temporary needs of the project and the longer term training of supervisors and management.

Many companies in the construction industry are also engaged in manufacturing. Application of proven industrial engineering techniques in manufacturing plants can yield significant benefits and lower costs through work measurement, improved flow and handling materials and components, improved production methods and clerical routines. The

layout of new facilities should be planned with sufficient time and details for equipment on long lead times to be obtained. Schemes should take account of production programme, operating requirements, provision of utilities and raw materials, work movement and the need of labour and supervision. A good interchange of ideas between designer and operating personnel is essential. Having decided on the correct approach to materials handling and production technology, the equipment should be specified and selected in adequate detail.

Plant effectiveness and high utilization are the key to profitability, but it should be noted that no matter how well selected for its task or whether it falls in the upper or lower quality range, the plant will not yield profitability unless it is regularly and efficiently maintained.

The engineering operations of the pharmaceutical industry have special characteristics. The construction of a pharmaceutical manufacturing plant includes :

- Production process and feasibility studies
- Civil, mechanical and electrical designing
- Requesting bids
- Construction supervision
- Final testing and start-up
- Construction on turn-key basis of special pharmaceutical departments according to GMP or other standards.
- Construction of biohazard laboratories
- Construction of radioisotope laboratories, etc.

The basic engineering service should include :

- Process analysis
- Determination of production capacity
- Feasibility study
- Selection of equipment

- Determination of warehouse capacity
- Selection of standards (GMP or others)
- Preliminary design
- Rough estimate of investment costs, etc.

The detailed engineering design should include :

(i) Civil works such as
- Soil analysis and specifications for the foundations
- Planivolumetric and architectural study
- Structure analysis
- Waste disposal study
- Specifications for construction materials with particular reference to those areas where the contamination is controlled
- Landscaping, etc.

(ii) Design of mechanical and electrical systems
- Analysis of requirements for utilities
- Sizing of production units of utilities and distribution network
- Pharmaceutical engineering specifications
- Instrumentation and automation
- Air conditioning systems
- Mechanization of the warehouses and the internal transportation system.

To improve the availability of most essential drugs for the health requirements of developing countries and to promote industrialization in the pharmaceutical sector, UNIDO is preparing a series of technical profiles offering guidance to developing countries in establishment of units for production of pharmaceutical dosage forms, vacccines, bulk drugs, etc. These will cover design, layout, process flow, equipment and other technical inputs, and are expected to serve as reference papers for phased setting up of industrial units initially commencing with pharmaceutical preparations for oral use and progressively incorporating production of parenteral dosage forms. The following criteria for planning, design, construction and operation of a model formulation are to be used:

(i) The units are designed to enable manufacture of most commonly used pharmaceutical preparations. These can be adapted for specific infrastructure.

Many developing countries and especially the least developed countries do not possess the necessary infrastructure for pharmaceutical industry. In this case there is an option between to develop the municipal water - piping, drainage or gutter system and electric supply systems and to develop independent services for the manufacturing plant only. In most cases the latter provision is the economically feasible solution. The essential services should include :

- Electricity
- Gas
- Boiler house
- Stand-by emergency generator
- Water
- Demineralized and/or distilled water
- Drainage
- Compressed air and vacuum

(ii) Expansion in capacity of plants can be easily adopted, the designs have adequate provision for capacity adjustments and increases. The manufacturing area is located in a one floor building. However one technical floor exists above the production area which houses the air conditioning ducts, steam, water and electrical network. The effective height of this technical floor is only 2.2 m.

(iii) Another special feature of the manufacture of pharmaceutical products that the formulation of particular dosage forms should be carried out in aseptic conditions. The sterility in the filling area should be achieved by air filtration. The basic design of the filling area is one single filling room, having a changing area and an air lock. The ante-room must be equipped for washing hands or showers and the changing of footwear. In the changing area the personnel put on protective clothing. In principle, the filling area should be windowless or at least if natural light is preferred the windows must be permanently closed and sealed. The most satisfactory but expensive method for the ventillation is by sterile air conditioning. The second alternative is using laminar flow techniques. It should be determined which method would be economically more feasible.

(iv) The units are designed with options for manual, semi-automatic and automatic operations. For most of the developing countries the major production equipment is recommended to be up-to-date model with moderate automation or alternative use of semi-automatic and manual operations, particularly in the packaging department. However it should be emphasized that many aspects have to be taken into consideration during the procurement and throughout the engineering phase of projects. This very important engineering activity can be summarized as equipment management:

(a) <u>Selection of equipment</u>

- identification and appreciation of the need
- knowledge of what is available on the market
- determination of the appropriate equipment for suiting the needs
- evaluation of equipment
- compatibility with other equipment
- environmental requirements

(b) Procurement of equipment

- compliance with the requirements
- availability of service and maintenance
- availability of accessories, spare parts and comsumables
- provision of service manual
- provision of operation manual
- stability of supplier
- price and availability of the equipment
- warranty

(c) Inspection of equipment

- initial inspection
- acceptance testing
- provision of specified components, instructions, etc.

(d) Installation of equipment

- preparation for use
- staff training
- safety considerations

(e) Follow-up

- preventive maintenance (periodic inspectiou)
- evaluation of the use
- maintenance and repair

(v) The units fulfil GMP requirements

It should be noted that most of the Technical Assistance Projects of UNIDO are of pilot scale production of pharmaceutical dosage forms. In these projects the engineering operations have not been carried out to the extent which has been presented here. The aim of the above presentation was to give a basic guide for the engineering operations and highlight some of the most characteristic features of the engineering operations in the pharmaceutical industry for developing countries. The extent of engineering operations has to be determined in each project in the feasibility study and should be carried out accordingly. Since the engineering phase of a project creates the basis for the manufacturing operations, to assure the production of safe and potent drugs is dependent upon the quality of the engineering work performed.

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5. Strategy for establishment of production operations

Based on the assumption that only technically and economically feasible production facilities can be viable in the long term, the objectives of development and establishment of a pharmaceutical plant in the developing countries should be kept within a realistic scope. The production programmes should also be realistic, since most of the too ambitious programmes could not even reach the stage of implementation.

The development of local production capacity in developing countries generally proceeds backwards from the simplest stage of packaging to a highly sophisticated process of manufacturing early intermediates, and even raw materials, from which basic drug ingredients are formed. Countries without any local production import their total demand in a finished form. Countries in the second group have only packaging facilities and import some of their essential demand in economy packs to be repacked locally. Countries in the third group have local facilities to formulate dosage forms from imported bulk drugs. Finally, there are about 5 to 6 more advanced developing countries which possess the local capacity to produce either early or late intermediates, or even some basic chemicals required for the production of these intermediates.

It is obvious that the strategy for establishment of pharmaceutical manufacturing facilities will differ according to the above stages of development. Similarly, the production programme, the selected technologies of a newly established pharmaceutical plant should determine the strategy of establishing production operations.

1. Management

Irrespectively of the actual technical level of the project, the managers with authority for decision-making should be appointed as soon as the implementation of the project is started. In this way two independent goals can be achieved. On one hand the managers involved in all phases of implementation from the start of production operations could be familiarized themselves with all aspects of the establishment of a pharmaceutical manufacturing plant and on the other hand they

will become highly motivated since they are the ones who will be contacted and consulted during the day to day implementation and therefore they can feel the satisfaction by creating the new unit. The role of these personal aspects cannot be over-emphasized. The early appointment has also the obvious advantage that early decision can be made on the development of new cadres.

1.1 Training

Training courses can be planned with a long lead time and in such a way the required trained manpower will be available by the time when the production operations start. It should be noted that not only the supervisors and management should be trained but training courses should be conducted in all of the different technical levels from the unskilled labour to the management. Depending on the actual stage of development of the pharmaceutical industry in a developing country some training courses can be organized and conducted locally but above a certain technical level trainees should be sent abroad to receive an intensive and adequate training. To organize the training courses in the region or overseas falls within the terms of reference of UNIDO.

The training can, however, take place also in the licensor's plant. The training has obvious advantages as follows:

- there are many experiences which cannot be imparted through documentation, but can be exchanged by personal discussion
- the trained persons may be the best coordinators between the licensor and contractor

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

1.2 Experts

To create an efficient management there is also another approach. Technical assistance experts recruited by the UNIDO can assist local counterparts during the implementation of the project and also during the first years after starting manufacturing operations. These experts can be even appointed as acting managers or officers-in-charge if the efficient management from the side of the local counterpart cannot be assured. Experts as managers cannot be recommended to act more than two years, since two years should be a sufficient period to train local management.

To create a local management, the above two approaches - training and experts' assistance - are recommended to be applied in combination. To achieve the targets of the production programme the responsibilities must be clearly defined and authorities should be delegated. The general manager should be responsible for planning, budgeting, evaluation, supervision and reporting. The recruitment should be carried out also by the general manager. The production manager and quality control manager should be responsible for the production and quality control, respectively, and both of them have to be supervised by the general manager.

The licensor should also depute a production expert. Depending upon the production programme, the period of deputation varies from 2 to 12 months. The process of extraction of raw materials, based on medicinal plants, is relatively simple, and the expert's stay is limited to 2-3 months. However, deputation of a microbiologist to supervise biotechnological processes requires a longer period and varies from 6 to 12 months.

2. Production

The production operations can be started as soon as the engineering work has been completed and the equipment has been installed. Actually, the start of production operations can be counted from the period of installation of equipment, since installation means more than setting up a machine and connecting to the necessary supplies. During the installation the equipment should be checked for its entire performance, capacity and safety and therefore at the same time some trial batches can be manufactured. As soon as the trial batches passed through the quality control meeting the requirements, the production operations can be scaled up to meet the demand. However, a step-wise increase of the production output is recommended to meet the target, since during the scaling up many problems arising from the very fact that increased quantities are processed should be solved. During this period, but esentially when the production operations are in full swing, the availability and the continuous supply of the starting raw materials, filling and packaging materials and auxiliary materials as prerequisites for the production should be assured. Since in many developing countries these materials are not available locally, they have to be imported. To assist the developing countries to identify the sources of supply a "Directory of Sources of Supply of 26 Essential Bulk Drugs, their Chemical Intermediates and some Raw Materials" has been prepared by the UNIDO Secretariat and it is available in English, French, Spanish, Russian, Chinese and Arabic. Although some directories of chemical producers already exist it is believed that this is the first attempt to compile a world-wide directory of suppliers of pharmaceutical products, so that the Directory may serve as a tool to purchasers who experience difficulties in identifying sources of supply. This publication can be seen as a means of assisting developing countries to obtain their requirements of pharmaceuticals at the best possible prices, and with more suitable delivery schedules.

2.1 Packaging of finished drugs

Packaging of finished drugs is the simplest pharmaceutical production operation in which no sophisticated equipment is used. This operation can be carried out manually or with simple hand tools, however, depending on the demand, the use of semi-automatic machines can also be recommended. The accurate recording should be established along with some simple quality control methods such as visual control of the finished products. However, even in this simple stage stability tests

(actually tests for durability) for the packaging materials are recommended to be carried out, especially in the tropical countries.

It is an important aspect since in many developing countries not only the finished products have to be imported in economy packs but also the packaging materials. It should be noted that different packaging materials are required for small package units despatching to retail pharmacies and for bulk quantities for use in hospitals and institutions. The packaging material of choice should protect the drugs during transport and storage but at the same time it should be economic. As a general trend, the glass containers are being increasingly replaced by plastic ones.

2.2 Formulation of pharmaceutical dosage forms

The strategy of production operations of pharmaceutical formulation is a step-wise development starting from the simple dosage forms, such as tablets and syrups to the more sophisticated ones, such as injectables. Parallel with the production activities, the quality control is recommended to be developed.

The production of pharmaceutical dosage forms requires hundreds of auxiliary materials and the quality control of these products (analytical tests of raw materials, phase products and finished products) requires hundreds of chemicals again. All of these auxiliary materials, and obviously the active ingredients and packaging materials should be procured with a lead time of about 6 months. As soon as they arrive they should be tested and stored properly. It should be kept in mind that the lack of a single auxiliary chemical out of the necessary 20 or more could result in long delays in the production. Furthermore, to assure the same quality of these chemicals for the finished product it is recommended that they should be procured from the same supplier.

The management should decide to introduce the manufacture of sterile products only after the necessary arrangements have been made. The preparatory phase should be sufficiently long to familiarize the staff and personnel with the principles of sterile techniques. The switch over from the manufacture of non-sterile products to that of sterile products can be considered from the technological point of view as one of the most significant changes in the production operation and therefore it is recommended to be made only if all necessary provision have been made, including experienced staff. The introduction of manufacture of sterile products should reflect in the duties of the quality control unit as well. New techniques such as sterility tests and environmental control should be introduced, which significantly extend the activities of the quality control unit, since these methods are biological control methods. The evaluation of the results obtained by the biological control methods require a statistical approach and therefore it is basically different from that of the conventional chemical analytical methods.

2.3 Production of intermediates and basic chemicals

The production of early or late intermediates, or even some basic chemicals required for the production of intermediates of drugs is the last stage of the development of pharmaceutical industry. The strategy for the production operations at this advanced level should also be a step-wise development. Starting from the laboratory-scale production through the pilot-scale manufacture, one can reach industrial-scale production in all cases when the demand is high enough to make the industrial-scale operations economically feasible. At this level, it seems to be necessary to establish a research and development (R and D) department to improve and maintain the technologies and to deal with the trouble-shooting. This research activity can be extended for establishing new technologies, when these technologies are not available. This type of research could cover the establishment of new, technically and economically feasible extraction methods for active substances of medicinal plants. If these technologies can be introduced in industrial-scale, the products, that is the active substances of different medicinal plants, could be processed further or exported. The export revenues could be used for the further development of local pharmaceutical manufacturing capability.

To achieve economic feasibility at this stage of pharmaceutical industry the selection of technology has an utmost importance. For example, in the case of synthetic drugs a large number of steps can be involved. The question arises whether one should start with the production from the basic raw material or using early or late intermediates. In the case of ampicillin trihidrate, 6-amino penicillanic acid is an intermediate and pencillin 6 is basic raw material. At present the minimum economic size the production of penicillin G may cost more than US$ 20 million whereas a similar unit for ampicillin trihidrat from penicillin G can be installed within US$ 6 million. Therefore, investment becomes the guiding factor for deciding about going basic or not. The obsolence in process is quite frequent and fast in pharmaceutical technologies. In the case of antibiotics, strain developments have been quite revolutionary. Since the yields of penicillin strain have gone up by 25-30 times in the last few years, to match the enhanced capacity due to better yielding requires changing of capacity of equipment.

3. Maintenance

It is well known that in the majority of the developing countries, the service and the maintenance of pharmaceutical equipment is very poor. By improving the maintenance and service, a significant change could occur in the pharmaceutical industry. The effective need of new equipment could be decreased by improving the maintenance. This would result in less spending of foreign currency for the import of new equipment. Besides this economic aspect of maintenance, the engineering, managerial and organizational aspects of maintenance should be taken into account when the strategy of the maintenance activities are defined.

A machine is as good as its performance. To maintain this a regular service must be guaranteed. It consists of maintenance which should gradually turn to well planned, well organized, preventive maintenance at the most sophisticated pharmaceutical manufacturing operations. To secure this, spare parts might be available either through a local supplier of spart parts must be procured together with the equipment. As a rule, spare parts for two years of operation should be adequate.

In all cases when the maintenance department of a production unit cannot cope with the day-to-day trouble-shooting and cannot provide for the preventive maintenance, these services should be carried out by a third party, such as the suppliers of equipment.

To assist with specialist of maintenance of pharmaceutical equipment and to establish training centres in repair and maintenance of pharmaceutical machinery are those activities which fall within the terms of reference of UNIDO. UNIDO has helped in Hungary and in Turkey in the establishment of such training centres and has recruited and sent many experts to the field.

Summary

1. Effective management is a prerequisite of the successful production operations. This management can be developed by training and the assistance of experts.

2. The strategy of the production operations should be based on a step-wise development from the simple operations to the more sophisticated manufacturing activities. Parallelly, the quality control facilities are recommended to be developed. At the highest level of development, that is the production of intermediates and basic materials, the establishment of an R and D department is recommended. To achieve economic feasibility the selection of technology has utmost importance.

3. Maintenance should be strengthened and should gradually turn to well planned, well organized preventive maintenance of the more sophisticated pharmaceutical manufacturing operations.

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3. WG.393/3
4. WG.393/4

6. Good manufacturing p actices

The local production of different dosage forms of various drugs is increasing in many developing countries but most of the enterprises involved produce only a limited number of simple dosage forms. For such a situation it would be useful to evolve from the document known as "Good practices in the manufacture and quality control of drugs" (WHO Technical Report Series, 567, 16-28, 1975) a guideline for good manufacturing practices (GMP) in such specific conditions of manufacture.

The importance of the above is underlined by the fact that the technical assistance projects of the UNIDO aiming at the stablishment and development of the pharmaceutical industry in the developing countries can didactically put among three groups as follows:

- rehabilitation of existing manufacturing facilities
- rehabilitation and extension of existing manufacturing facilities
- establishment of new manufacturing facilities

The above-mentioned guideline for GMP in the first group would have utmost importance since during the rehabilitation of obsolete facilities one is facing many constraints. In such a situation only a step-wise approach towards the requirements of the GMP can be recommended.

Rehabilitation of existing manufacturing facilities in conformity with GMP

1. One of the typical objectives of pharmaceutical technical assistance projects is the rehabilitation of existing manufacturing facilities. Most of these facilities were established in the colonial time to produce only a few simple dosage forms.

The manufacturing area hardly meets any requirements and it is the same with the Central Medical Store to which it is usually attached. The equipment is obsolete, rusty, out of order and without safety fittings. The sanitation is not sufficient, usually there is no quality control unit and the documentation even if it is very bulky is usually not adequate. Finally, the staff in many cases means only a single expert and a handful of unmotivated unskilled personnel.

2. The rehabilitation of the existing unit is requested by the Government for the simple reason that only a very limited amount of funds can be allocated for this purpose. In such cases only a minimum remodelling can be recommended awarding a priority list. This remodelling cannot aim at more than increasing the general sanitary conditions of the unit. At least the manufacturing and storage areas should be remodelled in such a way as to prevent the entry of animals and insects. Equally important is the renovation of the cold store or the creation of one if this does not exist. The rest of the available can be used for cleaning and painting of the other parts of the facilities and repair the broken windows and cracked doors. A main door or gate shall be installed be prevent unauthorised persons (or even animals) to enter and the facilities should be fenced in if it is possible.

3. As soon as the new equipment has been procured the obselete but still usable instruments should be taken to the maintenance shop. The purchase of the equipment should be made very carefully because usually the sophisticated highly specialized, automatic machines with high capacity can be more easily identified and ordered than those for more general use and low capacity. In many cases, only semi-automatic or automatic machines are available on the market and the manual operation can be

obtained only as an option. From that point of view it has a great advantage if one can rely upon suppliers from the developing countries, which still manufacture reliable hand-operated or semi-automatic pharmaceutical equipment with moderate capacity.

4. The sanitary standards of the manufacturing facilities should be increased as high as possible. As a minimum requirement a written sanitation programme should be available indicating the areas to be cleaned and cleaning intervals; the cleaning procedures to be followed; and the personnel responsible for cleaning. In a next stage sufficient clean, well-ventilated toilet facilities, including those for hand washing and rooms for changing clothes, should be provided near working areas for the use of manufacturing personnel only.

5. Control of the health status of manufacturing personnel is not an easy task in many developing countries. Therefore, to be in conformity with the requirements that no persons known to be affected with a disease in a communicable form, or to be the carrier of such a disease, should be engaged in the manufacture of drugs, is very difficult. Since in many subtropical and tropical countries the diarrhoeal faeces is regarded as normal, the only possible option is to provide a regular medical check-up for the manufacturing personnel.

6. To keep the standards of the GMP in many cases requires only changes in the eating, smoking and unhygienic practices of the personnel, and better personal interest and care. However, these changes could be hardly achieved, without the personal motivation towards the establishment and maintenance of high-quality standards. The personnel can be motivated by a better understanding of the practical problems encountered in the manufacture and quality control of drugs.

For this reason yearly refresher training courses are recommended to be organized for the personnel at different levels (staff, technicians and labourers).

7. To assure uniformity from batch to batch, a master production and control record for each dosage form and each batch size of dosage form shall be prepared, dated and signed by a competent and responsible individual. Based on this master production and control record separate batch production and control record should be prepared for each batch of drug produced. Adequate records should be maintained also of the distribution of a finished batch of a drug in order to facilitate prompt and complete recall of the batch if necessary.

Rehabilitation and extension of existing manufacturing facilities in conformity with GMP

1. In many cases the developing countries start to develop their pharmaceutical industry keeping the existing manufacturing facilities as a nucleus for the new unit. In such a case certain compromises have to be made to find an acceptable solution how to attach the new annex to the old building. The extension shall meet requirements of the GMP, but this cannot usually be achieved without the complete remodelling of the old building. It is recommended that the manufacturing areas should transfer to the new annex and the old building would be used for the central services, quality control and the administration. A suitable storage area should be provided also in the old building for the finished products.

2. The new annex of the production facilities should be designed in such a way that further extensions could be easily made if necessary. Further stages of development and the actual level of GMP are basically determined by the financial resources available for the project. One should keep in mind during defining of the production programme of the manufacturing unit that the targets to be achieved shall be technically and economically feasible.

3. The requirements for an aseptic filling unit are more strict, but if the capacity of this unit is moderate it is more feasible to introduce laminar-flow techniques than to provide the unit with filtered sterile

4. In this stage of development all of the starting materials should be identified, properly stored, properly sampled and tested for compliance with requirements. The starting materials can be used for manufacture only after the release of quality control department, which should be independent of other departments. Similarly, not only the final products but also the phase products should be controlled for quality and stability.

Establishment of new manufacturing facilities in conformity with GMP

1. It is beyond the scope of this presentation to deal with the technical details of the current GMP for drugs. The principles of the GMP should be adopted for each of the developing countries according to their special conditions such as climate, general sanitary, religious and cultural beliefs, habits, etc.

2. The level of the GMP for production of pharmaceuticals should be determined in the feasibility study. If the financial resources are available to achieve any level of GMP it is a matter of organization, training and supervision. One of the main duties of the management is to motivate all personnel towards the establishment and maintenance of the manufacturing and quality control operations at a high standard in conformity with the GMP.

Summary

In the production of drugs, overall quality control is essential to ensure that the consumer receives drugs of high quality. This quality control is based upon a so-called double control system, that is on the quality control of the manufacturer and that of the national control institute. The double control does not mean a duplicate control since the two control units have different responsibilities. The national control laboratory, which is the executive body of the national control authority belongs to the Ministry of Health. Among its main responsibilities are the registration of drugs produced domestically or imported, the inspection of manufacturing facilities and release of drugs for the market. The quality control laboratory of the manufacturer is responsible for the quality of raw materials, phase products and finished drugs and for the conformity with the GMP regulations.

It is without question that the drugs produced should meet the requirement of the national or adopted pharmacopoeia but the level of GMP regulations should be based on the recommendations of the feasibility study. The GMP should never be the target itself, it is only as it says a practice by which the quality of the products can be assured. However, to establish and maintain GMP is not only a matter of finance but all personnel should be motivated towards these high quality standards.

References

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