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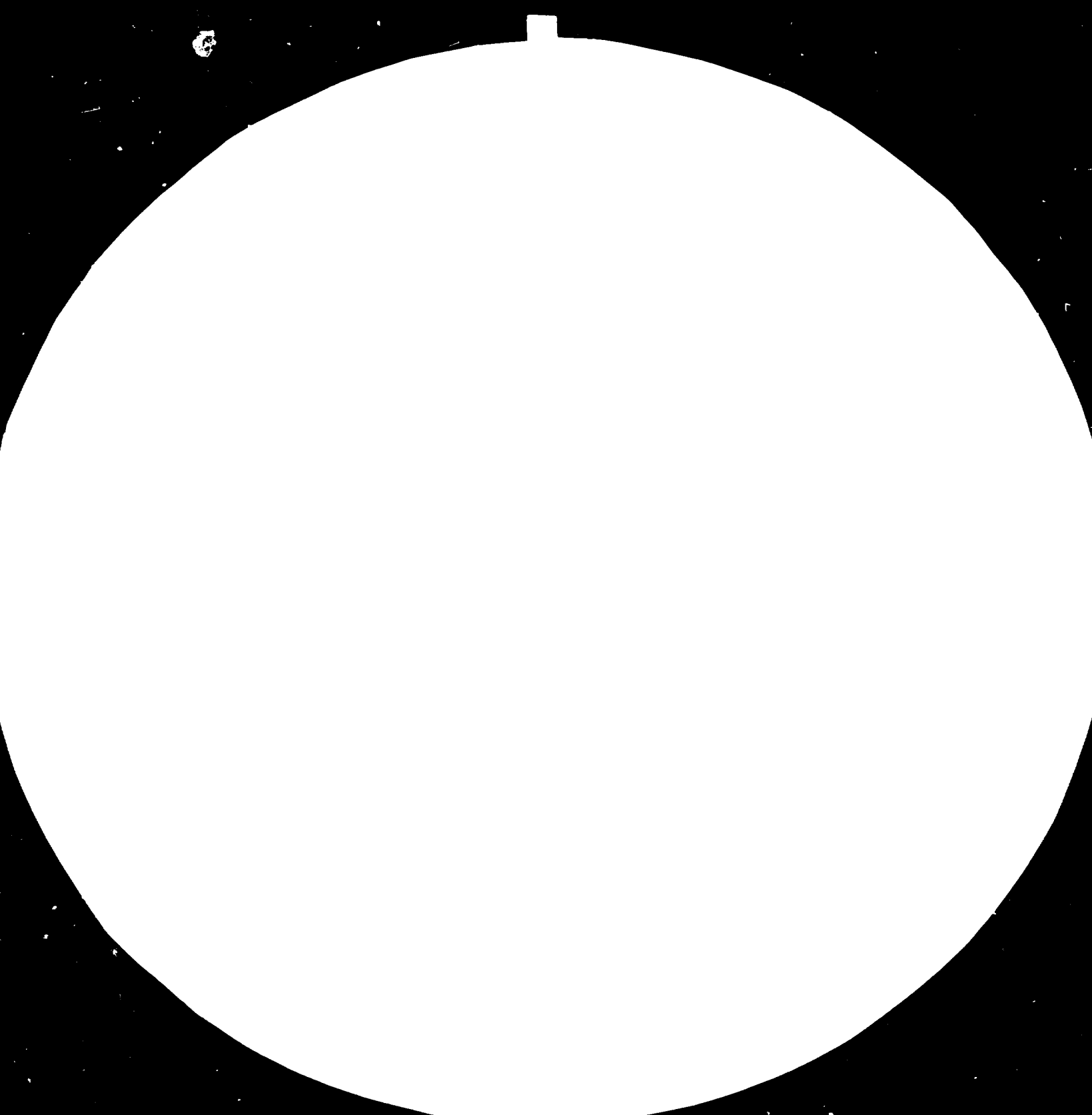


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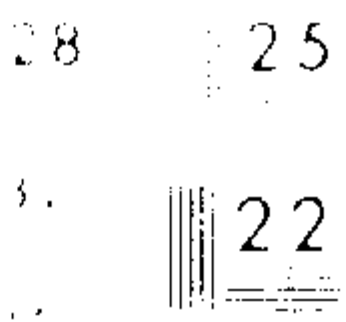
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TECHNO-ECONOMIC ANALYSIS OF THE MANUFACTURE OF PHARMACEUTICAL BULK SUBSTANCES

AMPICILLIN

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UNIDO Secretariat
Sectoral Studies Branch
Division for Industrial Studies

March 1983

~~IS/.....~~

TECHNO-ECONOMIC ANALYSIS OF THE MANUFACTURE OF AMPICILLIN

1. BASIC DATA OF THE BULK SUBSTANCE

1.1 International Non-Propietary Name: AMPICILLIN[1/]

1.2 Other Common Names:

1.3 Graphic Formula

1.4 Chemical Formula: $C_{16}H_{19}N_3O_4S.3H_2O$

1.5 Molecular Weight: 403.45

1.6 Chemical Abstracts Index Name: 4-Thia-1-azabicydo-/3.2.0/heptane--2-carboxylic acid, 6-/(aminophenyl-acetyl)amino _/-3.3-dimethyl--7-oxo-, trihydrate, /2S-/2 . 5 . 6 /S*/_/_/-.
/2S-/2 . 5 . 6 /S*/_/_/-.

1.7 CAS Registry Number: / 7177-48-3 _/

1.8 Other Forms: AMPICILLIN may be used in the anhydrous form /69-53-4_/ but commercial AMPICILLIN is usually the trihydrate. One kg of AMPICILLIN trihydrate is equivalent to 0.866 kg of anhydrous form. The monosodium salt / 69-52-3 _/ is used for the preparation of injectable solutions. One kg of AMPICILLIN sodium is equivalent to 0.941 kg of anhydrous form.

1/ Revised WHO Model List of Essential Drugs, 1983.

1.1 Brief ~~Description of the Product-Life~~ History of the Product A patent application was made by Beecham in 1958 for penicillin derivatives and for their preparation from 6-aminopenicillanic acid (6-APA). This patent was granted under Brit. Pat. 873,049 in 1961, which is the basic patenbt of semisynthetic penicillin derivatives and their preparation.

The principle of this patent covered process is the acylation of 6-APA by acids containing protected amino groups under adequately mild conditions ensuring the integrity of the penicillin structure.

The acylation of 6-APA by mixed anhydrides and the subsequent catalytic hydrogenation for the removal of the protecting groups to produce the free acid form are described in the patent as the preferred synthesis route.

The synthesis of AMPICILLIN, as one example of the new semisynthetic penicillin derivatives, is described in the basic patent. The obtained substance cvontained however only 48 per cent of AMPICILLIN.

A large number of semisynthetic penicillins has been synthetized on the basis of this patent during the last two decades. Out of these, AMPICILLIN is produced and used in the largest quantities. The leading position of AMPICILLIN on the penicillin sub-market is decisively due to its broad spectrum activity and relatively low price.

The number of manufacturers is large and increases from year to year as the basic patent has expired and further process patents are expiring.

Otherwise, it is characteristic that 59 patents concerning AMPICILLIN have been granted during the last six years.[2/] These relate partly to the improvement of the process (simplified technology, increased yield, purification of the bulk substance, etc. and partly to the preparation of new AMPICILLIN derivatives. Thus, the technology has continuously been improved up to now.

2/ International Classification of Procedures in Medicine, World Health Organization, Geneva, 1970, Vol. 2, p. 6-2.

1.9 Basic Patent: British Patent 873,049 (1961 to Beecham)

1.10 Therapeutic Category: broad-spectrum penicillins (6-004).[3]

2. BRIEF DESCRIPTION OF THE PRODUCTION PROCESSES

The production processes can be classified into two main groups:

One group includes the so-called "Dane salt" processes described in Brit. Pat. 991,558 (1965 to Beecham). "Dane salt" is the condensation product of phenylglycine sodium or potassium with a beta-diketone or a beta-oxoester; commonly, ethyl acetoacetate is used. 6-APA is then acylated with the mixed anhydride prepared from the "Dane salt" with ethyl chloroformate, in the presence of a weak organic base as a catalyst. Thus, a N-protected AMPICILLIN is obtained which in turn is hydrolyzed to give AMPICILLIN. According to the examples of the basic patent, the purity of the obtained AMPICILLIN is between 25 and 79% and the yield changes from 14 to 29%.

The production processes of the second group are characterized by the acylation of 6-APA, protected at the amino and carboxylic groups, with phenylglycine chloride hydrochloride in the presence of an acid binding agent and the protecting groups are removed by hydrolysis in the second step. This synthesis route is called the "sylication process", since the amino and carboxylic groups of 6-APA can be best protected by silyl radicals. ~~The basic patent for~~ This process was first described in ~~is~~ U.S. Pat. 3,249,622.

Thus, two key intermediates are involved in the production of AMPICILLIN: 6-APA and D/-/-phenylglycine. Both intermediates are exclusively used in the pharmaceutical industry. D/-/-Phenylglycine ~~compound~~ is transformed either to "Dane salt" or to phenylglycine chloride hydrochloride during the manufacturing process; ~~but~~ both of them can also be purchased.

~~2/ Patent Information on AMPICILLIN, various issues of Chemical Abstracts between Jan. 1977 and March 1983.~~ cancelled

2.1 The Dane Salt Process

2.1.1 Schematic illustration of the synthesis:

2.1.2 Chemical reactions

a) $C_8H_9NO_2 + C_6H_{10}O_3 + KOH = C_{14}H_{16}NO_4K + 2H_2O$

151.16 130.14 56.10 301.37 36.03

b) $C_{14}H_{16}NO_4K + C_3H_5ClO_2 = C_{17}H_{21}NO_6 + KCl$

301.37 108.53 335.53 74.55

c) $C_{17}H_{21}NO_6 + C_8H_{12}N_2O_3S = C_{22}H_{27}N_3O_6S + CO_2 + C_2H_6O$

335.35 216.28 461.55 44.01 46.07

d) $C_{22}H_{27}N_3O_6S + 5H_2O = C_{16}H_{19}N_3O_4S.3H_2O + C_2H_4O_2 + C_4H_8O_2$

461.55 90.07 403.47 60.05 88.10

2.1.3 Combined equation of the synthesis

$C_8H_9NO_2 + C_6H_{10}O_3 + KOH + C_3H_5ClO_2 + C_8H_{12}N_2O_3S + 5H_2O$

151.16 130.14 56.10 108.53 216.28 90.07 =

$= C_{16}H_{19}N_3O_4S.3H_2O + KCl + CO_2 + C_2H_6O + C_2H_4O_2 + C_4H_8O_2 + 2H_2O$

403.47 74.55 44.01 46.07 60.05 88.10 36.03

2.1.4 Chemical consumption coefficients

The analysis is based on the data given in UNIDO/PC. 14., Appendix III., Table I. for company A and B and in the Ger. Pat. 2.613.172 /1977/ to Bayer/.

1 2 3

Intermediates yields — Consumption coefficients

Chemical formula	Common name	T	A 1	B 2	C 3	A 2	B 2	C 2
		Consumption coefficients and yields						
		Theoret.	-	85%		85%	90%	
$C_{18}H_{19}NO_2$	Phenylglycine	0,375	0,790	47,47%	0,744	50,50	0,702	53,42
$C_6H_{10}O_3$	Ethyl aceteacetate	0,323	1,044	30,94%	0,983	32,86	0,928	34,81
$C_3H_5ClO_2$	Ethyl chloroformate	0,269	0,327	82,26	0,308	87,34	0,291	92,43
$C_8H_2N_2O_3S$	6-APA	0,536	0,667	80,36	0,631	84,97	0,596	89,83

Please see manuscript

The most efficient process of company C has been analysed further. According to laboratory experients conducted in an European country a yield of 85% on 6-APA can be achieved, however a yield of 90% can also be approached.

The consumption coefficients per kg AMPICILLIN, calculated with reference to different 6-APA yields, are illustrated in the following table.

Intermediates		Consumption coefficients /CC /kg/kg and yields /Y/ %						
Chemical formula	Common name	CC theoretic	80% CC	80% Y	85% CC	85% Y	90% CC	90% Y
$C_8H_2N_2O_3S$	6-APA	0,536	0,667	80,36	0,630	84,97	0,596	89,83
$C_8H_9NO_2$	Phenyl-glycine	0,375	0,790	47,47	0,744	50,50	0,702	53,42
$C_6H_{10}O_3$	Ethyl acetoacetate	0,323	1,044	30,94	0,983	32,86	0,928	34,81
$C_3H_5ClO_2$	Ethyl chloroformate	0,269	0,327	82,26	0,308	87,34	0,291	92,43

2.1.5 Costing estimate of AMPICILLIN synthesis

The AMPICILLIN manufacturing of companies A and B falls short of the international standard therefore the costs have been estimated only for process C and its developed forms /yields 85 and 90%/.

The material prices are the CIF import prices of the materials in a European country.

The conversion costs have been estimated in analogy with other similar process in a developing country.

Direct material costs	Unit price $/kg	80% yield $/kg	85% yield $/kg	90% yield $/kg
6-APA	70.00	46.62	44.10	41.72
Phenylglycine	14.00	11.06	10.42	9.83
Ethyl acetoacetate	2.00	2.09	1.97	1.85
Ethyl chloroformate	1.50	0.49	0.46	0.44
Other materials	-	4.84	4.56	4.31
Totals		65.10	61.51	58.15
Conversion costs		15.0	14.12	13.34
Costing estimate for 1 kg AMPICILLIN		80.10 82.84	75.63	71.49

As seen from the table, both the direct material costs and the estimated total costs are very sensitive to the yield. A 10% improvement of the yield, for example, results in a 10.8% decrease in the estimated total costs.

Thus, the total cost is sensitive to the intermediate prices as the share of the two intermediates together reaches 89% of the total material cost and a round 73% of the total cost of AMPICILLIN manufacture.

2.2 Acylation by Phenylglycine Chloride Hydrochloride

2.2.1 Schematic illustration of the synthesis

silylation

6-APA

dimethyldichloro-

acylation

b,

phenylglycine
chloride
hydrochloride

hydrolisis

ampicillin

2.2.2 Chemical reactions

a) $C_8H_{12}N_2O_3S + 2C_2H_6SiCl_2 = C_{12}H_{22}N_2O_3SSi_2Cl_2 + 2HCl$
216.28 2x129.06 401.46 2x36.47

b) $C_{12}H_{22}N_2O_3SSi_2Cl_2 + C_8H_9NOCl_2 = C_{20}H_{30}N_3O_4SSi_2Cl_3 + HCl$
401.46 206.8 571.07 36.47

c) $C_{20}H_{30}N_3O_4SSi_2Cl_3 + 4H_2O + C_8H_{11}N = C_{16}H_{19}N_3O_4S.3H_2O +$
571.07 4x18.02 121.18 403.47

$+ C_4H_{12}OSSi_2Cl_3 + C_8H_{12}NCl$
203.22 157.65

2.2.3 Combined equation of the synthesis

$C_8H_{12}N_2O_3S + 2C_2H_6SiCl_2 + C_8H_9NOCl_2 + 4H_2O + C_8H_{11}N =$
216.28 2x129.06 206.08 4x18.02 121.18

$= C_{16}H_{19}N_3O_4S.3H_2O + C_4H_{12}OSi_2Cl_2 + C_8H_{12}NCl + 3HCl$
403.47 203.22 157.65 3x36.47

2.2.4 Chemical consumption coefficients

The process variables of AMPICILLIN production in a developing country are given in the following table:

Intermediates		Consumption coefficients		Yield
Chemical formula	Common name	Theoretical	Of the process under study	%
$C_8H_{12}N_2O_3S$	6-APA	0.536	0.66	81.21
$C_2H_6SiCl_2$	Dimethyl-dichlorosilane	0.320	0.51	62.75
$C_8H_9NOCl_2$	Phenylglycine chloride hydro-chloride	0.511	0.64	~~77.42~~ 79.84

See manuscript pages

Yields from 85 to 90% are found in the literature. E.g., a yield of 87.4% is given in Brit. Pat. 1,039,599 /to Glaxo/, while 86% in U.S. Pat. 068,385 /to Canada Packers Ltd./. Similar results were observed in laboratory experiments where the process was modified in minor details and another acid binding agent was used.

On the basis of these data, a yield of 85% can safely be projected, while a 90% yield can most likely be reached by technological process development. Assuming that these figures are achieved, the consumption coefficients will change as follows:

Intermediate	Present yield	Improved yield 85%	90%
6-APA	0.66	0.63	0.60
Dimethyldichlorosilane	0.51	0.49	0.46
Phenylglycine chloride hydrochloride	0.64	0.61	0.58

2.2.5 Costing estimate of AMPICILLIN synthesis

The total cost per kg of AMPICILLIN at Company B /P.C. 52/.

Cost/elements Materials	Consumption coefficient kg/Kg	Unit price $/kg	Unit cost $/kg
6-APA	0.66	74.00	48.84
Phenylglycine chloride hydrochloride	0.64	18	11.52
Dimehtyldi-chlorosilane	0.51	8	4.08
Methylene chloride	4.10	1.40	5.74
Isopropanol	6.7	1.2	8.04
Dimethytaniline	0.4	3.1	1.24
other materials			0.10
Total			79.56
conversion cost			17.16
Total cost			96.72

In case of locally purchased materials, [illegible] comparative price might include duties and other costs, [illegible] ....

2.2.5.1 Comparison of material prices

The c.i.f. prices of materials imported for the studied process were compared to those of a European country for the same period. The results are given below:

	A	B	C	D
		$/kg		
6-APA	74.00	70.00	74.76	
Phenylglycine	—	44.00	—	
Phenylglycine Chloride Hydrochloride	18.00	24.00	26.0	
Phenylglycine-Dane-salt		not available		
Mehtylenechloride	1.40	0.44	—	
Isopropanol	1.20	0.56	0.62	
Dimethylaniline	3.10	1.86	—	
Triethylamine		1.67		
Methylisobutilketon		1.37	5.57	
Ethylacetoacetate		2.00		
Ethyl chloroformate		1.50		
~~Methylacetoacetate~~				
Dimethyldichlorosilane	8.00	1.80		

2.2.5.2 Effect of changes in the conversion costs on the price of AMPICILLIN

The total cost per kg of bulk substance is $96.72 and the conversion cost is $17.16, namely 17.74%. Hence, a 10% decrease in the conversion cost results in 1.77% reduction of the total costs.

In the studied case, the overhead element of the conversion cost seems to be hich in comparison to the same element of other products with similar or more complex technology. On the other hand, it should also be mentioned that any possible reduction of the conversion costs would not result itself in a competitive AMPICILLIN price, because the direct material costs are higher ($79.56/kg AMPICILLIN) than the imported c.i.f. price of the bulk substance ($78.00/kg).

2.2.5.3 Effect of changes in the purchasing price of materials on the total costs of ~~ampicillin~~ AMPICILLIN manufacture

The following table shows the changes in the total production costs, if the best available prices given in par. 2.2.5.1 ar roduced into the costing estimate.

Cost elements Materials	Consumption coefficient	Unit price $/kg	Unit cost $/kg
6-APA	0.66	70.00	46.20
Phenylglycin chloride hydrocloride	0.64	18.00	11.52
Dimethyldichclorosilane	0.51	1.80	0.92
Methylene chloride	4.1	0.44	1.80
Isopropanol	6.7	0.56	3.75
Dimethylaniline	0.4	1.86	0.74
Other materials			0.10
		Total	65.03
Conversion cost			17.16
Total cost			82.19

2.2.5.4 Combined effect of reduced conversion costs and increased yield on the total manufacturing cost of ~~ampicillin~~ AMPICILLIN

(given in the standard process)

It has been assumed that purchasing prices cannot be reduced for one reason or another.

As stated in par. 2.2.6, the conversion cost seem to be high in this particular case. For the sake of convenience, a 30% reduction of the overhead element is assumed in the following table.

Cost element		85% yield		90% yield	
Materials	UP,$/kg	CC	UC,$/kg	CC	UC,$/kg
6-APA	74.00	0.63	46.62	0.60	44.40
Phenylglycine chloride	18.00	0.61	10.98	0.58	10.44
Dimethyldichlorosilane	8.00	0.49	3.92	0.46	3.68
Other materials			14.45		13.64
Methylene chloride Isopropanol Dimethylaniline	Total		75.97		72.16
Conversion costs			13.53		12.78
Total bulk drug cost			89.50		84.94

CC - Consumption coefficient.

UC - Unit cost per kg of bulk substance.

UP - Unit price.

2.2.9 Optimum reduction possibilities of total manufacturing cost of AMPICILLIN

The following table is based on the techno-economic assumptions of par. 2.2.8 combined with the effect of introducing the best available prices into the analysis.

Cost element		Y 85%		Y 90%	
Materials	UP,$/kg	CC	UC,$/kg	CC	UC,$/kg
6-APA	70.00	0.63	44.10	0.60	42.00
Phenylglycine chloride	18.00	0.61	10.98	0.58	10.44
Dimethyldichlorosilane	1.80	0.49	1.06	0.46	0.83
Other materials			6.11		5.77
			62.25		59.04
Conversion costs			13.53		12.78
Total bulk drug cost			75.78		71.82

CC - Consumption coefficient.

UC - Unit cost per kg of bulk substance.

UP - Unit price.

2.2.10 Summary of findings

(a) The process is technically close to competitive, because the 81.24% yield is acceptable on the basis of the number of steps and unit operations involved in process and it differs from the laboratory-scale yield only by approx. 10%. On the other hand, this difference represents an important reserve in the process economics.

(b) The c.i.f. prices of some materials of the studied process differ significantly from those prevailing on the European market at the same time. These differences cannot be explained by possible differences in the insurance and transport elements of the c.i.f. price. The c.i.f. prices of the key intermediates (6-APA, D-/-/-phenylglycine) were practically equal in both countries. Nevertheless, they deserve special attention, since their combined value represents approx. 89% of the direct material costs and 73% of the total manufacturing costs.

(c) The overhead element of the conversion cost in the studied process seems to be high in comparison to similar figures for the same country and for a comparable process.

(d) The break-even point between the studied c.i.f. prices and total manufacturing costs can be reached by the combined effect of (i) purchasing materials at competitive prices; (ii) increasing yield to 85%, and (iii) reducing the overheads element of the conversion costs by 30% and adjusting the obtained conversion costs according to the increased yield.

(e) Profitability has been demonstrated only in that case where the use of the best technology and best management was assumed.

(f) There is a hard currency loss of $1.56/kg of AMPICILLIN in the studied process. The hard currency saving is $10.33 with competitive import prices and it is between $3.03 and $4.84/kg of AMPICILLIN with process development and using present prices. The maximum hard currency saving is $16.56/kg of AMPICILLIN, if competitive prices and 90% yield are taken into account.

2.3 Techno-Economic Comparison of the "Dane salt" and Silylation Processes

For economic comparison, the three essential variables were assumed to take such values which might be achieved in the near future, namely (a) competitive material prices, (b) moderately reduced conversion costs, and (c) an 85% yield (approx. 4% improvement). The results are illustrated in the following table:

Cost elements	Unit cost, $/kg	
	"Dane salt" process	Silycation process
6-APA	44.10	44.10
Phenylglycine	10.42	-
Phenylglycine chloride hydrochloride	-	10.98
Other materials	6.99	7.17
	61.51	62.25
Conversion costs	14.12	13.53
Total bulk drug cost	75.63	75.78

Taking into account the methodological limitations of comparing costing estimates, the economic feasibility of the two studied processes can be considered practically equal.

Assuming that the principal hard currency elements (part of depreciation, energy) of the conversion costs are equal in both processes, the hard currency saving is also equal in each alternative. Therefore, the decision of chosing between the alternative processes should primarily be based on technical considerations.

In case of AMPICILLIN, the essential parameters are: cold energy demand, minimum temperature and the sensitivity of process parameters to the quality and yield of bulk substances.

New manufacturers usually opt for the silycation process.

3. OTHER INFORMATIONS

The manufacture of AMPICILLIN from 6-APA has been simplified to a great extent as a result of technical development during the past decades.

The demand for the cold energy, the quantity and quality of which are outstanding. Most of the process technologies require the temperature range from -25 C^{o} to -30 C^{o}, while there are technological alternatives available that are capable of eliminating these very low temperatures.

The AMPICILLIN manufacture does otherwise not need specific machines and equipment. It can be produced in a multi-purpose plant.

When carried out in a target plant, the lowest economical capacity is estimated to 30-50 tons/year.

The estimated investment costs of an AMPICILLIN plant with a capacity of 30-50 tons/year amount to 2,0-3,0 M. $ with utilities, in the year 1982.

The AMPICILLIN manufacture does not cause any environment pollution. The effluents of the production do not require any specific treatment.

The manufacture does not need any specific labour safety measures or prescriptions.

The process technology is rather sensitive to the precise keeping of the parameters prescribed, to the quantitative proportions of the materials participating of the reaction and particularly to the quality of the materials employed. As the competition is very sharp, a continuous process development is needed to provide the economicalness. A high degree of qualification is required in the areas of quality control, management and process development.

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PATENT INFORMATION ON AMPICILLIN AND 6-APA MANUFACTURING PROCESSES[1]/

1. GB 2001985 /1979/ appl. date 770805
   Penam and cephem production
   Lark S.P.A.
   CA: 91/25/211428N

2. AT 351162 /1979/ appl. date 760810
   Alpha-aminobenzylpenicillin
   Biocraft Laboratories
   CA: 91/13/107976D

3. DE 2747724 /1979/ appl. date 771025
   Protecting functional groups
   Bayer A.-G.
   CA: 91/11/91954G

4. ZA 7800178 /1978/ appl. date 770120
   D/-/-alpha-aminobenzylpenicillin with a low content N,N-dimethylanilin
   Laboratorios Bago S.A
   CA: 90/21/168585B

5. JP 78124289 /1978/ appl. date 770406
   Ampicillin and Amoxicillin
   Banyu Pharmaceutical Co., LTD.
   CA: 90/19/152173E

6. US 4123611 /1978/ appl. date 701021
   N-protected amino compounds
   Osaka University
   CA: 90/19/152172U

7. DE 2727528 /1979/ appl. date 770618
   N/1-cyanoalken-2-yl/-alpha-aminocetic acids and beta-lactam antibiotics
   Bayer A.-G.
   CA: 90/17/137843E

8. PL 93437 /1977/ appl. date 740307
   Isolation of beta-lactam antibiotics from aqueous solutions
   Instytut Przemyslu Farmaceutycznego
   CA: 90/15/121587P

9. JP 7882791 /1978/ appl. date 761227
   6-Acylaminopenicillanic acids
   Banyu Pharmaceutical Co., Ltd.
   CA: 90/13/103979P

10. JP 7884988 /1978/ appl. date 770106
    Alpha-aminopenicillins
    Banyu Pharmaceutical Co., Ltd.
    CA: 90/1/6393K

1/ Result of the computer search in all issues of Chemical Abstracts published between Jan. 1977 and March 1983.

ALWAYS small Gabler at the end of CA ref. list.

11. JP 7873594 /1978/ appl. date 761214
Penicillin derivatives
Mitsubishi Chemical Industries Co., Ltd.
CA: 89/23/197573F

12. DE 2755903 /1978/ appl. date 761216
Penicillins
Dobfar S.P.A.
CA: 89/17/146896F

13. BE 858670 /1978/ appl. date 770120
D/-/-alpha-aminobenzylpenicillins with low N,N-dimethylaniline content
Laboratorios Bago S.A.
CA: 89/5/43405R

14. JP 7809786 /1978/ appl. date 760712
Ampicilling and Amoxicillin
Tobishi Pharmaceutical Co., Ltd.:
Toho Iyaky Kenkyusho Co., Ltd.
CA: 89/5/43398R

15. JP 7703093 /1977/ appl. date 750626
6-Aminopenicillanic acid and 7-aminodeacetoxycephalosporanic derivative
CA: 88/23/170188S

16. ES 448741 /1977/ appl. date 750126
6-Aminopenicillanic or 7-aminodesacetoxycephalosporanic acid derivatives
Dobfar S.P.A.
CA: 88/15/105387B

17. JP 77106884 /1977/ appl. date 760302
Acylating 6-aminopenicillanic acid
Sangyo Kagaku Kenkyu Kyokai
CA: 88/15/105322B

18. ES 418652 /1976/ appl. date 730612
Subtituted amides
Instituto Luso-Farmaco S.A.R.L.
CA: 88/9/62387G

19. DE 2619247 /1977/ appl. date 760430
Protection of functional groups
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20. JP 7793791 /1977/ appl. date 760202
Acylation of 7-aminocephems and 6-aminopenams
Sangyo Kagaku Kenyu Kyokai
CA: 88/7/50886F

21. CS 168433 /1977/ appl. date 740911
6-/D-/-/-Alpha-aminophenylacetamido/penicillanic acid
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TECHNO-ECONOMIC ANALYSIS OF THE MANUFACTURE OF AMPICILLIN BULK SUBSTANCE AND ITS KEY INTERMEDIATES 6-AMINOPENICILLANIC ACID, D (-)-PHENYLGLYCINE AND BENZYLPENICILLIN

1. BACKGROUND AND HISTORY

AMPICILLIN has already been marketed for more than two decades. The basic patent and a large number of process patents have expired. New process patents have been granted during the past five years, too, which indicates continuous development of the production technology. It is reasonable to assume that not all technical innovations have been patented and techno-economically important process developments are handled as part of the secret know how.

The number of AMPICILLIN bulk substance manufacturers has continuously increased.

Partly as a result of constant technical development, partly due to the ever increasing number of manufacturers, there is a strong, direct competition among AMPICILLIN bulk substance producers on the international market.

AMPICILLIN bulk substance prices decreased after the expiry of the basic patent, stagnated during the past years and show a moderately increasing tendency at present. Manufacturers that produce AMPICILLIN starting from either purchased 6-APA or Benzylpenicillin cannot usually compete commercially, because their total production costs are close to or higher than the world-market price of AMPICILLIN bulk substance. Such manufacturers realize profit during the production of the pharmaceutical dosage forms and the principal advantages of producing the bulk substance are a reduced dependence on imports and hard currency savings.

2. ANALYSIS OF THE PRODUCTION OF AMPICILLIN BULK SUBSTANCE AND KEY INTERMEDIATES

2.1 AMPICILLIN Production

Two alternative processes, the Dane-salt and Phenylglycine Chloride Hydrochloride routes, were studied when 6-APA was taken as the starting key intermediate. No significant difference has been found between the two processes with regard to economic feasibility of the production (Table I).

The studied processes are somewhat below the international technical level. The total production costs are higher in both cases than the world-market price of the bulk substance. The data of the studied processes were compared to published, laboratory and pilot-plant scale results. It was found that total production costs of the bulk substance could be reduced below world-market price within a short time, if methodical technical development work were conducted or a better technology were purchased.

The costs of the two key intermediates, particularly that of 6-APA, represent dominant elements of the total production costs in both processes. Hence the purchase price of 6-APA fundamentally affects the total production costs of the AMPICILLIN bulk substance. With present 6-APA world-market prices, both the best technology and the most effective management are required to keep total production costs below the world-market price of the AMPICILLIN bulk substance (Table I).

The economic feasibility of the bulk substance manufacture depends less on the scale of production, though the minimum economic scale is usually given between 25 to 50 tons per year.

The specific investment indicator is lower than the average, namely USD 0.8 to 1.0 per each USD AMPICILLIN production value in case of a 50 ton/year plant.

The hard currency saving is USD 16.50 per kg of AMPICILLIN, disregarding the single hard currency expenditure of the investment and those elements of the conversion costs, for example energy, that might also have to be paid in

hard currency. The total hard currency savings is USD 825,000/year, in case of 50 tons of AMPICILLIN bulk substance production.

The last step of AMPICILLIN manufacture can be performed in a multi-purpose plant.

The key intermediates, raw and other materials are available on the world market.

2.2 6-APA Production

Production processes can be divided into two categories: (1) organic synthesis and (2) bioconversion of penicillin to 6-APA. Out of the studied processes, the chemical synthetic route is slightly below while the enzymatic decomposition is slightly above the average technical level. Accordingly, the total production costs of the chemical route are a little higher and those of the enzymatic process are somewhat lower than the world-market price of 6-APA. There is technical development reserve in both processes, particularly with the chemical route. However, the total production costs of 6-APA will be higher than the world-market price of this key intermediate after an immediately possible technical development and the total production costs of the synthetic route could reach the present total production costs of the enzymatic process only after very successful technical development, or if a high-level technology were purchased.

Other advantages of the enzymatic production of 6-APA include easier technical realization and better quality of the product.

The costs of the two key intermediates, particularly that of benzylpenicillin, play a dominant role in the total production costs of 6-APA. With the present world-market prices for benzylpenicillin, only the best chemical technology can result in total production costs lower than the world-market price of 6-APA. The total production costs of 6-APA manufactured with enzymatic process are somewhat lower than the world-market of price 6-APA (Table II).

The chemical process can be realized in a multi-purpose plant. The enzymatic process needs additional minor equipment.

The economic feasibility of the manufacture does not depend much on the production volume. The minimum economic scale is usually given between 25 and 50 tons/year.

The specific investment indicator of the enzymatic process is lower than the average, namely USD 0.6 to 0.7 per each USD of 6-APA production value, in case of 30 to 35 tons/year 6-APA production plant.

The hard-currency savings is USD 15.25 per kg of 6-APA, disregarding the single hard currency expenditure of the investment and those elements of the conversion costs that might also have to be paid in hard currency.

The total hard currency savings is USD 480,000/year in case of a plant with 6-APA capacity required to produce 50 tons of AMPICILLIN per year.

The key intermediate, raw and other materials are available on the world market.

2.3 Benzylpenicillin Production

Large-scale biotechnology was first used in the pharmaceutical industry with the fermentation of benzylpenicillin and it is gaining more and more importance in the production of drugs.

Benzylpenicillin is produced by growing a mutant of Penicillium chrysogenum strain in a sterile fermentation process, using mostly raw materials of agricultural origin for the preparation of the substrate.

High-level microbiological background is required for (a) the maintenance and improvement of the production capacity of the Penicillium strain, (b) the preparation of seed cultures, (c) sterility and quality control, and (d) the continuous adaptation of the technology for the use of indigenous raw materials.

Fermentation pertains to the category of sensitive, high-level technologies. Satisfactory production can be achieved only if optimum parameters are guaranteed during the whole process. Fermentation also requires a well-developed industrial infrastructure.

When evaluating the production capacity of a Penicillium strain, both the antibiotic level (IU/ml) and the fermentation cycle have to be taken into account. These factors, in turn, are closely related to (a) the composition and quality of the culture medium, (b) the geometrical dimensions of the fermenter, and generally (c) all process parameters (pH, aeration, temperature, etc.) affecting the fermentation.

Both the production capacity and the recovery efficiency of the studied process are below international standards. In spite of these facts, the total production costs of benzylpenicillin are below the majority of the c.i.f. import prices of most countries, probably due the relatively cheap price of agricultural raw materials, therefore high added value of the fermentation. Nevertheless, the total production costs of benzylpenicillin in the studied process are higher than the lowest import c.i.f. price of the product.

Based on laboratory and pilot-plant scale experiments, both the production capacity of the strain and the recovery efficiency can be developed to international standards. If this level is achieved, the total production costs will be lower than the best present c.i.f. import prices. The total production costs can be reduced furher by reaching maximum technical development targets or buying the best existing technology (Table III).

Benzylpenicillin is produced in a plant specifically established for this purpose. The economic feasibility of the manufacture depends very much on the production capacity. The minimum economic scale is usually given between 400 and 800 m^3 fermenter volumes equivalent to 275 to 550 tons of benzylpenicillin potassium production per year.

The specific investment indicator is higher than the average, namely USD 1.8 to 2.2 per each USD of benzylpenicillin potassium production value, in case of 400 m^3 total fermenter capacity.

The hard currency savings is not less than USD 13.00 per Kg of benzylpenicillin potassium, or USD 925,000 per year, if a quantity required for the production of 50 tons of AMPICILLIN is taken into consideration.

2.4 D(-)-alpha-Phenylglycine Production

The studied process approaches the international technological standard both from technical and economic points of view. The total production costs are just a little higher than the world-market price of D(-)-alpha-Phenylglycine. According to the analysis, the internationally competitive level can be reached by optimizing the large-scale production parameters and, as a result, the projected total production costs will decrease below the world-market price of the product. Based on laboratory and pilot-plant scale experiments, there is a reserve in technical development and the projected total production costs can be reduced further.

There is no key intermediate in the synthesis. None of the raw materials plays a dominant role in the direct material costs. All raw materials are relatively cheap and easily available.

The recovery efficiency of tartaric acid and organic solvents affects significantly the process economics.

The economic feasibility of the production depends to a large extent on the production capacity. The minimum economic scale is estimated around 100 tons per year.

The process technology is more complex than the average. The use of sodium cyanide requires special treatment of the process effluent.

3. EFFECT OF BACKWARD INTEGRATION ON PROCESS ECONOMICS

The possibilities and effects of backward integration on the production of AMPICILLIN bulk substance were investigated. The findings are summarized in Table V. Out of the alternatives detailed in Table I to IV, those were selected for the analysis of the effect of backward integration which have been achieved on the laboratory and/or pilot-plant scale, or which are

considered attainable by technical development within a short period of time. The selected processes were marked with an asterix in Tables I to IV.

Table V shows the effect of the degree of backward integration on the (1) direct material costs, (2) key intermediate costs within the direct material co ts, (3) conversion costs and (4) total production costs. It has been concluded that the total production costs of AMPICILLIN bulk substance do not depend very much on the degree of backward integration. If all key intermediates are manufactured, the maximum decrease in the total production costs is 7.7 per cent. The same figure shows a 6.4 per cent reduction, if D(-)alpha-phenylglycine is purchased and other key intermediates are produced. The maximum decrease, 4.6 per cent, is observed with the introduction of benzylpenicillin production into the vertical integration.

On the other hand, the cost structure changes significantly with the degree of backward integration. The dominant role of the key-intermediate costs decreases gradually; it even becomes a "normal" cost element when all key intermediates are locally produced. The most significant change occurs in this case also with the production of benzylpenicillin, when the cost of key intermediates represents the 31 per cent of the direct material costs and 14.7 per cent of the total production costs, respectively.

The direct material cost ratio gradually decreases while the conversion cost ratio is accordingly increases as the vertical integration proceeds. The greatest changes are observed again with the introduction of benzylpenicillin production into the backward integration.

4. AVAILABILITY AND PRICING OF AMPICILLIN BULK SUBSTANCE AND KEY INTERMEDIATES

Both AMPICILLIN bulk substance and the key intermediates studied in the described processes are available on the world market. With the exception of phenylglycine, all others are produced in a few developing countries.

Among the factors affecting the availability and pricing, it plays a very important role that the key intermediates are exclusively used in the pharmaceutical industry, furthermore that 6-APA and benzylpenicillin potassium are also exclusively produced by the pharmaceutical industry. Phenylglycine

is produced both in the pharmaceutical sector and other branches of the chemical industry.

Within the pharmaceutical industry, some producers manufacture intermediates only for their own AMPICILLIN bulk substance production and do not sell the latter, only use it for own dosage form manufacture.

Among the known intermediate suppliers, there is none which does not produce AMPICILLIN bulk substance itself. Hence it is logical to assume that intermediates are priced in such a way as to prevent effective direct competition with own bulk substance supplies. The pricing of intermediates is probably based on such considerations that adjust the total manufacturing costs of local production to a higher level than the world-market price of the AMPICILLIN bulk substance. It should be noted that such pricing is limited to a certain extent by the competition among intermediate suppliers and the demand-supply situation at a particular time.

The demand-supply situation depends also on other uses of the same intermediate. For example, Benzylpenicillin Potassium is a drug itself and is also used as a raw material for the production of 7-ADCA (7-aminodesacetoxycephalosporanic acid), one of the starting materials for the production of semi-synthetic cephalosporins.

6-APA is a key intermediate in the production of AMPICILLIN and other semisynthetic penicillins as well.

Phenylglycine is also used in the production of other semi-synthetic penicillins and cephalexin, a semisynthetic cephalosporin derivative.

5. AVAILABILITY OF PROCESS TECHNOLOGY

Technologies for the production of AMPICILLIN bulk substance and its key intermediates are available. Except phenylglycine, all others are produced in a few developing countries.

Based on the techno-economic analysis of the studied processes, however, the technologies used in developing countries are generally below international standards and are far from the level of leading manufacturers. One way of looking at this fact is that the technologies used in developing countries contain economic reserves which can be realized as values by technical development.

6. ALTERNATIVE STRATEGIES TO ESTABLISH LOCAL PRODUCTION IN DEVELOPING COUNTRIES

6.1 Full Backward Integration

One possibility is the complete vertical integration of the AMPICILLIN bulk substance production, including the manufacture of benzylpenicillin. This alternative gives independence from key intermediate prices partly influenced by AMPICILLIN bulk substance competitors.

Full backward integration can be accomplished in such countries where the organic synthetic and fermentation sub-sectors of the pharmaceutical industry exist. Where these sub-sectors are established first for the production of AMPICILLIN bulk substance, implementation of the strategy is a difficult technical task, particularly in case of fermentation.

This alternative requires own research and development background.

Efficient industrial and financial management are also essential factors. If this strategy is the preferred alternative, the techno-economic analysis of other potential uses of the intermediates has also to be done.

If only AMPICILLIN bulk substance production is taken into account, the specific investment indicator is USD 1.8 to 2.2 in case of 50 tons per year capacity. The break-even time of the investment is more than 20 years.

The hard currency saving is USD 44,000 per kg of AMPICILLIN, namely USD 2.2 million/year for a 50 ton production.

6.2 Partial Background Integration

(a) If the vertical integration is planned to include only the production of 6-APA, the implementation of the strategy is much simpler, but then the process economics of AMPICILLIN bulk substance production depends, to a great extent, on the price of benzylpenicillin influenced by suppliers that directly compete on the AMPICILLIN market, as well.

Own research and development background is desirable in this alternative, too, in order to keep up with international technical development and not to rely upon purchased technology transfer only.

Other potential uses of 6-APA should also be studied.

The specific investment indicator, considering only AMPICILLIN manufacture, is USD 1.15 to 1.30 per USD AMPICILLIN production value. The break-even time of the investment is approx. 8 years.

The hard currency saving is not less than USD 26 per kg AMPICILLIN, equivalent to USD 1.3 million/year in case of a 50-ton production.

(b) In only the last step of AMPICILLIN synthesis is performed locally from purchased 6-APA and phenylglycine, the dependence on key intermediate prices affected by AMPICILLIN competitors is the greatest.

The specific investment indicator is USD 0.80 to 1.00 per each USD AMPICILLIN production value.

The projected break-even time of the investment is approx. 25 years and the hard currency saving is USD 16.50 per kg of AMPICILLIN, taking into a 50-ton production/year into account in both cases.

Annual / value 0

6.3 Purchase of AMPICILLIN Bulk Substance

Since the AMPICILLIN bulk substance is easily available on the world market at competitive prices, the alternative decision to keep on purchasing the AMPICILLIN demand and use resources for the production of bulk substances with limited availability and/or better economic feasibility, is also worth consideration.

6.4 Increase of Key Intermediate Suppliers

If manufacturers outside or within the pharmaceutical sector could be induced to produce key intermediates without synthetizing AMPICILLIN, the pricing of key intermediates would follow a less oligopolistic pattern. Such alternative would be attractive only to industries with large unexploited fermentation capacity and biotechnological research background, but no interest in organic chemical synthesis and/or pharmaceutical marketing.

6.5 Some Factors Affecting Alternative Strategies

a. Purchasing

There are two possible variations with all alternative strategies: (a) long-term agreement, or (b) buying at spot prices on the world market of AMPICILLIN bulk substance and intermediates.

The advantage of variation (a) is the guaranteed supply and independence from increases of the market prices; the disadvantage is that no profit can be realized from the eventual decreases of the spot prices.

The advantage of variation (b) is the profit making from the decreasing spot prices; the disadvantage is that the production costs are very sensitive to spot price increases and there might be even availability problems if the balance of demand and supplies is disturbed to an unusual extent.

b. Technology

Decision should also be made whether establishing own research and development, or buying all technical improvements. At the early stages, co-operation with the technology supplier seems to be the most expedient alternative possibility, but it should be medium-term objective to establish own research apparatus, however modest, capable of developing the existing production technologies.

c. Management

The higher is the vertical integration, the more dominant is the contribution of conversion costs to the total production costs. The conversion costs could not be analysed in this work in details in the absence of break down figures and because cost components such as depreciation, interest on investment loans and working capital, taxes, insurances, royalties, overheads, etc. vary from country to country and even from manufacturer to manufacturer within the same country.

The reduction of conversion costs needs effective management of all resources and sales activities. Once all practical reserves in process development have been exhausted, management becomes the only dominant element of the total production costs and the decisive factor of competition.

Table I: Actual and projected cost structures of AMPICILLIN Trihydrate

Bulk substance production starting from 6-APA

a) Dane-Salt Process

Cost element	Cost, USD per kg of product, at a yield of 80%	85% *	90%
6-APA	46.62	44.10	41.72
Phenylglycine	11.06	10.42	9.83
Other materials (OM)	7.42	6.99	6.60
Direct material costs(DMC)	65.10	61.51	58.15
Conversion costs (CC)	15.00	14.12	13.34
Total production costs (TPC)	80.10	75.03	71.49

b) Phenylglycine Chloride Hydrochloride (PCH) Process

Cost element	Cost, USD per kg of product, at a yield of 81,21% A	81,21% B	81,21% C	85% A	85% B	85% C	90% A	90% B	90% C
6-APA	48.84	46.20	46.20	46.62	44.10	44.10	44.40	42.00	42.00
PCH	11.52	11.52	11.52	10.88	10.98	10.98	10.44	10.44	10.44
OM	19.20	7.31	7.31	18.37	7.17	7.17	17.32	6.60	6.60
DMC	79.56	65.03	65.03	75.97	62.25	62.25	72.16	59.04	59.04
CC	17.16	17.16	14.40	16.40	16.40	13.53	15.48	15.48	12.78
TPC	96.72	82.19	79.13	92.37	78.65	75.78	87.64	74.52	71.82

A: actual cost structure and projected cost structures after technical development;

B: revised cost structure (based on competitive European c.i.f. import prices) and projected cost structures after technical development;

C: revised cost structure with reduced conversion costs and projected cost structures after technical development.

* Variant selected for analysis of backward integration.

Table II: Actual and Projected Cost Structures of 6-APA

a) Chemical Process

Production Starting from Benzylpenicillin Potassium

Cost element	Cost, USD per kg of product, at a yield of 71.75% A	71.75% B	75% A	75% B	80% A	80% B
Benzylpenicillin potassium	52.80	52.80	50.51	50.51	47.37	47.37
Other materials	17.87	9.40	16.48	8.72	15.49	8.19
Total material costs	70.67	62.20	66.99	59.23	62.86	55.56
Conversion costs	13.75	13.75	13.15	13.15	12.33	12.33
Total production costs	84.42	75.95	80.14	72.38	75.19	67.89

A: actual cost structure and projected cost structures after technical development

B: revised cost structure (based on competitive European c.i.f. import prices) and projected cost structures after technical development.

b) Enzymatic process

Cost element	Cost, USD per kg of product, at a yield of 76.2% *	80%
Benzylpenicillin potassium	49.72	47.37
Other materials	5.03	4.95
Direct material costs	54.75	52.32
Conversion costs	12.95	12.33
Total production costs	67.70	64.65

* variant selected for analysis of backward integration

Table III Actual and projected cost structure of Benzylpenicillin Potassium production by fermentation

Cost element	Cost, USD per kg of product A	B *	C
Material costs, fermentation	6.42	4.45	3.65
Material costs, recovery	5.25	4.55	4.27
Total material costs	11.67	9.00	7.92
Conversion costs	14.88	10.32	8.46
Total production costs	26.55	19.32	16.38

A: actual cost structure; 28 000 IU/ml fermentation yield and 65% recovery efficiency
B: projected cost structure; 35 000 IU/ml fermentation yield and 75% recovery efficiency
C: projected cost structure: 40 000 IU/ml fermentation yield and 80% recovery efficiency
* variant selected for analysis of backward integration.

Table IV Actual and projected cost structures of D(-)-Phynylglycine production

Cost element	Cost, USD per kg of product at a yield of 52.3%	59.3% *	63.7%
Benzaldehyde	1.88	1.65	1.54
Ammonium chloride	1.11	0.98	0.91
Other materials	4.92	4.37	4.11
Direct material costs	7.91	7.00	6.56
Conversion costs	6.40	5.65	5.26
Total production costs	14.31	12.65	11.82
Note:			
Yield, first step:	66.67%	70.00%	75.00%
Yield, second step:	78.45%	84.86%	84.86%
Overall yield:	52.30%	59.30%	63.65%

* Variant selected for analysis of backward integration.

Table V Effect of backward integration

on the projected total production costs of

AMPICILLIN Trihydrate

Cost element	Cost, USD per kg of product			
	A	B	C	D
6-APA	44.10	-	-	-
Benzylpenicillin potassium	-	31.32	-	-
Phenylglycine	10.42	10.42	10.42	-
Cost of key intermediates	54.52	41.74	10.42	-
Other materials	6.99	10.16	23.17	28.38
Direct material costs	61.51	51.90	33.59	28.38
Conversion costs	14.12	22.28	37.21	41.41
Total production costs	75.63	74.18	70.80	69.79

Key intermediates

A: 6-APA and Phenylglycine
B: Benzylpenicillin potassium and phenylglycine
C: Phenylglycine
D: none

Table VI Effect of backward integration on the projected costs structure of AMPICILLIN Trihydrate production

Cost element	Percentage of total production costs			
	A	B	C	D
6-APA	58.3	-	-	-
Benzylpenicillin potassium	-	42.2	-	-
Phenylglycine	13.8	14.1	14.7	-
Cost of key intermediates	72.1	56.3	14.7	-
Other materials	9.2	13.7	32.7	40.7
Direct material costs	81.3	70.0	47.4	40.7
Conversion costs	18.7	30.0	52.6	59.3
Total production costs	100.0	100.0	100.0	100.0
Reduction of total production costs	100.0	98.1	93.6	92.3

Note: figur · do not always add up due to rounding ?

Division for Industrial Studies
Sectoral Studies Branch

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TECHNO-ECONOMIC ANALYSIS OF THE MANUFACTURE OF BENZYLPENICILLIN POTASSIUM

1. BASIC DATA OF THE BULK SUBSTANCE

1.1 International Non-Propietary Name: BENZYLPENICILLIN[1/]

1.2 Other Common Names: Penicillin G, Potassium (U.S.P.), Benzylpenicillin (B.P.), Crystalline Penicillin G.

1.3 Graphic Formula

1.4 Chemical Formula: $C_{16}H_{17}KN_2O_4S$

1.5 Molecular Weight: 372.48

1.6 Chemical Abstract Index Name: 4-Thia-1-azabicyclo/3.2.0/heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-/(phenylacetyl)amino/-, monopotassium salt, /2S-(2α, 5α, 6β)/-.

1.7 CAS Registry Number: /113-98-4/

1.8 Other Forms: Penicillin G Sodium

1.9 Basic Patent:

1/ Revised WHO Model of Essential Drugs 1983.

1.10 Therapeutic Category: Penicillins, Gram-positive-cocci-active group (6-000).[2/]

1.11 Brief History of the Product

Fleming discovered penicillin, an antimicrobial agent produced by growing the mould Penicillium notatum, already in 1928. Commercial penicillin was biosynthetized in 1940 as an amorphous powder and later, in 1946, as a crystalline material. The appearance of this first antibiotic on the market was the start of a new era in the history of chemotherapy.

BENZYLPENICILLIN, for years the most popular penicillin, is produced on an industrial scale by growing a mutant of Penicillium Chrisogenum.

The life-cycle curve of BENZYLPENICILLIN has not yet reached its peak. The growing trend, however, can primarily be attributed to its use as a starting material in the production of 6-aminopenicillanic acid, a key-intermediate in the manufacture of semi-synthetic penicillins and cephalosphorins. The production process is being still actively developed, as reflected in the number of patents published[3/] during the past 15 years.

Period	Number of Process Patents
1967-1971	13
1972-1975	18
1976-1979	7
1980-1981	16
1982-1983[4/]	7

altogether 61 patents listed in Annex 1.

2/ International Classification of Procedures in Medicine, World Health Organization, Geneva, 1970, Vol. 2, p. 6-2.

3/ Chemical Abstracts, various issues from 1967 to 1983.

4/ 1983 data include only patents published before 31 March 1983.

2. BRIEF DESCRIPTION OF THE PRODUCTION PROCESS

The production process of BENZYLPENICILLIN consists of two principal steps: (i) fermentation, and (ii) recovery of BENZYLPENICILLIN from the fermentation mixture and subsequent purification of the product.

2.1 Fermentation

BENZYLPENICILLIN is produced by sterile, aerobic fermentation. Production is usually performed in batches, a few producers have started to use semi-continuous fermentation.

The production capacity of Penicillium strains is nowadays between 25,000 and 55,000 IU/ml (equivalent to 15.6 to 34.3 Kg/m^3 of BENZYLPENICILLIN Potassium, based on a 120 to 200-hour fermentation cycle). Higher yields are known to exist, but the fermentation and recovery processes require such conditions that do not necessarily improve the economic feasibility of the production.

Usual fermenter size is 70 to 80 m^3 or 120 to 150 m^3. The operating volume represents around 75 to 80 per cent of the fermenter capacity.

2.2 Recovery and Purification

BENZYLPENICILLIN is recovered from the filtered fermentation broth by extraction with isoamyl acetate or n-butyl acetate. BENZYLPENICILLIN is then converted into Potassium salt by extracting the organic solvent phase with an aqueous buffer solution and BENZYLPENICILLIN Potassium is purified by crystallization.

The overall yield of the production changes between 65 to 80 per cent, depending on the applied recovery technique.

3. DATA FOR THE TECHNO-ECONOMIC ANALYSIS

3.1 Material prices

The indicative prices of BENZYLPENICILLIN Potassium have oscillated between the end of 1982 and the beginning of 1983, as follows:

Quality	Price range, USD	
	Kg	BU*/
Sterile, injection grade	51.20-56.00	32.00-35.00
Non-sterile, oral grade	27.20-28.00	17.00-17.50

Note: The price of technical grade, once-crystallized BENZYLPENICILLIN Potassium required for the production of 6-aminopenicillanic acid is available on the market at prices always lower than the oral grade.

3.2 Production Costs of the Studied Process

Cost Elements	Cost in USD/kg of product	
Direct material costs of fermentation	6.42	
Direct material costs of recovery and purification	5.25	
Total direct material costs		11.67
Conversion costs		14.88
Total production costs		26.55

3.3 Data of the Reference Process

Fermenter size	115 m^3
Operating volume	85 m^3

*/ BU billion unit; one mg of BENZYLPENICILLIN Potassium is equivalent to 1595 units (Merck Index, 9th ed., p. 151). In this study a conversion rate of 1 mg = 1600 units has been used.

	Operating volume/fermenter size ratio	74 %
X	Production capacity of the strain	28000 IU/ml
	Fermentation cycle	144 hours
	Number of fermentations/year	56
	~~Overall yield~~ Recovery efficiency	65 %
	Quantity of BENZYLPENICILLIN Potassium recovered from 1 m^3 of operating volume	11.4 kg (≃18,2 BU*)
	Quantity of BENZYLPENICILLIN Potassium produced in a single fermentation	967 kg (≃1547 BU)
	Quantity of BENZYLPENICILLIN Potassium produced in 1 m^3 of operating volume per year	637 kg (≃1019 BU)
X	Quantity of BENZYLPENICILLIN Potassium produced in one fermenter per year	54,145 kg (≃86,632 BU)
X	Direct material costs per 1 m^3 of fermentation broth ~~mixture~~	73.03 USD
	Material costs of recovery and purification per one kg of BENZYLPENICILLIN Potassium	5.25 USD
	Conversion costs per one kg of BENZYLPENICILLIN Potassium	14.88 USD

4. ANALYSIS OF THE STUDIED PROCESS

4.1 Comparison of Material Prices

The comparison cannot be performed because details of direct material costs are not available for either the fermentation or the recovery and purification steps. It can only be stated that the total direct material costs represent 44 per cent of the total production costs and the distribution of total direct material costs between fermentation and processing of the broth is 55 per cent and 45 per cent respectively.

4.2 Effect of Improvement of the Production Capacity of Penicillium Strain on the Total Production Costs of BENZYLPENICILLIN Potassium

Based on laboratory experiments and pilot-plant scale results,[5/] the production capacity of the strain can be increased to 35,000 U/ml by optimizing fermentation parameters. The substrate costs, fermentation time and other variables remain unchanged. According to other sources, the fermentation level of leading manufacturers has increased above 50,000 U/ml. Hence it is reasonable to assume improvement of the present production capacity of 28,000 of U/ml of the strain to 30,000 U/ml, 35,000 U/ml and 40,000 U/ml.

Assuming no change in the direct material costs per m^3 of fermentation broth and reducing conversion costs in proportion with the increase in productivity, the total production costs of BENZYLPENICILLIN Potassium will change as follows:

5/ Data received from a European manufacturer.

Fermentation level	Reference process 28 000 U/ml	Technically developed process 30 000 U/ml	35 000 U/ml	40 000 U/ml
BENZYLPENICILLIN Potassium yield per $1m^3$ of operating volume, kg	11.4	12.2	14.2	16.3
BU	18.2	19.5	22.8	26.0
Direct material costs, USD/Kg,				
- fermentation	6.42	5.99	5.14	4.49
- recovery	5.25	5.25	5.25	5.25
- total	11.67	11.24	10.39	9.74
Conversion cost, USD/kg	14.88	13.89	11.90	10.12
Total production cost, USD/kg	26.55	25.13	22.29	20.16

Hence, if a strain productivity of 35,000 U/ml is achieved as a result of technical development, for instance, the total production costs of BENZYL-PENICILLIN Potassium can be reduced by about 16 per cent from USD 26.55/kg to USD 22.29/kg.

4.3 Effect of Technical Development of the Recovery and Purification Step on the Total Production Costs of BENZYLPENICILLIN Potassium

Based on pilot-plant scale experiments, the recovery of the BENZYL-PENICILLIN Potassium from the fermentation broth can be increased from the present 65 per cent to 75 per cent, primarily by using a modern extraction equipment.

According to some sources, efficiency of processing can be increased to 80 per cent.

Assuming no change in the fermentation level and reducing conversion costs in proportion with the increased productivity, the total production costs of BENZYLPENICILLIN Potassium will change, as follows:

Recovery efficiency, %	Reference process 65%	Technically developed process 70%	75%	80%
BENZYLPENICILLIN Potassium yield per 1 m^3 of operating useful volume, kg	11.4	12.3	13.1	14.0
BU	18.2	19.6	21.0	22.4
Direct material costs, USD/Kg,				
- fermentation	6.42	5.96	5.56	5.22
- recovery	5.25	4.88	4.55	4.27
- total	11.67	10.84	10.11	9.49
Conversion costs, USD/Kg	14.88	13.82	12.90	12.09
Total production costs, USD/kg	26.55	24.66	23.01	21.58

Hence, if the recovery efficiency is successfully improved by technical development, for example, to 75 per cent, the total production cost of BENZYLPENICILLIN Potassium can be reduced by about 13 per cent, from USD 26.55/Kg to USD 23.01/Kg.

4.4 Combined Effect of Increased Strain Production Capacity and Improved Recovery Efficiency

A technical development target of 35,000 U/ml strain production capacity and 75 per cent processing yield seems to be realistic on the basis of laboratory and pilot-plant scale experiments.

If this goal were achieved, the total production costs of BENZYL-PENICILLIN Potassium would be, as follows:

BENZYLPENICILLIN Potassium yield per	
1 m^3 of useful volume, kg	16.4
BU	26.3
Direct material costs, USD/Kg,	
- fermentation	4.45
- recovery	4.55
- total	9.00
Conversion costs, USD/Kg	10.32
Total production costs, USD/Kg	19.32

The optimum combination of technically developed parameters (40,000 U/ml, 80%) results in the following total production costs for BENZYLPENICILLIN Potassium:

BENZYLPENICILLIN Potassium yield	
per 1 m^3 of useful volume, kg	20.00
BU	32.00
Direct material costs, USD/Kg,	
- fermentation	3.65 ~~4.49~~
- processing	4.27
- total	7.92
Conversion costs, USD/kg	8.46
Total production costs, USD/kg	16.38

$\frac{11.4}{20.0} \cdot 6.42$

5. OTHER RELEVANT INFORMATION

A significant proportion of the direct materials used in BENZYLPENICILLIN Potassium fermentation originates from the agriculture, hence production is quite independent from other sectors of the chemical industry.

The maintenance and improvement of the production capacity of Penicillium chrysogenum mutants as well as the continuous adaptation of the strain to local raw materials require high-level microbiological activities.

Both the production capacity (U/ml) and the fermentation cycle should be considered as criteria for the selection of strains. The production capacity of the strain depends to a large extent on the (i) quality and composition of the culture medium, (ii) geometrical dimensions and shape of the fermenter, and (iii) all parameters affecting the fermentation process (pH, temperature, aeration, etc.). Good yields can be achieved only if the optimum parameters are maintained during the process.

BENZYLPENICILLIN fermentation is a high-level biotechnology and requires a well-developed industrial infrastructure.

6. SUMMARY OF THE FINDINGS

(a) The production of the non-sterile BENZYLPENICILLIN Potassium, used for oral dosage forms or as a raw material for 6-APA production is economically feasible, if not less than 11.2 kg (18 BU) of bulk substance is obtained from each m^3 of operating volume and the period of fermentation cycle is not more than 144 hours including discharging and cleaning of the equipment.

(b) The dominant elements of production cost are (i) the production capacity of the strain, and (ii) the recovery efficiency. Both of them play a nearly equal role in the reduction of total production costs.

(c) The conversion costs of BENZYLPENICILLIN Potassium production are relatively high, as usual with fermentation processes. Because its value represents 56 per cent of the total production costs, more attention should be paid to the conversion costs than in case of the organic syntheses, in general, particularly to the possible reduction of the variable costs.

(d) The minimum economic scale and the capacity utilization have high importance in the process economics.

(e) The direct materials costs are lower than usual with the synthetic processes and their hard currency containment (import contents) is low, hence the added value is high.

(f) Taking into account the realistic technical development possibilities, the total production costs of the studied process can be reduced by around 27 per cent, from USD 26.55/kg to USD 19.32/kg.

7. PATENT INFORMATION ON BENZYLPENICILLIN PRODUCTION AND RELATED PROCESSES BASED ON PUBLICATIONS IN THE CHEMICAL ABSTRACTS BETWEEN 1967 and 1983*/.

1967-71

1./ GB 1219288 /1971/ appl. date: 670526
Nonanaphylactic benzylpenicillin by gel filtration
Beecham Group Ltd.
CA: 75/2/9892y

2./ DE 2030103 /1970/ appl. date: 690618
Extraction or concentration of antiviral substances, especially penicillins, from the clarified fermentation mash of molds
Beecham Group Ltd.
CA: 74/21/110423a

3./ DE 2012912 /1971/ appl. date: 690321
Acylation of 6-aminopenicillanic acid
Tarchominskie Zaklady Farmaceutyczne "Polfa&
CA: 74/19/100036n

4./ US 3545747 /1970/ appl. date: 681216
Isolation of antibiotics
Upjohn Co.
CA: 73/13/65029t

5./ DE 1922201 /1970/ appl. date: 680215
Hypoallergenic penicillins by use of cell-free enzymic preparations
Aktiebolag Astra
CA: 73/12/59300h

6./ DE 1913486 /1969/ appl. date: 680321
Penicillins
Yeda Research and Development Co. Ltd.
CA: 72/13/66932y

7./ FR 1526417 /1968/ appl. date: 670518
Hypoallergenic penicillins
Beecham Group Ltd.
CA: 71/8/33414g

8./ ZA 6800291 /1968/ appl. date: 670308
Production of semisynthetic penicillins
Ankerfarm S.p.A.
CA: 70/17/76461s

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*/ Data include publications only until 31 March 1983.

9./ DE 1247320 /1967/ appl. date: 611207
3-Carboxyquinoxalin-2-yl penicillin
Boots Pure Drug Co. Ltd.
CA: 69/7/27460m

10./ CS 124390 /1967/ appl. date: 64014
Manufacturing biosynthetic preparations /by aerobic fermentation
CA: 69/1/1798c

11./ CS 124071 /1967/ appl. date: 650717
Processing potato starch wastes as nutrient medium for industrial fermentation.
CA: 68/25/113359w

12./ RO 44574 /1966/ appl. date: 631111
Biosynthesis of penicillin G and penicillin V
Romania, Ministry of the Chemical Industry
CA: 68/3/11717u

13./ GB 1078847 /1967/ appl. date: 630803
Purification of benzylpenicillin
Beecham Group Ltd.
CA: 67/18/84866f

1972-76

14./ HU 9332 /1975/ appl. date: 730801
Penicillins G and V
Biogal Gyógyszergyár
CA: 82/23/153749u

15./ JP 74108010 /1974/ appl. date: 721223
Tentative protection of carboxyl groups
Fujisawa Pharmaceutical Co., Ltd
CA: 82/17/112093g

16./ JP 7428432 /1974/ appl. date: 680809
Penicillins by fermentation
Kyowa Hakko Kogyo Co., Ltd.
CA: 82/11/71599f

17./ IN 131467 /1974/ appl. date: 710524
6-Acylaminopenicillanic acid
Karamchand Premchand Private Ltd.
CA: 82/9/56047f

18./ DE 2418719 /1974/ appl. date: 730418
Acylation of amino acids, peptides, 6-aminopenicillanic acids, and 7-aminocephalosporanic acids and their derivatives which contain acid groups
Politechnika Gdanska
CA: 82/7/43440d

19./ JP 7485082 /1974/appl. date: 721223
Carboxy group-containing compounds
Fujisawa Pharmaceutical Co., Ltd.
CA: 82/5/31338p

20./ DE 2356630 /1974/ appl. date: 721121
6-Aminopenicillanic acid
Beecham Group Ltd.
CA: 82/3/15244z

21./ FR 2188608 /1974/ appl. date: 720614
Semisymthetic penicillins
CA: 81/21/134618p

22./ JP 7380593 /1973/ appl. date: 720207
Penicillins
CA: 80/23/133425r

23./ RO 55510 /1973/ appl. date: 700323
Fermentation medium for penicillin G manufacture
Fabrica de Antibiotice
CA: 80/11/58390y

24./ DE 1966702 /1973/ appl. date: 680619
6-Isocyanatopenicillinic acid derivatives and their use in making 6-aminopenicillinic acid derivatives
Koniklijke Nederlandsche Gist-en Spiritusfabriek N.V.
CA: 79/23/137136z

25./ DE 2302183 /1973/ appl. date: 720118
N-Acylation of 3-substituted-7-amincephem-4-carboxylic
Yeda Research and Development Co., Ltd.
CA: 79/17/105260u

26./ JP 7229586 /1972/ appl. date: 710315
Enzymic acylation of 6-aminopenicillanic acid
Otsuka Pharmaceutical Co., Ltd.
CA: 78/11/70201a

27./ DE 1966428 /1972/ appl. date: 680215
Water-insoluble penicillin acylase
Aktiebolag Astra
CA: 77/25/163056b

28./ RO 53122 /1971/ appl. date: 680815
Culture medium for the preparation of penicillin G
Fabrica de Antibiotice
CA: 77/17/112493j

29./ GB 1276397 /1972/ appl. date: 700713
Culture medium for penicillin G production
Fabrica de Antibiotice
CA: 77/11/73683z

30./ DE 2118693 /1971/ appl. date: 700420
Penicillins and cephalosporins
Takeda Chemical Industries, Ltd.
X CA: 76/15/85828t

31./ DE 2033699 /1972/ appl. date: 700707
Culture medium for the manufacture of penicillin G by Penicillium chrysogenum
Fabrica de Antibiotice Iashi
CA: 76/15/84532e

1977-79

32./ US 4164445 /1979/ appl. date: 750327
Ethanol as the major source of carbon and energy in penicillin production
Squibb, E.R., and Sons, Inc.
CA: 91/19/156038h

33./ JP 7944097 /1979/ appl. date: 770912
Antibiotics
Kyowa Hakko Kogyo Co., Ltd.
CA: 91/11/89521v

34./ DE 2824535 /1978/ appl. date: 770607
Penicillanic acid 1, 1-dioxides
Pfizer Inc.
CA: 90/15/121589r

X 35./ BE 865178 /1978/ appl. date: 761222
X Sterilization of fermentation media
Union Carbide Corp.
CA: 90/9/70595e

X 36./ CS 169411 /1977/ appl. date: 740619
Penicillin G and V
CA: 88/11/72987s

37./ PL 84732 /1977/ appl. date: 720707
Semisynthetic penicillins
Politechnika Gdanska
CA: 88/5/37790a

38./ JP 76128994 /1976/ appl. date: 750501
Penicillin amides
Teijin, Ltd.
X CA: 78/7/23266b

1980-81

39./ DE 3019244 /1980/ appl. date: 790521
Penicillanic acid derivatives
Loevens Kemiske Fabrik Productionsakttesflskar
CA: 95/21/187233F