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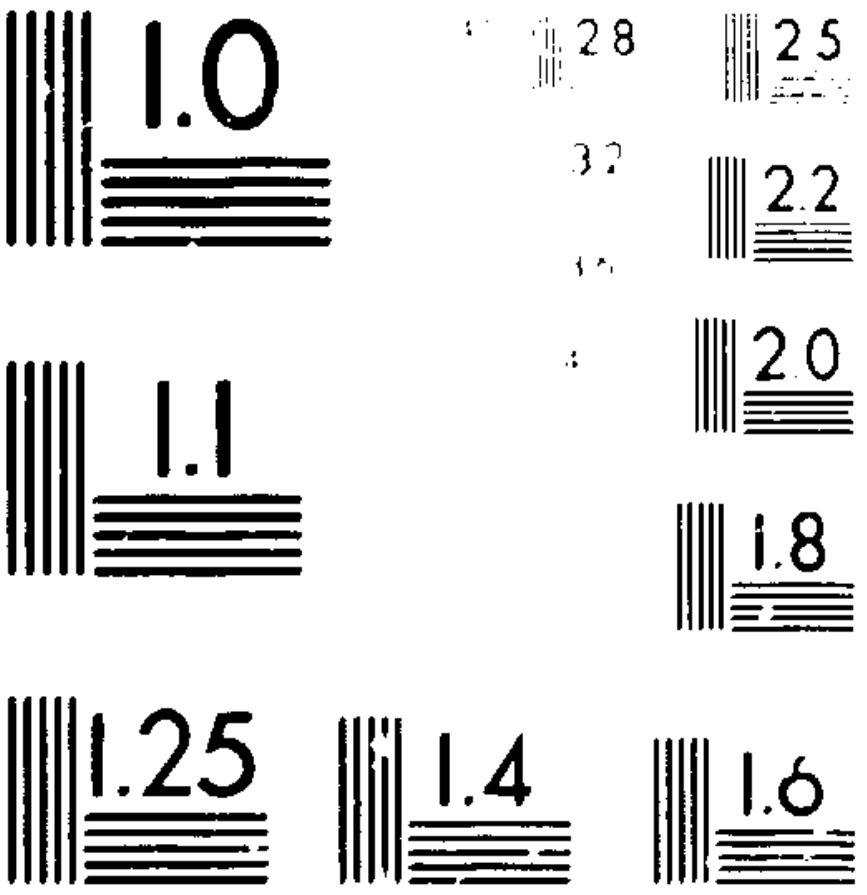

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MULTIPURPOSE PLANT FOR PRODUCTION OF UNIDO ESSENTIAL DRUGS BASED ON RAW MATERIALS AND INTERMEDIATES *

prepared by

the UNIDO Secretariat

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INTRODUCTION

1. The UNIDO Committee of Experts on Pharmaceuticals set up according to the recommendation of the First Consultation on the Pharmaceutical Industry had convened its meeting on 11-13 October 1982 in Paris, France. The Committee recommended that UNIDO, in collaboration with the producers from developed and developing countries, and assisted by consultants and experts with industrial knowledge and experience, should undertake a study which should provide non-confidential reference information relevant to the transfer of technology for the manufacture of intermediates and bulk drugs, taking into account technical aspects, such as level of production, magnitude of investment, inputs, infrastructure, etc. Such studies could significantly aid individual developing countries in bilaterial negotiations for transfer of technology. 1/

2. The economic feasibility of the production of bulk drugs and intermediates on an industrial scale depends among others on some special prerequisites such as:

- sufficient size of domestic market
- availability of financial resources for investment
- good technology, and
- availability of infrastructure, etc.

According to these prerequisites the production of a single bulk drug would be viable if the market requirements made the implementation of the appropriate technology economically feasible and the financial resources for this investment which are high were available. It should be noted that the costs of investment of a manufacturing line for a single bulk drug are reasonable only if it could be produced in large quantity with an up-to-date technology and with a high yield.

With the exception of some developing countries with large population such as Argentina, Brazil, India, Mexico, etc., the establishment

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1/ Meeting of the Committee of Experts on Pharmaceuticals, Paris, 11-13 October 1982, UNIDO/PC.59

of manufacturing lines on an industrial scale for a single bulk drug may be uneconomic since these projects can hardly be justified by the domestic market.

3. In order to help those developing countries with small or moderate market demands, the idea of multipurpose plant for the manufacture of essential drugs has been recommended. It has been accepted and applied for small market and/or small quantities for a considerable number of years in the developed world.

Based on the experiences of the developed world, the multipurpose plant for production of essential drugs was proposed to those developing countries which approached UNIDO with their interest. This activity of UNIDO seems to be very promising since projects have already been implemented and others are under implementation.

4. As reflected in the discussions of the Committee of Experts on Pharmaceuticals in Paris, developing countries should produce the bulk drugs and their intermediates included in the illustrative list of essential drugs of UNIDO as an alternative way to overcome the problems of the supply, availability and prices of intermediates which also dominate the prices of the final products in most cases.

5. According to the above recommendations and some of the prerequisites of the implementation of a pharmaceutical project described above, this document will consider how the multipurpose plant could be applied for the production of essential drugs. Thus, the production of pharmaceuticals in small quantities in a flexible unit with a small investment can be achieved.

Based on the above facts and arguments an attempt will be made to present the concept of the multipurpose plant, and study how the 26 essential drugs of UNIDO can be fitted into these flexible manufacturing facilities.

MULTIPURPOSE PLANT CONCEPT FOR PRODUCTION OF BULK DRUGS AND INTERMEDIATES

6. As known, Lewis [2/] in the early time of chemical technology has introduced the concepts of unit process and unit operation. Examples of the first are chemical reactions such as oxidation, condensation and alkylation; the second is illustrated by operations such as filtration, distillation and centrifugation. This system had the advantage that both entities could be described independently of the particular procedure, thus establishing knowledge of more general application. The synthetic drugs can be manufactured by several consecutive steps of unit processes performed with a series of unit operations.

Based on the similarity of the production technologies of different synthetic drugs regarding the unit processes and unit operations involved, facilities for production of different pharmaceuticals can be designed and equipped. This type of facility can be referred as multipurpose plant since several synthetic drugs can be manufactured in this plant either sequentially or to some extent simultaneously using a single series of equipment. It is important to note that if a single series of equipment is used, the capacities of the machines on the production line have to be balanced. A double series of equipment or at least more than one apparatus at some particular steps of the manufacturing process will obviously make the plant more flexible.

ADVANTAGES OF MULTIPURPOSE PLANT FOR PRODUCTION OF BULK DRUGS AND INTERMEDIATES

7. The main technical and economic advantages of a multipurpose plant for the production of bulk drugs and intermediates are as follows:

- It is ideally suited to produce a number of different synthetic drugs and in small quantities
- Relatively small investment is required
- New products can be introduced at later stages with minimum investment or even without investment
- The production of any particular drug can be increased to a certain extent with marginal investment to cope with an increased demand.

2/ Lewis, W.K., 1923, in Walker W.H.: Principles in Chemical Engineering, MacGraw-Hill, New York

SELECTION OF ESSENTIAL DRUGS FROM UNIDO ILLUSTRATIVE LIST WHICH CAN BE PRODUCED IN A MULTIPURPOSE PLANT

8. During the selection of drugs to be produced in a multipurpose plant one should keep in mind that certain steps as unit processes of the production technology have to be omitted either because they cannot be carried out in the existing facilities, or because they require special, more sophisticated instrumentation. Since completely different equipment is required, fermentation processes cannot be involved in the multipurpose plant for synthetic drugs. However, simple biotechnological processes, such as enzymatic decomposition steps can be performed. Production process of a particular drug including a series of synthetic reactions may be based either on raw materials or an early or late intermediates in a given multipurpose plant.

9. Based on the above criteria, some drugs can be immediately excluded from the 26 essential drugs of UNIDO because their production technologies cannot be adapted in a multipurpose plant. Benzyl-penicillin, cyanocobalamine, erthyromycin, streptomycin and tetracycline have to be omitted because their production is based on fermentation. The production of ethinyl-estradiol + norgestrel, insulin and retinol requires special and more sophisticated instrumentation and blood derivatives have a completely different technology as biological products. In the case of the remaining 17 drugs, the alternative technologies should be studied in order to identify those unit processes which can be carried out technically. For the illustration of the above, basic technical information on these drugs, such as brief process description, process parameters and equipment, has been collected (Annex 1).

It should be noted that Annex 1 has limitations. First of all, the technical literature rarely gives technological details, therefore the process descriptions obtained from well-established and widely used pharmaceuticals text books can only serve as an alternative among many other synthetic processes. The process parameters such as temperature, pressure and pH are obviously incomplete.

10. A preliminary process economic analysis should also be carried out to determine whether the technology of choice is economically feasible. Seventeen drugs have been selected out of the 26 essential drugs of UNIDO, which could be manufactured, based on raw materials or early or late intermediates, whenever the total sequence of the synthetic reactions cannot be performed, in a multipurpose plant. The list of these drugs is given in Annex 2.

11. Finally, it should be also noted that the main equipment referred in the Annex 1 for the production of synthetic drugs is the stainless steel reactor with its necessary ancillary parts as coolers, heat exchangers, pressure gauges, pH meters, etc. Other details regarding the necessary equipment are given in Annex 3.

DESIGN AND EQUIPPING OF A MULTIPURPOSE PLANT

12. Based on the similarity of the production technologies of different synthetic drugs, multipurpose plants can be designed and equipped. The list of the most important equipment for a typical multipurpose plant is given in Annex 3. The capacity of such a plant should be optimally balanced to minimize the investment costs but meet the domestic demand. The design of capacity can be facilitated by the balanced diagram of intermediates, which gives an estimate of the input and output quantities of intermediates for each unit process. It should be noted that also the time requirements of the individual unit processes have to be taken into account in this respect.

13. It should be emphasized that final decision on the design and lay-out can be made when the production technologies to be transferred are available. Similarly, the purchase of equipment can only be made after the agreement on transfer of technologies.

ANNEX 1

Technical Information on 26 Essential Drugs of UNIDO

Name of Drug	Brief Description of Process	Process Parameters			Equipment
		Temperature	Pressure	PH	
1. ACETYL SALICYLIC ACID	Salicylic acid is acetylated by heating with acetic anhydride in acetic acid as a solvent. Acetyl salicylic acid is then crystallized out by cooling the hot liquid. Then it is washed with acetic acid and water, and dried.	10-90° C	1 atm	1-9	SSR*
2. AMPICILLIN	D (-) - 2 - Phenylglycol chloride hydrochloride is reacted with 6 - aminopenicillanic acid in an aqueous solution of acetone	0° C		2-3	SSR
3. ASCORBIC ACID	Diaceton-ketogulonic acid is added to a dichloroethane-ethanol mixture and reacted at 65° C	20-65° C			SSR
4. BENZYL PENICILLIN	Produced by submerged fermentation using molds mutated from penicilium chrysogenum				Fermenter

* SSR Stainless Steel Reactor

Name of Drug	Brief Description of Process	Process Parameters			Equipment
		Temperature	Pressure	PH	
5. BLOOD DERIVATIVES	Manufactured by cold-ethanol fractionation of human plasma	-5 - 0° C	3-7		SSR
6. CHLOROQUINE PHOSPHATE	4.7-dichloroquinoline is heated with 1-diethylamino-4-amino-pentane for 7 hours. The mixture is dissolved in diluted acetic acid and made alkaline. The base is extracted with ether, dried, distilled and fractionated. Then it is combined with phosphoric acid.	88-180° C		mild acidic mild alkaline	SSR
7. CYANOCOBALAMINE	Produced by submerged fermentation using intestinal microorganisms				Fermenter
8. DAPSONE	Benzene and sulfuric acid is reacted to give phenyl sulfone which is nitrated, then reduced to give dapsone				SSR
9. DIETHYL CARBAMAZINE	1-methyl piperazine dihydrochloride and diethyl carbamyl chloride are reacted in sodium hydroxide solution and extracted with ether. The ether solution is saturated with dry hydrogen chloride, filtered	10-150°C		From neutral to alkaline	SSR

Name of Drug	Brief Description of Process	Process Parameters			Equipment
		Temperature	Pressure	PH	
10. ERYTHROMYCIN	Produced by submerged fermentation using streptomyces erythreus	26° C			Fermenter
11. ETHAMBUTOL HYDROCHLORIDE	2-amino-1-butanol and ethylene dichloride are heated and then treated with methanol and sodium hydroxide. The product is recrystallized with ethanol. Finally recrystallized with 4n ethanolic hydrochloric acid.	83-165° C		Alkaline to acidic	SSR
12. ETHINYLESTRADIOL + NORGESTREL (LEVO)	Synthesized in 30 - 60 consecutive reaction steps				SSR
13. FUROSEMIDE	3-sulfamyl-4,6-dichlorobenzoic acid and furfurylamine are heated in diethylene-glycol-dimethylether. It is crystallized with 1n hydrochloric acid. It is purified with 1n sodium bicarbonate solution, precipitated with hydrochloric acid, and recrystallized with diluted ethanol.	206° C			SSP
14. HYDRALAZINE HYDROCHLORIDE	1-chlorophthalazine is heated with ethyl alcohol and hydrazine hydrate. The product is then filtered and washed with ethyl alcohol. Then it is crystallized from methyl alcohol. The final product is obtained on warming in diluted hydrochloric acid.	172°C		Mild Acidic	SSR

Name of Drug	Brief Description of Process	Process Parameters			Equipment
		Temperature	Pressure	PH	
15. INSULIN	It is extracted from the pancreases of slaughtered animals				SSR
16. ISONIAZID	4 parts of 4-cyanopyridine in 12 parts of water reacted with 4 parts of hydrazine hydrate in presence of 0.08 parts of sodium hydroxide. Crystallized from ethanol	100° C	Normal	Alkaline	SSR
17. MEBENDAZOLE	4-Chloro-3-Nitrobenzophenone, Ammonia, Methanol and Sulfolane are heated and the reaction mixture is evaporated. The product is then precipitated and dried and crystallized. The mixture of 4-Amino-3-Nitro-Benzophenone, Methanol and Hydrochloric Acid is hydrogenated. The solvent is evaporated and the residue is triturated in 2-Propanol. The product is filtered, washed and dried. 3,4-Diamino-Benzophenon Hydrochloride is added to a mixture of S-Methyl Isothiourea Sulfate, Methyl Chloroformate, Sodium Hydroxide and Acetic Acid. Finally Sodium Acetate is added. The final product is washed, dried and crystallized.	20 - 125° C	5-8	1 atm	SSR

Name of Drug	Brief Description of Process	Process Parameters			Equipment
		Temperature	Pressure	PH	
18. PARACETAMOL	P-Nitro Chlorobenzene is hydrolysed and para-nitrophenol is precipitated with diluted Sulphuric Acid. Para-nitrophenol is reduced to P-Aminophenol, then is is acetylated with Acetic Anhydride. The crude product is purified with activated carbon, filtered, washed and dried.			Acidic to alkaline	SSR
19. PIPERAZINE	Mono-Ethanol-Amine is the starting material for the synthesis of Piperazine Hexa Hydrate. The latter is converted into Adipate Citrate and Phosphate.			Acidic	SSR
20. PRIMAQUINE	6-Methoxy-2-Amino Quinoline is synthesized by three steps starting from P-Anisidine. This is treated with 1,4-Dibromopentane and Potassium Phthalimide followed by Hydrazin Hydrate.				SSR
21. PROPRANOLOL HYDROCHLORIDE	4.4 parts of 1-chloro 3- (1-naphthoxy) 12 propanol and 16 parts of isopropylamine heated in a sealed vessel. Cooled and water	70-80° C	Normal	10 N Hcl	SSR

Name of Drug	Brief Description of Process	Process Parameters			Equipment
		Temperature	Pressure	PH	
Continuation 21. PROPANOLOL HYDROCHLORIDE	added. Acidified with 2 N H cl and washed with ether. Decolourized neutralized and cooled. Filtered washed and crystallized from cyclohexane. Base converted to hydrochloride treating acetone solution with Hcl. Crystallized from propanol.				SSR
22. RESERPINE	By extraction from rauvolfia plants using methanol or acetic acid				SSR
23. RETINOL	It is prepared by saponification of fish-liver oil and concentration of the Vitamin A in the non-saponifiable matter by solvent extraction				SSR
24. STREPTOMYCIN	Produced by submerged fermentation using actinomyces griseus				Fermenter
25. SULFADIMIDINE	N1-Substituted Sulfanilamid product is condensated from 2-Amino-4,6-Dimethylpyrimidine and Sulfonyl Chloride				SSR
26. TETRACYCLINE	Produced by submerged fermentation using streptomyces aureofaciens or streptomyces viridifaciens				Fermenter

ANNEX 2

Selected drugs from UNIDO illustrative list of essential drugs which could be produced in a multipurpose plant.

1. ACETYLSALICYLIC ACID
2. AMPICILLIN
3. ASCORBIC ACID
4. CHLOROQUINE PHOSPHATE
5. DAPSONE
6. DIETHYLCARBAMAZINE
7. ETHAMBUTOL HYDROCHLORIDE
8. FUROSEMIDE
9. HYDRALAZINE HYDROCHLORIDE
10. ISONIAZID
11. MEBENDAZOLE
12. PARACETAMOL
13. PIPERAZINE
14. PRIMAQUINE
15. PROPRANOLOL HYDROCHLORIDE
16. RESERPINE
17. SULFADIMIDINE

ANNEX 3

Qty.	Item	Capacity
	Service equipment	
1	Steam Boiler	1000 kg /hr
1	Demineralized water plant	$3m^3$/hr
1	Dealkalised water plant	$3.5m^3$/hr
1	Water chilling plant	60 tr
1	Brine chilling plant	10 tr
1	Cooling tower (9F drop, $5^{\circ}F$ approach)	400 igpm
2	Pump sets	400 igpm x 25 m hd
2	Air compressor	30 cfm
1	Hot oil circulation unit	70,000 kcal hr
1	Electrical control panel	
	Process equipment	
2	Glass lined reactor, jacketted with anchor agitator	1000 lit
1	GL condenser	$4.0m^2$
1	SS condenser	$4.0m^2$
1	GL receiver	600 lit
4	SS reactor, jacketted with agitator	600 lit
3	SS condenser	$3m^2$
2	SS receiver	500 lit
1	High vacuum SS distillation unit comprising 200 L jack, distillation kettle, SS condenser, 200 L SS jack, distillation kettle, SS condenser, 200 L SS jack, receiver and oil sealed high vacuum pump	200 lit
1	SS jacketted pan with anchor agitator	300 lit
4	SS reactor jacketted with agitator	1000 lit
4	SS condenser	$4m^2$
2	SS jacketted receiver	600 lit
2	MS rubber lined vessel with stirrer	600 lit
2	SS basket centrifuge	1200 mm Ø
1	SS basket centrifuge	1000 mm Ø
2	MS rubber lined filter box	600 lit

Qty.	Item	Capacity
1	SS jacketted filter box	600 lit
1	SS pressure leaf filter	10 mg. sold cap.
3	Steam heated tray dryer of tray area	$30m^2$
1	- ditto -	$15m^2$
1	- ditto -	$10m^2$
1	Steam heated vacuum dryer	$12m^2$
4	Watering vacuum pump sets	$160m^3$/hr
1	High vacuum pump set	$520m^3$/hr
4	Pump sets (ss centrifugal)	50 lpm-25 mh
2	MS rubber lined pump sets	50 lmp-25 mh
1	Glass reactor assembly with necessary ancillaries	100 lit
1	SS jacketted filter	-
1	SS nutche filter with receiver	50 lit
1	SS pulveriser	25kg/hr
1	SS mechanical sieve	-
2	SS ion exchange resin column	0.6 mø x 1.8 m ht
1	SS blender	25 kg./batch