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SECTORAL WORKING PAPERS

In the course of the work on major sectoral studies carried out by the United Nations Industrial Development Organization (UNIDO), Studies and Research Division, several working papers are produced by the secretariat and by outside experts. Selected papers that are believed to be of interest to a wider audience are presented in the Sectoral Working Papers series. These papers are more exploratory and tentative than the sectoral studies. They are therefore subject to revision and modification before being incorporated into the sectoral studies.

Preface

This working paper was prepared by the Sectoral Studies Branch of UNIDO as an input to the study entitled "Opportunities for the manufacture of pharmaceutical chemicals in developing countries", Sectoral Studies Series No. 36, PPD.48, in order to assess the therapeutic prospects of selected drugs by the year 2000.

The products included in this paper are those that were selected for final analysis of domestic production opportunities in the above study.

Contents

EXPLANATORY NOTES

A comma (,) is used to distinguish thousands and millions.

A full stop (.) is used to indicate decimals.

Use of a hyphen between dates (e.g., 1960-1965) indicates the full period involved, including the beginning and end years.

Metric tons have been used throughout.

Besides the common abbreviations, symbols and terms and those accepted by the International System of Units (SI), the following abbreviations and contractions have been used in this report:

CAS	Chemical Abstracts Service
INN	International Nonproprietary Name
NF	National Formulary
R+D	Research and development
USP	United States Pharmacopeia

ACETYLSALICYLIC ACID (Aspirin, ASA)

1. Pharmaceutical use: minor analgesic, antipyretic and anti-inflammatory.

2. Other use: none.

3. Preparation exclusivity

ASA was first synthetized in 1853,[1] therefore, there is no product patent to-day.

Competition is intense on the non-prescription market both at branded and INN generic preparation levels.

4. Manufacturing process exclusivity

The computerized CAS search shows process R+D activities in recent years, therefore sales of ASA might be restricted by process claims in some countries. Bio-synthesis of the key intermediate, salicylic acid, has also been published.[2] Manufacturers with petrochemistry integration have a comparative advantage.

5. Preparation acceptance

ASA is included in the official WHO model list of essential drugs and also among the drugs for primary health care. Both regulatory authorities and the medical profession recommend its therapeutic use. The principal dosage form is tablets (300 mg and 500 mg).

6. Market size

ASA is freely available on the world market in crystalline and directly compressible forms. The latter is the technical choice of preference for tableting.

The market in industrialized countries at substance level was about 25,000 tons and $US 115 million in 1982.[3] The United States demand in 1986 was 13,400 tons.[4]

7. Demand trend

ASA demand is favourably affected by the phasing out of pyrazolone derivatives such as phenylbutazone, dipyrone, etc., particularly in Europe. Combination preparations of ASA, e.g., with paracetamol, caffeine and codeine are widely marketed. The prevention of heart attacks is a new indication that will increase the use of ASA among

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1/ The Merck Index, 10th Ed., p. 123.

2/ U.S. pat. 3,274,074 (1966)

3/ Chemical and Engineering News, 16 Sep. 1985, p. 42

4/ Chemical Market Reporter, 23 Feb. 1987.

geriatric patients. The linkage of ASA to Reye's syndrome has reduced consumption, particularly by children. On the balance, the life cycle curve of ASA is reaching the saturation level and will continue to track population growth in industrialized countries. Higher growth is expected in developing countries. The worldwide demand in thousand tons is estimated at a 3 per cent annual growth rate as follows:

1986	40,600
1990	45,500
2000	61,400

The value of the ASA world market at substance level was approximately $US 83 million in 1986.

Present therapeutic competition is paracetamol as a minor analgesic and ibuprofen as a minor analgesic and non-steroidal anti-inflammatory drug. ASA is expected to retain, even moderately increase its market share in its therapeutic group because it is the cheapest option as an analgesic, antipyretic and anti-inflammatory drug.

8. Price

The mean unit price of ASA in international trade was $US 2.04/kg at the end of 1986. The directly compressible grade costed $US 2.70/kg. The posted price was $US 4.50 in the USA at the same time. Acetylsalicylic acid is also sold in a coated form at a premium price of $US 8.80/kg.

The key intermediate, salicylic acid, was selling at $US 2.70/kg; phenol was available at $US 0.55/kg and acetic anhydride at $US 0.96/kg.[5/] All these starting materials and intermediates are petrochemicals, therefore, their prices are sensitive to changes in crude oil prices.

9. Main producers

The major manufacturers of ASA operate in the United States, in Western Europe, in the USSR and in the People's Republic of China. Medium- and small-size companies produce ASA all over the world, except in tropical Africa. Established plant capacities vary from 600 tons to 9,000 tons per year. Part of the production is for captive use.

10. Summary evaluation

ASA remains a very popular and the cheapest non-prescription minor analgesic, antipyretic and anti-inflammatory agent. It is practically recession proof. Developing countries represent the major market opportunity because the per capita consumption is about 10 g/year,

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5/ Chemical Marketing Reporter, 29 Dec. 1986. Note that posted prices do not necessarily represent levels at which transactions actually may have occurred.

whereas the same figure for industrialized countries is about 30 g/year.[6/] Manufacturers of the directly compressible grade and the coated form achieve better profitability. Alternative processes should be studied in more details.

11. Reliability of the evaluation: very good.

6/ Unpublished UNIDO study.

CHLOROQUINE

1. Pharmaceutical use: antimalarial, extra-intestinal antiamoebic.

2. Other use: none.

3. Preparation exclusivity

The synthesis by the condensation of 4,7-dichloroquinoline with 1-diethylamino-4-aminopentane was first described in 1939,[7/] therefore product patent does not exist.

The branded and INN generic competition is intense on the prescription market.

4. Manufacturing process exclusivity

The process patents of competing synthesis routes have probably expired although the computerized CAS search shows R+D activities also in recent years. Manufacturers with petrochemistry integration have a minor comparative advantage. Access to novoldiamine at a competitive price is an important intermediate linkage.

5. Preparation acceptance

Chloroquine is included in the official WHO model list of essential drugs and also among the drugs for primary health care. Both regulatory authorities and the medical profession support the use of chloroquine. Preparations include tablets (150 mg and 200 mg), injection (5%, 5 ml), and syrup (50 mg/5 ml).

6. Market size

Chloroquine substance is freely available in international trade in powder form. Directly compressible grade exists and it is the technical choice of preference for tableting.

Chloroquine is sold mainly in developing countries.

7. Demand trend

Chloroquine is the most frequently used antimalarial drug and its consumption shows a moderate growth of about 3 per cent on global level, mainly because its use is very cost effective. The worldwide demand in thousand tons is estimated as follows:

1986	1,450
1990	1,630
2000	2,200

The value of the chloroquine world market at substance level was approximately $US 40 million in 1986. Therapeutic competition from new antimalarials or eradication of the mosquito vector are not envisaged in the near future.

7/ The Merck Index, 10th Ed., p. 304.

Treatment with chloroquine or suitable analogues may offer a new approach to the management of diabetes.[8]

8. Price

The mean unit price of chloroquine fosfate in international trade was $US 28/kg at the end of 1986. Chloroquine sulfate could be purchased at $US 42/kg.

The key intermediates, 4,7-dichloroquinoline and novoldiamine, costed $US 37.15/kg and $US 15.78/kg, resp., in 1983. Diethyl malonate was available at $US 3.17/kg, triethyl orthoformate at $US 3.90/kg and 3-chloroaniline at $US 4.20/kg.[9] All the starting materials are petrochemicals, therefore, their prices are sensitive to changes in crude oil prices.

9. Main producers

The major manufacturers of chloroquine operate in Western and Eastern Europe, in the People's Republic of China and in India. Established plant capacities vary from 10 to 350 tons per year. Part of the production is for captive use.

10. Summary evaluation

Chloroquine is the most popular and cheapest antimalarial drug worldwide. Market opportunities include mainly tropical African countries. Chloroquine sulfate and the directly compressible grade of chloroquine fosfate are scarcely available, therefore, represent an opportunity in international trade.

11. Reliability of the evaluation: very good.

8/ British Medical Journal, 21 Feb. 1987, p. 465.

9/ UNIDO/IS.518 of 15 February 1985, Technical and economic analysis of the manufacture of chloroquine phosphate, p. 11.

CLOTRIMAZOLE

1. Pharmaceutical use: antifungal.

2. Other use: veterinary.

3. Preparation exclusivity

The synthesis of Clotrimazole was first described in 1969,[10] therefore product patents must have expired. There is a limited brand-name competition on the prescription market.

4. Manufacturing process exclusivity

Process R+D activities have not been searched but sales of clotrimazole might be restricted by process claims in some countries. The preparation of the key intermediate, 2-chlorotriphenyl-methyl chloride, from 2-chloro-benzoic acid needs special expertise.

5. Preparation acceptance

Clotrimazole is a therapeutic alternative to miconazole which is official in the WHO model list of essential drugs. Clotrimazole is official in the USP. Both regulatory authorities and the medical profession support its use. Principal dosage forms include a 1 per cent (vaginal) cream, 1 per cent topical solution and vaginal tablets (100 mg).

6. Market size

Clotrimazole is used as a microfine powder. It is not available in international trade. Clotrimazole ranked 146 in the industrialized countries in 1985 with a market value of $US 140 million at the preparation level. Tonnage figures are not available; 200 tons would be a rough estimate; the corresponding value at substance level is $US 14 million.

7. Demand trend

Clotrimazole is a broad-spectrum antifungal agent of first choice for the topical treatment of tinea and candida infections. The annual average percentage growth 1981-85 was 9 per cent in value.

The therapeutic indication is as important in developing countries as in industrialized countries.

Present therapeutic competitor is mainly miconazole.

8. Price

The unit price of clotrimazole was $US 70/kg at the end of 1986. The key intermediate is probably produced for captive use only. Manufacturers

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10/ The Merck Index, 10th Ed., p. 343.

with petrochemistry integration have a minor comparative advantage. 2-chlorobenzoic acid costed $US 8.60/kg.[11]

9. Main producers

The originator and main producer is Bayer. Production is for captive use only.

10. Summary evaluation

Clotrimazole is one of the preferred choices for the topical treatment of fungal infections. The therapeutic sub-market is continuously growing worldwide and the pharmaceutical chemical is not available in international trade. Market opportunities include, therefore, both the industrialized and developing countries.

11. Reliability of the evaluation: moderate but current therapeutic use and future prospect analysis is good.

11/ Chemical Marketing Reporter, 29 December 1986. Note that posted prices do not necessarily represent levels at which transactions actually may have occurred.

PARACETAMOL (Acetaminophen, APAP)

1. Pharmaceutical use: minor analgesic.

2. Other use: none.

3. Preparation exclusivity

The synthesis from p-nitrophenol was first described in 1878,[12] therefore product patent does not exist.

The branded and INN generic competition is intense on the non-prescription market.

4. Manufacturing process exclusivity

The computerized CAS search shows process R+D activities in recent years, therefore sales of APAP might be restricted by process claims in some countries. Biosynthesis has also been published.[13] Manufacturers with petrochemistry integration have a comparative advantage.

5. Preparation acceptance

Paracetamol is included in the official WHO model list of essential drugs. Both regulatory authorities and the medical profession support the use of paracetamol. Preparations include tablets (120 mg and 500 mg), and elixir and syrup (120 mg/5 ml).

6. Market size

Paracetamol substance is freely available in international trade in fine powder, crystalline and directly compressible forms. The latter is the technical choice of preference for tableting. The market in industrialized countries at preparation level was estimated at 14,200 tons and $US 100 million in 1982.[14]

7. Demand trend

Paracetamol is well tolerated, lacks many of the side-effects of acetylsalicylic acid which is an advantage mainly in long-term and/or repeated use. The demand is favourably affected by the phasing out of pyrazolone derivatives, e.g., phenylbutazone, oxyphenbutazone, dipyrone, etc., particularly in Europe. Combination preparations of paracetamol, e.g., with acetylsalicylic acid, caffeine or codeine are successfully marketed. Poisoning caused by external potassium cyanide contamination and related to a specific brand of paracetamol dropped sales in 1985 but the market has recovered in the meantime.

12/ The Merck Index, 10th Ed., p. 7.

13/ J. Pharm. Sci., 64, pp. 1737-1759 (1975), Arch. Biochem. Biophys., 161, pp. 551-558 (1974) and Plant Medica, 15, pp. 97-103 (1967)

14/ Chemical and Engineering News, 16 September 1985, p. 42.

Paracetamol is still in the growing section of the life cycle curve. An overall annual growth rate of 5 per cent is expected till 1990, and a rate of 3 per cent between 1990 and 2000. Hence the worldwide demand in thousand tons is estimated as follows:

1986	17,920
1990	22,870
2000	31,660

The value of the paracetamol world market at substance level was approx. $US 86 million in 1986.

Present therapeutic competitors are acetylsalicylic acid and ibuprofen, particularly if the latter becomes a non-prescription drug in many countries. Therapeutic competition from new minor analgesics is not envisaged in the near future.

8. Price

The main unit price of paracetamol in international trade was $US 4.30/kg at the end of 1986. The directly compressible grade sold at $US 5.30/kg. The posted price was $US 6.30 in the USA at the same time.[15/]

The key intermediate, p-aminophenol, costed $US 7.15/kg; p-nitrophenol was available at $US 2.30/kg, nitrobenzene at $US 0.73/kg, benzene at $US 0.26/kg, acetic anhydride at $US 0.96/kg and phenol at $US 0.55/kg.[16/] All these starting materials and intermediates are petrochemicals, therefore, their prices are sensitive to changes in crude oil prices.

9. Main producers

The major manufacturers of paracetamol operate in the United States, in Western Europe, in the People's Republic of China, in the Republic of Korea, in Japan and in India. Smaller quantities are produced in Argentina, Brazil, Eastern Europe, Mexico and Taiwan. Established plant capacities vary from 50 to 4,000 tons per year. Part of the production is for captive use.

10. Summary evaluation

Paracetamol is the most popular and a very cost-effective minor analgesic worldwide. Market opportunities include Northern and Eastern Europe which traditionally used pyrazolone-type analgesics. Developing countries, particularly those having long-term trade relation with English-speaking countries, represent a continuously increasing market for paracetamol. Manufacturers of the directly compressible grade achieve better profitability. Alternative synthesis routes should be studied in more details.

11. Reliability of the evaluation: very good.

15/ Chemical Market Reporter, 29 December 1986. Note that posted prices do not necessarily represent levels at which transactions actually may have occurred.

16/ Ibid.

PENTAMIDINE

1. Pharmaceutical use: antileishmaniasis drug.

2. Other use: veterinary antiprotozoal.

3. Preparation exclusivity

The synthesis of pentamidine was first described in 1946,[17] therefore product patent does not exist.

The isethionate salt is marketed under the INN name, whereas the mesylate under a brand-name on the prescription market.

4. Manufacturing process exclusivity

Process R+D activities have not been searched in the CAS files.

5. Preparation acceptance

Pentamidine is included in the official WHO model list of essential drugs as a powder for injection (200 mg) in vials.

6. Market size

Pentamidine salts are not available in international trade.

Visceral, mucocutaneous and cutaneous leishmaniases affect large numbers of patients mainly in developing countries. The metastatic mucous forms of leishmaniasis cause severe mutilation and suffering in tropical Latin America. The incidence of these complications which depend on the infecting strain of Leishmania, following a primary skin lesion, varies from 2 per cent in Panama to 80 per cent in Paraguay. The visceral form of leishmaniasis (Kala azar) appears to be increasing in incidence (and there may be a risk of severe epidemics) in eastern India and in East Africa.[18]

7. Demand trend

Only three groups of specific antileishmanials are available. There are no drugs for prophylaxis.

Sodium stibogluconate and meglumine antimonoiate are the only safe and highly specific antileishmanial drugs. However, even these must be given in prolonged courses, and there is some tendency for accumulation of antimony in some patients, with subsequent risk of cardiac and other toxicity. Both drugs are very expensive and short in supply.

17/ The Merck Index, 10th Ed., p. 1023.

18/ Pharmaceuticals for Developing Countries, National Academy of Sciences, Washington, D.C. (1979), p. 39.

Pentamidine is used as a second-line drug with variable response. Amphotericin B is used as a last resort and only under carefully controlled hospital conditions.[19]

Pentamidine was extensively used, especially in francophone Africa, in the prevention of trypanosomiasis. It is not favoured to-day because pentamidine-resistant strains of trypanosomes are common, toxic side-effects are fairly frequent and early infections may be concealed by pentamidine. Its use in therapy is unlikely to produce complete cures; it is ineffective against trypanosomes in the brain. Chemoprophylactic attempts to protect cattle have been marred by drug resistance.

8. Price

No information is available.

9. Main producers

There are two manufacturers in Western Europe but production is for captive use only.

10. Summary evaluation

Pentamidine appears to be a less important antileishmanial drug than the pentavalent antimon compounds, of which sodium stibogluconate is also official in the official WHO model list of essential drugs.

The antitrypanosomal indication of pentamidine is even less important. Market opportunities include tropical developing countries, mainly in Latin America, eastern India and East Africa.

Other antileishmanial drugs should be studied in more details because the demand side is industrially attractive.

11. Reliability of the evaluation: moderate but current therapeutic use and future prospect analysis is good.

19/ Ibid., pp. 39 and 71.

PRAZIQUANTEL

1. Pharmaceutical use: antischistosomal drug.

2. Other use: veterinary anthelmintic.

3. Preparation exclusivity

The synthesis of praziquantel was published in 1975,[20] therefore product patent exists in industrialized countries.

Praziquantel was jointly developed by Bayer and E. Merck.

4. Manufacturing process exclusivity

Process patents are valid in several countries.

5. Preparation acceptance

Praziquantel is included in the official WHO model list of essential drugs in the form of tablets (600 mg). It was awarded the 1987 Prix Galien in France for the considerable advance it represents in the treatment of human parasitic infections, in particular schistosomiasis.

6. Market size

Praziquantel is scarcely available in international trade.

Schistosomiasis is endemic in 74 countries where over 600 million people are exposed to the risk of infection and an estimated 200 million more are actually infected.[21]

7. Demand trend

Schistosomiasis is a serious and increasing problem (associated particularly with irrigation and hydro-electric dam projects) in many areas of Africa, in Brazil, in the Philippines, and part of Indonesia; it can also be regarded mainly as a cause of morbidity. The liver damage it can cause and its severe distorting effects on the urinary and gastro-intestinal tracts greatly affect the quality of life. Molluscidides and vaccines are considered promising for its ultimate control. Chemotherapy is increasingly used - but the greatest impact could come from improvements of sanitation and water supplies.[22]

20/ The Merck Index, 10th Ed., p. 1109.

21/ Tropical Disease Research, 7th Programme Report, UNDP/World Bank/WHO, p. 3/3 (1984).

22/ Pharmaceuticals for Developing Countries, National Academy of Sciences, Washington, D.C. (1979), p. 39.

Metrifonate and oxamniquine have been found safe and effective oral drugs in the treatment of S. mansoni, S. haematobium and S. japonicum infections. Differences in drug susceptibilities have been observed in different populations and drug resistance has been reported.

Phase III clinical trials with praziquantel were found effective in about 67 per cent of the cases after one year of treatment with a daily dose of 40 mg/kg. No data have been available on the anthelmintic indication.

Praziquantel is the drug of choice for infections caused by S. japonicum and S. mekongi, and various kinds of flukes. Praziquantel is widely used as a veterinary anthelmintic.

Praziquantel was launched as a schistosomicide in the Philippines (1979), Federal Republic of Germany (1980), Brazil (1982), Thailand (1982) and Egypt (1983). Other indications are also registered in Colombia, Ecuador, Mexico, Peru and Venezuela.

New drugs include Agrimophol (phase III clinical trial), Amoscanate (pre-registration) and Oltipraz (phase III clinical trial).[23/]

8. Price

The unit price of praziquantel in international trade was $US 380/kg at the end of 1986.

9. Main producers

Praziquantel is manufactured by Bayer and E. Merck for captive use. Availability in international trade suggests the existence of a third producer.

10. Summary evaluation

The antischistosomal sub-market represents an industrially attractive opportunity because the number of patients is high, the disease is reproduced, therapy takes one year at an average daily dose of 3 g/patient and the unit price of praziquantel is high. Risks include patent protection and financial unability of patients to purchase the drug.

11. Reliability of the evaluation: moderate but current therapeutic use and future prospect analysis is good.

23/ Pharmaprojects, V&O Publications Ltd., Richmond, England, p. 648 (1984).

PYRIMETHAMINE

1. Pharmaceutical use: antimalarial.

2. Other use: veterinary antimicrobial, usually as a sulfonamide synergist.

3. Preparation exclusivity

The synthesis of pyrimethamine was first described in 1951,[24/] therefore product patent does not exist. There is a branded and INN generic competition on the prescription market.

4. Manufacturing process exclusivity

The process patents of the competing synthesis routes have probably expired.

5. Preparation acceptance

Pyrimethamine in combination with sulfadoxine is included in the official WHO model list of essential drugs. Both regulatory authorities and the medical profession support the use of this combination. The principal dosage form is pyrimethamine 25 mg + sulfadoxine 500 mg tablets.

6. Market size

Pyrimethamine is freely available in international trade.

7. Demand trend

Pyrimethamine + sulfadoxine combination is a complementary preparation in the WHO model list of essential drugs. Its use is recommended only when drugs in the main list are known to be ineffective or inappropriate for a given individual. Pyrimethamine is administered also alone for the prevention of malaria attacks.

8. Price

No information is available, either on pyrimethamine or important starting material and intermediate prices.

9. Main producers

The major manufacturers of pyrimethamine operate in Western Europe and Japan. Smaller quantities are produced in Eastern Europe. Part of the production is for captive use.

10. Summary evaluation

The scarcity of data does not permit meaningful evaluation.

11. Reliability of data: not applicable.

24/ The Merck Index, 10th Ed., p. 11 2.

SALICYLIC ACID

1. Pharmaceutical use: keratoplastic and keratolytic.

2. Other use: veterinary antiseltic and antifungal, keratolytic.

Uses in the USA are: acetylsalicylic acid, 65 per cent; salicylate esters and salts, 20 per cent; foundry resins, 7 per cent; miscellaneous including rubber retarder and dyestuff intermediate, 8 per cent.[25]

3. Preparation exclusivity

The synthesis of salicylic acid was first described in 1874,[26] therefore product patent does not exist.

There is INN competition on the non-prescription market.

4. Manufacturing process exclusivity

The computerized CAS search shows process R+D activities in recent years, therefore, sales of salicylic acid might be restricted by process claims in some countries. Biosynthesis has also been published.[27]

Manufacturers with petrochemistry integration and acetylsalicylic acid production have a comparative advantage.

5. Preparation acceptance

Salicylic acid is included both in the official WHO model list of essential drugs and among the drugs for primary health care. Both regulatory authorities and the medical profession support the topical use of salicylic acid. The keratoplastic and keratolytic preparation is a 5 per cent topical solution, whereas the antifungal ointment or cream contains 3 per cent of salicylic acid as the keratolytic agent in combination with 6 per cent of the fungistatic benzoic acid.

6. Market size

Salicylic acid is freely available in international trade. Sales in the USA were about 24,000 tons and about $US 49 million in 1986; it was predicted to grow by 0 to 1 per cent annually in the future.[28]

7. Demand trend

Demand for salicylate esters and salts shows a fairly strong growth, especially in the flavor and fragrance industry. Other end uses

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25/ Chemical Market Reporter (CMR), 2 March 1987.

26/ German pat. 426.

27/ U.S. pat. 3,274,074 (1966 to Kerr-McGee).

28/ CMR, op.cit.

decline and salicylic acid is becoming more and more closely tied to acetylsalicylic acid business. The therapeutic sub-market for salicylic a d is a variety of skin diseases associated with hyperkeratosis.

The current demand and future trend in the non-salicylate areas in developing countries cannot be estimated due to the lack of data.

Present therapeutic competitors include topical resorcinol preparations. New and cheap antifungal compounds are not expected to come from R+D activities.

8. Price

The price of salicylic acid was $US 2.71/kg (technical), $US 2.93/kg (USP, crystals) and $US 3.70/kg (USP, powder). The main starting material, phenol, costed $US 0.55/kg;[29] the phenol price is sensitive to changes in crude oil prices.

9. Main producers

Same as those listed for ASA (page 2) except perhaps for the small producers.

10. Summary evaluation

Salicylic acid is the key intermediate of acetylsalicylic acid. The production of the two pharmaceutical chemicals should be seen only together.

11. Reliability of the evaluation: very good.

29/ Chemical Marketing Reporter, 29 December 1986. Note that posted prices do not necessarily represent levels at which transactions actually may have occurred.

SULFONAMIDES

1. Pharmaceutical use: antibacterial and antimalarial.

2. Other use: veterinary medicine, feed additives.

3. Preparation exclusivity

The synthesis of sulfadoxine was first described in 1962;[30] the basic patent of sulfamethoxazole dates back to 1959.[31] Other sulfonamides, as a rule, are older than these compounds, therefore, product patents do not exist anymore. Composition claims have probably expired.

The branded and INN generic competition is intense on the prescription market.

4. Manufacturing process exclusivity

Process R+D activities in CAS files have not been searched. Manufacturers with petrochemistry integration have a comparative advantage.

5. Preparation acceptance

Salazosulfapyridine, sulfacetamide, sulfadimidine, sulfadoxine and sulfamethoxazole are included in the official WHO model list of essential drugs. Sulfadimidine and sulfamethoxazole are examples of their therapeutic group and various sulfonamides such as sulfadiazine, sulfamerazine, sulfathiazole, etc. could serve as equivalent alternatives. Both regulatory authorities and the medical profession support the use of sulfonamides.

Preparations include tablets (500 mg), oral suspension (500 mg/5 ml) and eye ointment and eye drops, as well as the antibacterial sulfamethoxazole + trimethoprim and the antimalarial sulfadoxine + pyrimethamine combinations.

6. Market size

Sulfonamide substances are freely available in international trade. The market in industrialized countries at substance level was estimated at 24,000 tons and $US 90 million in 1982.[32] The world market should be about twice as large because the relative importance of the antibacterial therapeutic sub-market is higher in developing countries than in industrialized countries. Cost considerations speak also for sulfonamides in developing countries and the antimalarial use is dominant in the third world.

30/ The Merck Index, 10th Ed., pp. 1276 and 1278.

31/ Ibid.

32/ Chemical and Engineering News, 16 September 1985, p. 42.

7. Demand trend

The sulfonamide market is saturated even declining in industrialized countries and is estimated to grow at a very moderate rate in developing countries. Hence the worldwide demand in thousand tons is estimated as follows:

1986	94,000
1990	97,000
2000	108,000

Present therapeutic competitors are antibiotics and, to a small extent, antimalarials on the prescription market. Major advantages of sulfonamides are their low cost and ease of administration; the major disadvantage is their limited effect.

Other end uses accounted for 28 per cent of the total market in the USA in 1985.

8. Price

The mean unit prices of sulfonamides in international trade at the end of 1986 are listed below:

Phthalylsulfathiazole	$US 8.00/kg
Salazosulfapyridine	...
Sulfacetamide sodium	...
Sulfadiazine	$US 11.90/kg
Sulfadimidine	$US 9.80/kg
Sulfadimidine sodium	$US 10.90/kg
Sulfadoxine	$US 40.50/kg
Sulfaguanidine	$US 4.80/kg
Sulfamerazine	$US 15.50/kg
Sulfamethoxazole	$US 17.60/kg
Sulfanilamide	$US 4.15/kg

Aniline was available at $US 0.33/kg, chlorosulfonic acid at $US 0.41/kg and acetanilide at $US 0.71/kg.[33/] The starting materials are petrochemicals, consequently their prices are sensitive to changes in crude oil prices. The side-chains are pyrimidine, pyridazine and isoxazole derivatives.

9. Main producers

The major manufacturers of sulfonamides operate in Western and Eastern Europe, in the People's Republic of China and in India. The side chains for sulfonamides are usually synthetized in the same plant.

10. Summary evaluation

Sulfonamides are the cheapest antibacterial drugs worldwide. The economically most attractive sub-market is the sulfamethoxazole + trimethoprim combination which is expected to show a moderate growth in

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33/ Chemical Marketing Reporter, 29 December 1986. Note that posted prices do not necessarily represent levels at which transactions actually may have occurred.

developing countries. Single members of the group represent a stable but stagnating demand in developing countries. Production of sulfonamides should be seen together with that of diuretics and oral hypoglycoemics manufactured by similar chemical conversions in the same plant.

11. Reliability of the evaluation: good.

SULFONYLUREAS

1. Pharmaceutical use: non-insulin dependent ("maturity onset") adult diabetes mellitus.

2. Other use: none.

3. Preparation exclusivity

The first member of the group, carbutamide, was synthetized in 1955.[34/] Glipizide dates back to 1970.[35/] Other sulfonylureas are older than glipizide, therefore, product patents exist only for the latter, if at all.

Chlorpropamide, tolbutamide and tolazamide brands and INN preparations compete on the prescription market.

4. Manufacturing process exclusivity

Process R+D activities in CAS files have not been searched. Manufacturers with petrochemistry integration have a comparative advantage. Access to starting materials, fine chemical intermediates and special side chains at competitive prices is an important chemical barrier to new entry.

5. Preparation acceptance

Oral hypoglycemic agents are not included in the WHO Model List of Essential Drugs. Acetohexamide, chlorpropamide, tolazamide and tolbutamide are official in the USP/NF. Both regulatory authorities and the medical profession support the use of sulfonylureas.[36/]

The principal pharmaceutical dosage form is tablets.

6. Market size

Chlorpropamide and tolbutamide are freely available in international trade. Acetohexamide and tolazamide are sold mainly in the United States. Tonnage and $US values of the world market are not available but the relative importance of the therapeutic submarket is much higher in industrialized than in developing countries.

7. Demand trend

The second generation sulfonylureas - glipizide and glibenclamide - have rapidly gained acceptance in the United States. These two products accounted for over 25 per cent of oral hypoglycemic prescriptions and almost 16 per cent of all diabetes therapy in 1985. Chlorpropamide

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34/ The Merck Index, 10th Ed., p. 255 and 635.

35/ Ibid.

36/ FDA's Seventh Annual Review of Drug Utilization in the US - 1985.

remained on the top of this class with 39 per cent of scripts, although it had held up to 53 per cent of the market before glipizide and glibenclamide were launched.[37/]

8. Price

Tolbutamide was available in international trade at $US 6.50/kg at the end of 1986. The derived unit price of chlorpropamide was $US 45/kg in 1985.

Toluene was available at $US 0.18/l, chlorosulfonic acid at $US 0.41/kg and phenylethylamine at $US 3.30/kg.[38/] The starting materials are petrochemicals, consequently their prices are sensitive to changes in crude oil prices.

Average prescription costs to patients - based on brand name prices - ranged from $US 14.30 for tolbutamide to $US 24 for tolazamide.[39/]

9. Main producers

The major manufacturers of sulfonylureas operate in the United States, the Federal Republic of Germany and Eastern Europe. There are many small and middle-size producers all over the world. A significant part of the production is for captive use.

10. Summary evaluation

Oral hypoglycemics represent a stable and moderately growing market in all countries where a significant part of the population is older than 40 years. Developing countries are gradually gaining importance, particularly for the second generation drugs. Production of sulfonylureas should be seen together with that of antibacterial sulfonamides and diuretics manufactured by similar chemical conversions in the same plant.

11. Reliability of the evaluation: good.

37/ Ibid.

38/ Ibid.

39/ Chemical Marketing Reporter, 29 December 1986. Note that posted prices do not necessarily represent levels at which transactions actually may have occurred.

SULFONAMIDE DIURETICS

1. Pharmaceutical use: antihypertensives and diuretics.

2. Other use: none.

3. Preparation exclusivity

Chlorothiazide was first synthetized in 1957,[40] whereas furosemide and hydrochlorothiazide respectively in 1962.[41] Therefore, there is no product patent to-day.

Competition is intense on the prescription market both at branded and INN generic preparation levels.

4. Manufacturing process exclusivity

Process R+D activities in CAS files have not been searched. Manufacturers with petrochemistry integration have a comparative advantage. 2,4-Dichlorobenzoic acid and furfurylalcohol are important intermediate linkages in the production of furosemide.

5. Preparation acceptance

Furosemide and hydrochlorothiazide are included in the official WHO Model List of Essential Drugs as examples of their therapeutic group. Chlorothiazide is official in the USP. Both regulatory authorities and the medical profession support the use of the above diuretics.

The principal preparations are: chlorothiazide tablets 250 mg and 500 mg, hydrochlorothiazide tablets 50 mg and 100 mg, and furosemide tablets 40 mg and injection, 10 mg/ml in 2-ml ampoules.

6. Market size

Hydrochlorothiazide and furosemide are available in international trade. Chlorothiazide is not regularly demanded. Tonnage and $US values of the world market are not available but the relative importance of the therapeutic submarket is much higher in industrialized than in developing countries.

7. Demand trend

Thiazides, as one of the possible alternatives, are used to initiate therapy of mild hypertension either alone or in combination with other antihypertensives. The thiazides are the diuretics of choice in the management of edema due to mild-to-moderate congestive heart failure.[42]

40/ The Merck Index, 10th Ed., pp. 305, 615 and 692.

41/ Ibid.

42/ Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th ed. (1980), pp. 902 and 906.

Furosemide is the most frequently prescribed high-ceiling diuretic for the treatment of edema of cardiac, hepatic, or renal origin. Prompt diuresis occurs after parenteral administration.[43]

8. Price

Prices are not vailable for these pharmaceutical chemicals. 3-Chloroaniline was available at $US 0.41/kg, 4,6-Dichloro-3-sulfamoylbenzoic acid at $US 95 and furfuryl alcohol at $US 1.58/kg.[44]

9. Main producers

The major producers of thiazides operate in the United States, in Western and Eastern Europe, in the People's Republic of China and in India. Captive use is significant in a few countries only.

The largest furosemide manufacturer, Hoechst, operates production units in the United States, in Western Europe and in several developing countries. This production is for captive use. There are many small and medium-size manufacturers in Western and Eastern Europe, in the People's Republic of China and in India. Established capacities vary from 5 to 100 tons per year.

10. Summary evaluation

The basic pharmacological action of thiazides is the same as for chlorothiazide. Hydrochlorothiazide and furosemide represent a stable and growing market in terms of quantity in all countries. Increasing generic competition has resulted in decreased values of furosemide sales in industrialized countries. Developing countries are gaining importance because of changing morbidity patterns. Hydrochlorothiazide is the most cost-effective drug of this category and furosemide demand has favourably been affected by the decreasing price trend since the expiry of the product patent.

Production of thiazides and furosemide should be seen together with that of antibacterial sulfonamides and sulfonylureas manufactured by similar chemical conversions in the same plant.

11. Reliability of the evaluation: moderate but current therapeutic use and future prospect analysis is good.

43/ Ibid.

44/ Chemical Marketing Reporter, 29 December 1986. Note that posted prices do not necessarily represent levels at which transactions actually may have occurred.

TRIMETHOPRIM

1. Pharmaceutical use: antibacterial.

2. Other use: veterinary medicine.

3. Preparation exclusivity

The synthesis of trimethoprim from guanidine and beta-ethoxy-3,4,5-trimethoxybenzylbenzalnitrile was first described in 1962,[45/] therefore product patent does not exist. Composition claims have probably expired.

Trimethoprim is mainly used in combination with sulfamethoxazole, and to a lesser extent, with other sulfonamides. The branded and INN generic competition is intense on the prescription market.

4. Manufacturing process exclusivity

The computerized CAS search shows process R+D activities in recent years, therefore, sales of trimethoprim might be restricted by process claims in some countries.

There are many different synthesis routes which should be studied in sufficient details to come to meaningful conclusions.

Access to trimethoxybenzaldehyde at a competitive price is an important intermediate linkage.

5. Preparation acceptance

The combination preparations of sulfamethoxazole 100 mg + trimethoprim 20 mg and sulfamethoxazole 400 mg and trimethoprim 80 mg, respectively, are included in the official WHO model list of essential drugs. WHO permits the substitution of sulfamethoxale with sulfonamides of equivalent therapeutic effect. Both regulatory authorities and the medical profession support the use of these combinations. The most important dosage form is the tablets.

6. Market size

Trimethoprim is freely available in international trade. Trimethoprim was ranked 56 in industrialized countries with a market value of about $US 300 million at the preparation level in 1985.

7. Demand trend

The market is saturated for trimethoprim + sulfamethoxazole combination products in industrialized countries and a moderate growth can be expected in developing countries.

45/ The Merck Index, 10th Ed., p. 1387.

Present therapeutic competitors are the antibiotics. New therapeutic competition is expected from carbapenems, monobactams and quinolones, particularly in industrialized countries.

8. Price

The mean unit price of trimethoprim was $US 30.90/kg at the end of 1986. The key intermediates are trimethoxybenzaldehyde and beta-methoxy-propionitrile or beta-ethoxipropionitrile in the standard processes; acrylonitrile, malonic esters and urea, cyanoacetic acid esters and guanidine, malodinitrile, etc. can also be used as starting materials.

9. Main producers

The major manufacturers of trimethoprim operate in Western and Eastern Europe and probably in some developing countries. Part of the production is for captive use.

10. Summary evaluation

Trimethoprim, in combination with sulfamethoxazol, is one of the effective and relatively cheap antibacterial drugs. The market is mature in industrialized countries and is expected to grow at a moderate rate in developing countries.

Alternative synthesis routes should be studied in more details.

11. Reliability of the evaluation: good.

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(Working paper to the study "Opportunities for the manufacture of pharmaceutical chemicals in developing countries")

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