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Athens, 29 November - 20 December 1967
Provisional agenda, item 2

ESTABLISHMENT OF MANUFACTURING UNITS FOR PHARMACEUTICALS IN DEVELOPING COUNTRIES 1/

Prepared by

David Isaksson

President of AB Kabi, Stockholm

Submitted by the Government of Sweden

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* A summary of this paper has been issued under the same title as document ID/CONF.1/G.73 SUMMARY, in English, French, Spanish and Russian.

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SUMMARY

Prepared by

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1. This study is based on a sectoral study on the pharmaceutical industry (I document & NR/Ind. Conf./S.3) presented to the Asian Conference on Industrialization, held in Manila in December 1965. It may, however, be read as an independent document.

2. The main points of the present study follow.

3. Manufacture of pharmaceuticals comprises two very different types of manufacturing techniques: basic manufacture (production of drugs in bulk) and pharmaceutical finishing (manufacture of finished drugs, starting with drugs in bulk).

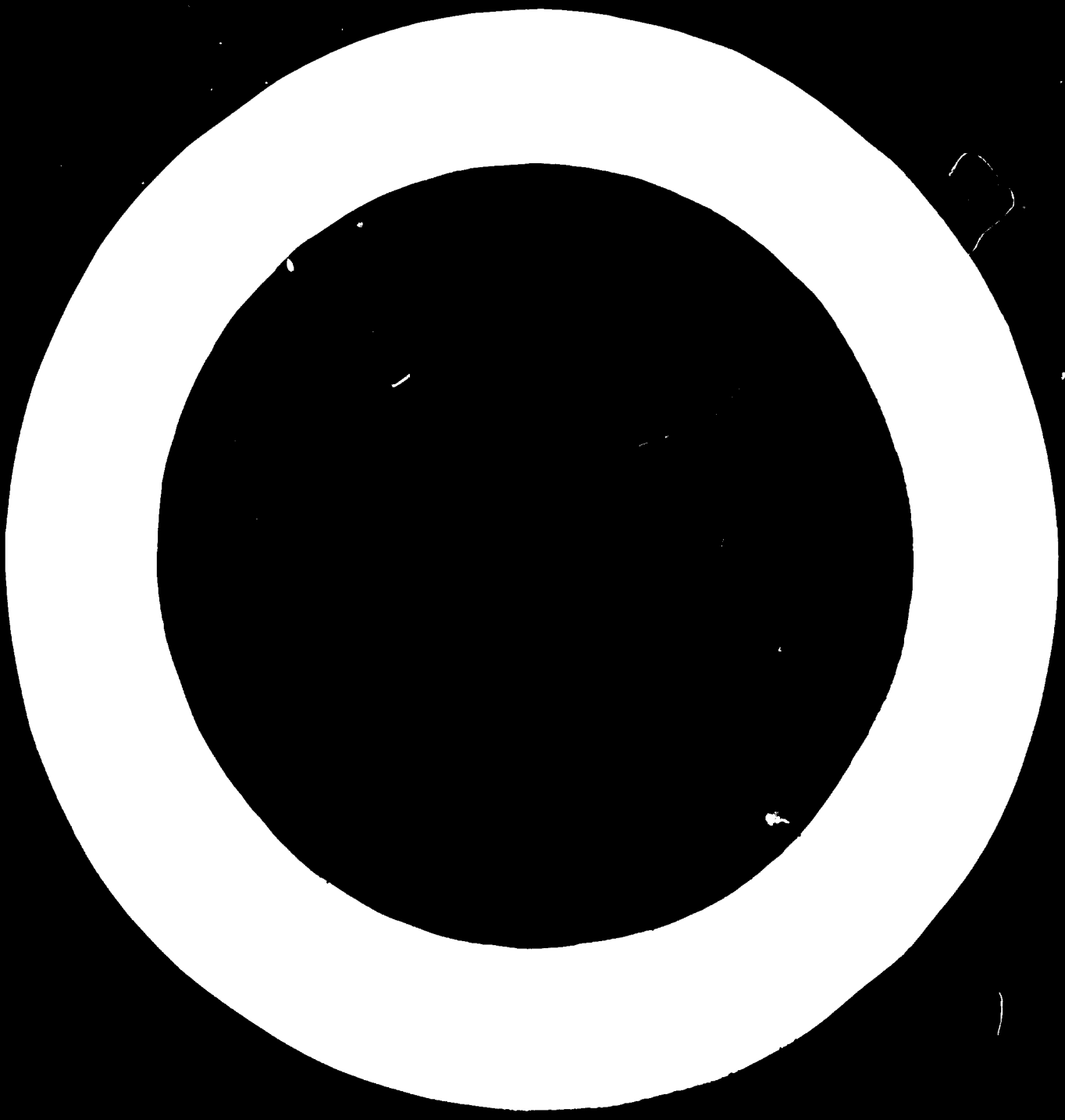
4. For basic manufacture, large-scale operation is necessary to secure a good economic basis; high investments are required; and only a few employees are needed.

5. For pharmaceutical finishing, the initial investment can be kept reasonably small and the need for manpower is much greater.

6. The major part of the cost for finished drugs arises from the pharmaceutical finishing.

7. It is recommended that developing countries build up manufacturing units for pharmaceutical finishing. License agreements with already well-established pharmaceutical companies will greatly facilitate and speed up the procedure. Basic manufacture is regarded of interest for most developing countries only after one or two decades.

1/ The report of the Asian Conference on Industrialization appears in document ID/CONF.1/R.R./2 (E/CN.11/719).



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INTRODUCTION

1. At the Asian Conference on Industrialization, arranged by United Nations Economic Commission for Asia and the Far East (ECAFE) on 6 - 20 December 1965 in Manila, a group of experts presented a Sectorial Study of the Pharmaceutical Industry (86 pages) which is referred to below as the Manila Study.

2. The Manila Study starts with a survey of the progress of the pharmaceutical industry in the developed countries. The characteristic features of the industry are outlined. The study also contains a rather detailed survey of the pharmaceutical industry in the ECAFE countries and the special problems confronting this industry are discussed. A lot of valuable statistics are included in the study.

3. The group of experts regret (paragraph 164 of the Manila Study) that they had not had access to information regarding the decisive economic factors for each step of a complete pharmaceutical manufacturing unit. Such information, which is essential when discussing what should be done in developing countries, was available when this Memo was written.

4. This Memo is based on the informative and valuable Manila Study. This Memo therefore can be regarded as a supplement to the Manila Study or a follow up of the Manila Study. It is, however, written in such a way that it can be read as an independent document.

THE STRUCTURE OF THE PHARMACEUTICAL INDUSTRY

5. A complete (or wholly developed) pharmaceutical company has four types of activities:

a. Research and development
b. Basic Manufacture
c. Pharmaceutical Finishing and
d. Marketing

6. Although all these activities concern pharmaceuticals, they are very different in most respects.

7. The meaning of the expression "a pharmaceutical company" varies from case to case. It might mean a company with only a marketing organization. It might also mean a company with a marketing organization plus one or more of the other types of activities.

8. In a similar way the expression "a pharmaceutical manufacturer" is not distinct. It might refer to activities c + d or b + c + d or it might refer to a complete organization with all four activities.

9. A lot of the vagueness and misunderstandings in the discussion regarding the pharmaceutical industry are due to the fact that the expressions used have several meanings. Before the four activities mentioned above are described in more detail, two definitions will be given.

FINISHED DRUGS AND DRUGS IN BULK

10. a. Finished drugs are drugs in the form in which they reach the consumer (the doctor, the hospital or the patient). Tablets of aspirin (acetylsalicylic acid) in a sealed, labelled bottle are an example of a finished drug. A labelled box with 10 vials, each containing one gram of streptomycin in a sterile solution is another example. Tablets and solutions for injection are different dosage forms. Other dosage forms are ointments, suppositories, syrups, eye drops etc.

Consequently a finished drug can be described as a drug in a dosage form, packed and labelled and ready to be used by the consumer.

Each finished drug contains one or more active ingredients and one or more inert ingredients. The finished drug streptomycin for injection contains streptomycin as the active ingredient and distilled water and some buffer salts as inert ingredients. Penicillin V tablets contain penicillin V as the active ingredient and some inert substances which are added to facilitate the tableting procedure.

Other expressions used instead of finished drugs are finished pharmaceuticals, finished products, formulated drugs, formulated pharmaceuticals and

pharmaceutical preparations. In the legislation in several countries the term pharmaceutical specialities is used. In this Memo the term finished drug will consistently be used.

b. The term a drug in bulk refers to a therapeutically active compound which is intended to be used for producing a finished drug. A drug in bulk is generally sold as a powder in reasonably big packages. (In some few cases it may be a liquid.) 100 tons of acetylsalicylic acid (aspirin), 5 tons of penicillin V or 100 g of vitamin B_{12} are examples of drugs in bulk.

Other expressions used instead of drugs in bulk are pharmaceuticals in bulk, active ingredients etc.

It is confusing when the word raw material is used when discussing the pharmaceutical industry. From the definitions given above it is evident that the main raw materials of a manufacturing unit making finished products are the same as the end products of a manufacturing unit making drugs in bulk.

RESEARCH AND DEVELOPMENT

11. As mentioned in the Manila Study (paragraph 194) the research activity is of greater importance in the pharmaceutical industry than in most other types of industries.

12. The purpose of the research and development activity is to discover or develop new drugs in bulk or new finished drugs (containing new or already known drugs in bulk). The discovery of new drugs in bulk requires a full set up of well trained scientists with different specialities and well equipped laboratories of different types including animal laboratories.

13. The experiences of later years show that only big and well established pharmaceutical companies can afford to undertake basic research in the pharmaceutical field.

14. However, the development of new finished drugs starting from drugs in bulk, available on the world market, can be done in a laboratory of modest size provided it has a suitable staff headed by someone with adequate scientific training. The development of new finished drugs is a vital part of the research and development activity in the pharmaceutical field.

The technique used for preparing a dosage form of a drug sometimes is of decisive importance for the therapeutic effect of the drug. Thorough knowledge of local medical traditions and climatic conditions is a great advantage in this type of research.

BASIC MANUFACTURE

15. a. Definition: Basic manufacture means production of drugs in bulk.

b. Methods used: Most drugs are manufactured either by synthetic methods or by fermentation. Some are extracted from glands or plants.

c. Raw materials: Generally many raw materials of various types are needed for the production of each drug. Two examples might be mentioned.

In the synthesis of meprobamate - a tranquilizer - five raw materials are needed. These raw materials are obtainable on the world market from some big chemical companies. Altogether about 5 kg of chemicals are needed for the production of 1 kg of meprobamate.

For the production of penicillin V in bulk about 30 raw materials are needed. Some of these are obtainable only from some few manufacturers in the world. Altogether between 50 and 100 kg of raw materials are needed for the production of 1 kg of penicillin V.

d. Equipment: For synthetic procedures as well as in fermentation, complicated and expensive equipment is required.

e. Need of personnel: A characteristic feature of the manufacture of drugs in bulk is that only a small staff is needed.

f. Size of operation: As indicated in the Manila Study it is necessary to have a large scale operation to be able to run basic production of drugs on an economic basis. As indicated in pharagraph 204 of the Manila Study basic manufacture of synthetic drugs should not be started until a general chemical industry has been established. For basic manufacture of fermentation products (antibiotics) a background of high

industrialization is needed, or at least desirable. To illustrate the need for large scale operation in basic manufacture of antibiotics, it might be mentioned that several companies in the developed countries have stopped their basic production of penicillin in recent years for economical reasons. They continue, however, to produce finished drugs based on penicillin in bulk which they buy on the world market.

The economical factors are discussed further in paragraphs 24 and 25 below.

g. Laboratory: A manufacturing unit for basic manufacture must have a well equipped analytical laboratory with an experienced staff. All types of material bought must be checked with regard to identity and purity. All drugs produced must be thoroughly controlled.

PHARMACEUTICAL FINISHING

16. a. Definition: Pharmaceutical finishing means the manufacture of finished drugs starting with drugs in bulk.

For pharmaceutical finishing a number of other expressions are often used. From the Manila Study some expressions might be quoted: Processing of basic drugs into pharmaceutical preparations (paragraph 75), processing of basic bulk drugs into dosage forms (paragraph 195) and formulating drugs (paragraph 25).

b. Methods used: For different dosage forms different methods are used, for example tableting, coating, sterile filtration, heat sterilization, filling and mixing.

c. Raw materials: When making tablets some inert ingredients are used to facilitate the tableting. These inert ingredients are more or less the same for all types of tablets. They are generally simple substances and easily available on the world market. Often they are used in rather small quantities. Such inert ingredients are starch, talcum, magnesium stearate and micronized cellulose.

Besides such inert ingredients only penicillin V in bulk is necessary to make

penicillin V tablets, only meprobamate to make meprobamate tablets, only aspirin (acetylsalicylic acid) to make aspirin tablets etc Penicillin V, meprobamate, aspirin and most other drugs in bulk are easily available on the world market. There is an over-production of many drugs in bulk in the developed countries. As a result of this the price level is low. Developing countries can benefit greatly from this.

The situation regarding raw materials for other dosage forms is in general similar to that for tablets.

d. Equipment: The equipment for pharmaceutical finishing is not so very complicated: Tableting machines, mixers, filling machines etc.

e. Need of personnel: A manufacturing unit for pharmaceutical finishing employs many times more people than a corresponding unit for basic manufacture. Especially the packing and labelling requires a lot of employees. (If the pharmaceutical finishing is done in very large scale the need for staff can be reduced through the installation of advanced packing and labelling machines.)

f. Size of operation: A manufacturing unit for pharmaceutical finishing can operate with sound economy in almost any size of operation. Such a unit can start by making tablets on a modest scale and thereafter gradually be increased. More tableting machines can be added as well as additional types of equipment.

g. Laboratory: A manufacturing unit for pharmaceutical finishing must have a well equipped analytical (control) laboratory with an experienced staff. All types of material bought must be checked with regard to identity and purity. All finished drugs produced must be thoroughly controlled.

MARKETING

17. The marketing of finished drugs is a more complicated procedure than the marketing of many other types of products.

18. A marketing organization must be able to find the right channels for distribution and it has a most important educational task. It has to sell not only products but also the proper use of them. The marketing organization must submit adequate pharmacotherapeutic knowledge to the doctors and nurses. It must keep in close contact with leading hospitals to be able to acquire knowledge about the specific needs of the country.

A GENERAL COMMENT

19. As a supplement to the brief description above of the four main activities of the pharmaceutical industry a short general comment might be added.

20. Most drug manufacturers have started their activity by establishing a unit for pharmaceutical finishing. Several well-known manufacturers in the developed countries employ basic manufacture of only some few drugs in bulk or no basic manufacture at all. Even the very big drug manufacturers in the developed countries have to buy many drugs in bulk.

21. The relation between basic manufacture and finishing in the drug field is comparable with conditions in other industries. A steelworks can be regarded as a unit for basic manufacture and a mechanical industry making, for example, tools can be regarded as a finishing unit. The similarity exists also on the marketing side: The manufacturer of tools must do an educational job to be able to sell his tools and have them used in the right way. So must the drug manufacturer with his drugs.

DEFINITION OF PRICE

22. When the price of a drug is mentioned in this Memo, it refers to the price charged by a pharmaceutical manufacturer with a normal marketing organization. The price thus includes all manufacturing costs plus the costs for the marketing.

23. To the price so defined the margins for distribution (wholesalers, pharmacies) have to be added to obtain the consumer price for the drug.

COST STRUCTURE

24. The characteristic feature of the cost structure for the pharmaceutical industry is that the costs for the drugs in bulk are a rather small part of the total costs for the finished drugs. This means that the value added is small in a unit for basic manufacture compared with the value added in a unit for pharmaceutical finishing.

25. The cost structure varies from drug to drug and to a certain extent from country to country. The following calculation is to be regarded as a typical example of an average drug:

Basic Manufacture	
Raw materials to be bought. Cost might vary from 5 to 15. A reasonable average might be	10
Value added /costs for staff (workers, supervisors, laboratory staff, officers), maintenance and depreciation of buildings and equipment, interest on money invested, profit, taxes, possible royalties etc./	15
Total price for the drug in bulk	25
Pharmaceutical Finishing	
Cost for the drug in bulk according to the above	25
Value added /costs for other raw materials, staff (workers, supervisors, laboratory staff, marketing people including medical representatives, officers), promotional material, maintenance and depreciation of buildings and equipment, interest on money invested, profit, taxes, possible royalties etc./	75
Total price for the finished drug	100

x) For definition - see page 7

CONCLUSIONS AND SUGGESTIONS

26. As mentioned in the Manila Study it is desirable that the consumption of drugs should be greatly increased in the developing countries. Furthermore it is desirable that such an increase can take place without impairing the balance of trade of the countries involved.

27. The way to solve this problem is to establish manufacturing units for drugs in these countries. It might be evident from the facts about the pharmaceutical industry presented above that emphasis should be placed on the establishment of manufacturing units for pharmaceutical finishing. Basic manufacture will only be of interest for most developing countries after one or two decades. There are mainly three factors which speak against basic manufacture:

High investments are required.

Only a very limited number of employees will be needed.

The value added is low.

28. In contrast a unit for pharmaceutical finishing has the following advantages:

The initial investment can be kept reasonably small and a gradual increase of the size of operation can be made.

Many people will be employed (some well educated specialists and many untrained workers).

The value added is high.

29. It is therefore suggested that some developing countries establish pharmaceutical companies with manufacturing units for pharmaceutical finishing and with marketing organizations.

30. It can be assumed that many pharmaceutical companies in the developed countries are willing to assist in the establishment of such pharmaceutical companies in developing

countries by supplying know-how, training staff etc. at a modest fee and/or royalty. Such an assisting company is referred to below as the licensor.

31. The collaboration between the licensor and the developing country should preferably include inter alia the following steps:

a. A study of the needs of drugs in the country should be made.

It is reasonable to believe that such a study will reveal that 80 - 90% of the total need of medicines can be adequately covered by a reasonably small number of finished drugs probably between 50 and 100. All efforts should be concentrated on these drugs during the initial years.

b. The manufacturing unit should be designed. It must be made in such a way that it is possible gradually to increase the size of operation.

The first part of the manufacturing unit preferably should contain a tableting department, a packing department, warehouses, laboratory and an office.

c. Some personnel should be trained in the licensor's manufacturing unit.

d. During the break-in period of the new manufacturing unit, the licensor should provide supervisors to assist in all ways.

e. It might be advantageous to have the licensor act as purchasing agent for drugs in bulk and other raw materials during the initial period. This will save the new unit a lot of control work.

f. During the initial manufacturing period samples from each batch should be sent to the licensor to obtain an extra control of the quality of the finished drugs produced.

GOVERNMENT LEGISLATION AND REGULATION

32. From the Manila Study four paragraphs are quoted:

185. In some countries of the region, the rate of import duty on raw materials

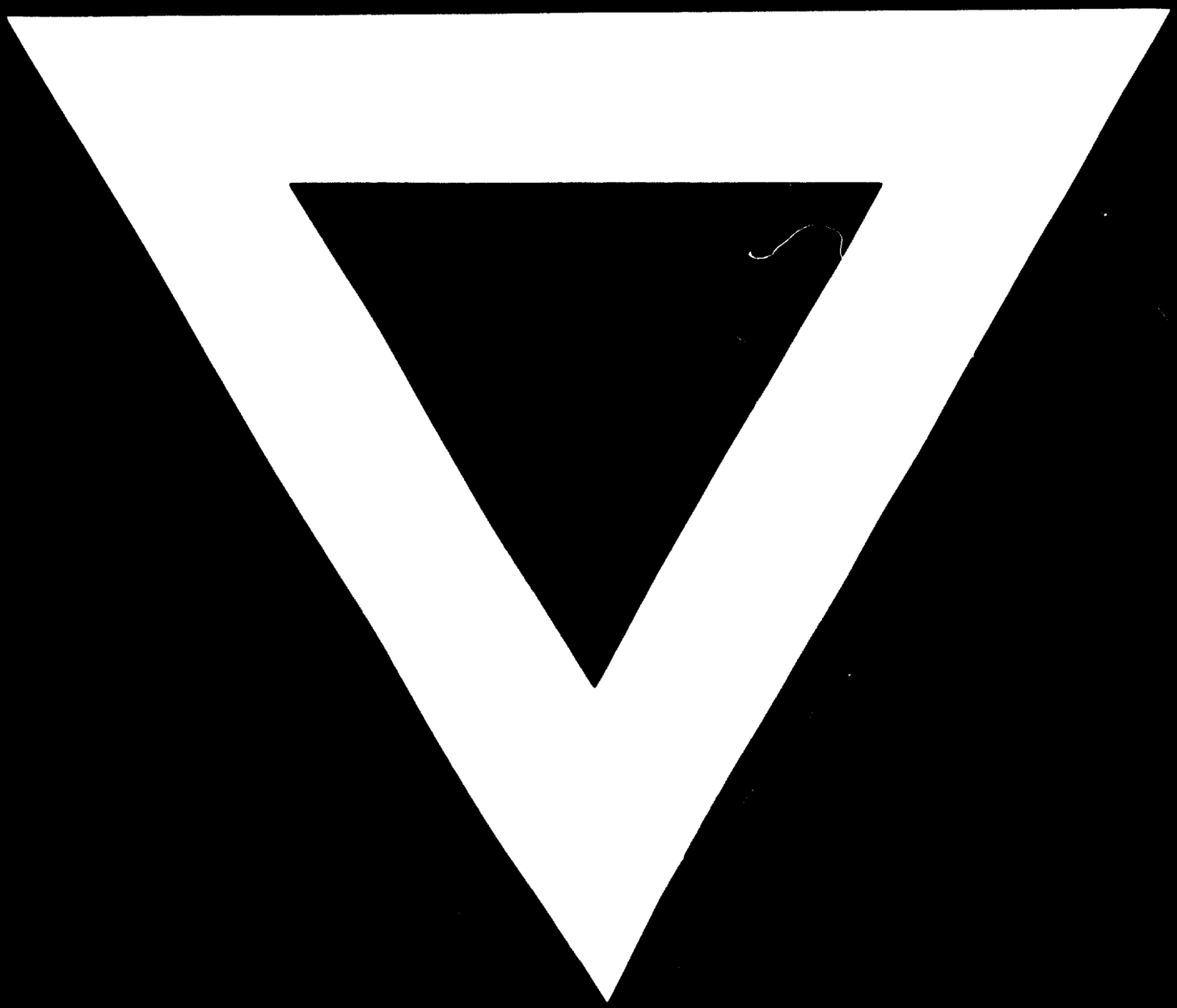
for the pharmaceutical industry is the same as, or even higher than, the rate for the finished pharmaceutical product, making it impossible for the manufacturer to compete with imports. This will have to be remedied.

(This paragraph is probably to be interpreted in the following way: In some countries of the region, the rate of import duty on drugs in bulk is the same or even higher than the rate on finished drugs, making it impossible for companies with finishing units to compete with imported finished goods. This will have to be remedied.)

186. Sometimes, finished products are dumped in ECAFE countries at prices with which the local industry cannot compete. This will have to be controlled by limiting imports to the amount required to supplement local production.

206. In order to prevent the production of non-standard drugs, to guide the development of the pharmaceutical industry along the proper lines, and to protect consumer interests, legislation should be introduced by governments to control production, imports, distribution and retail sales.

33. The points of view expressed in these paragraphs are realistic. As a matter of fact they are essential for success when trying to establish a pharmaceutical industry in any developing country.



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