Appendixes

Appendix I-A
A Case Study of Acetaminophen Production

Summary

The objective of this case study is to demonstrate the economic feasibility of applying a genetically engineered strain to make a chemical product not now produced by fermentation.

BACKGROUND

Acetaminophen (APAP) was chosen for the case study. As an analgesic it lacks some of the side effects of aspirin, and is the largest aspirin substitute on the market. Around 20 million pounds (lb) are manufactured annually. Mallinckrodt Inc., produces 65 to 70 percent; the remainder is manufactured primarily by CPC International and Monsanto Co. APAP is sold to health care companies which market it to retailers.

The McNeil Consumer Products division of Johnson & Johnson, which markets APAP under the trade name Tylenol has the largest share of the market. Over a dozen other companies in the United States sell it under other trade names.

One chemical manufacturer's bulk selling price for APAP is around $2.65/lb.[1] By the time the consumer purchases it at the drugstore the markup results in a selling price of around $25 to $50/lb, depending on dosage and package size. Thus the total value of APAP to the manufacturers is some $50 million annually while the total retail value falls in the range of $500 million to $1 billion.

APPROACHES

- A conservative approach was taken, in that only a conventional batch fermentation process was considered.
- Variables were selected pertaining to the choice of the microbial pathway; the nature of the feedstock; conversion efficiencies of feedstock to PAP; and the final yield of APAP.
- Costs were based on proprietary processes involving startup, large-scale fermentation, and recovery of PAP.
- Costs were itemized for materials and supplies; labor distribution; utilities (broken down by specific energy requirements according to process and equipment); equipment (grouped according to process); and building requirements (space needed allocated according to process).

CONCLUSIONS

- The projected cost for manufacturing APAP by means of batch fermentation using a genetically engineered strain, amounts to $1.05/lb. This cost is based on a plant producing 10 million lb of APAP annually.
- As a rule of thumb, the gross margin to manufacturers of a chemical such as APAP should approximate 50 percent of sales. The gross margin represents the profit before general and administrative, marketing and selling, and research and development expenses. The gross margin to a drug product made by Mallinckrodt, the largest manufacturer of APAP, amounted to 53 and 55 percent of sales in 1976 and 1977, respectively.[2] The gross margin to Monsanto, a much larger company than Mallinckrodt but a smaller manufacturer of APAP, amounted to 27 and 25 percent of total sales in 1976 and 1977, respectively.[3] If the gross margin for APAP is as high as 50 percent of sales, its current cost of manufacture should amount to $1.325/lb, based on a bulk selling price of $2.65/lb. Therefore, its projected cost when produced by fermentation is around 2[illegible] percent lower than its estimated cost when produced by chemical synthesis.
- If the selling price of APAP produced by fermentation is marked up 10 percent, the bulk selling price becomes $2.10/lb. This decrease of $0.55/lb could be transformed into cost savings of around $5 to $10/lb to the consumer. These economies would result in an annual cost saving to the consumer of $100 million to $200 million.
- Current processes for synthesizing APAP from nitrobenzene do not appear to pose significant pollution problems, although a number of side products are formed and must be removed.[4,5,6] However, a fermentation process would be even

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[1] *Chemical Marketing Reporter*, November and December 197[illegible].

[2] Mallinckrodt, Inc., *Annual Report*, 197[illegible].

[3] Monsanto Co., *Annual Report*, 197[illegible].

[4] G. Benner, "Process for Preparing N-Acetyl-p-Aminophenol," U.S. Patent 3,383,41[illegible], 196[illegible].

[5] [illegible], G. Benner, and A. S. Weinberg, "Purification of p-Aminophenol," U.S. Patent 3,6[illegible],3[illegible]8, 197[illegible].

[6] A. Baron and G. Benner, "Purification of p-Aminophenol," U.S. Patent 3,[illegible]17,68[illegible], 197[illegible].

leaner. Only A PAP would ccumulate: ll ther netabolites re aturally occurring. Even nicro-rganisms could te collected after each batch and rocessed into ake or ... high protein ...nal feed.

Biological parameters

MICROBIAL PATHWAY

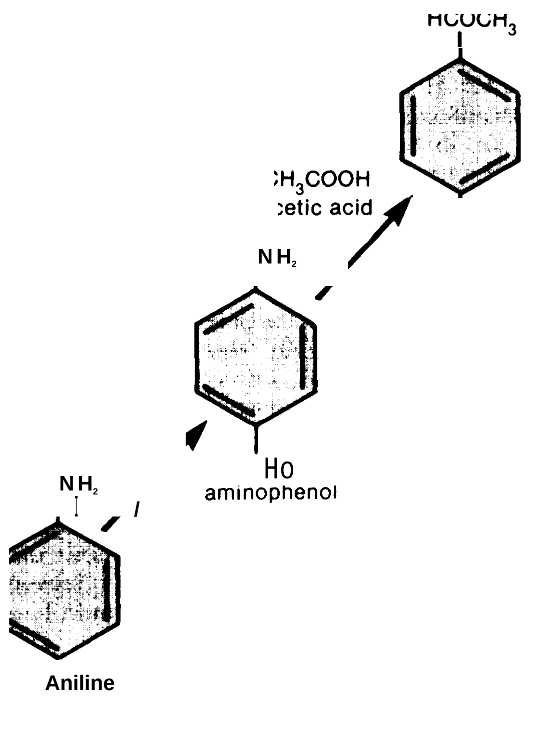
A proposed athway or onverting aniline to A PAP ia t the cetylation of an ntermediate, p-amino-henol, i is shown in gure I 1-A-l. arious I fungi have een identified in which these eactions occur.[7,8,9]

[7]R. V. Smith nd J. J. P. Rosazza, Microbial Models of Mammalian etabolism, J. Pharmaceut. Sci. 64 1737-1759, 1975.

[8]R. V. Smith and J. P. Rosazza, "Microbial Models of Mammalian etabolism: romatic Hydroxylation," Arch. Biochem. Biophys. 161:551-558, 1974.

[9]V. R. unzner, F. Kutschler, and A. Kammel, "Uber d die Mikro-ologische Umwandlung Haltiger substrate" oncerning he Microbiological ransformation c N- c containing Substrate), Plant edica 1 :97-103, 1967.

Figure I-A-I. loconversion c of Aniline to PAP[a]



PAP = I N acetyl-p-aminophenol = = etaminophen = = icetamidophenol = = droxyacetanilide = ylenol (tr (trade name of Neil La Laboratories).

SOURCE: nex Co Corp.

lternatively, niline ould e cetylated directly forming cetanilide, which in turn ould te hydrox-lated to A PAP. [10] A umber of Streptomyces spe-cies ave een ound o onvert cetanilide to PAP.[10] he athway nvolving p-aminophenol was chosen simply ecause the conversion efficiency f cetic acid to A PAP ould te slightly higher i acetic cid entered the verall reaction at the second step ather than at the first step.

HOST MICRO-ORGANISMS

The most uitable micro-organism for production f APAP in arge-scale fermentation may not neces-arily e one hat 1101' nally metabolizes aniline 01' -aminophenol. While a bacterium might serve as uitable host for insertion nd expression f the re-isite genes, yeast may represent etter choice. will robably more losely resemble the organism rom which he genes are olated.

Fermentation efficiencies

CONVERSION EFFICIENCIES

The olar and weight conversion efficiencies for the ioconversion of feedstock to product re pro-jected in able I 1-A-1. The ioconversion of aniline to

[7]Smith, et al., op. cit.

[9]Kunzner, et al., op. rit.

[10]J. J. Theriault and T. P. Longfield, "Microbial Conversion cetanilide to 2-Hydroxyacetanilide and 4-Hydroxyacetanilide," Appl. Microbiol. 15:1431-1436, 1967.

[11]Ibid.

Table I=A-I.—Fermentation Efficiencies to Meet the Requirements for the Production of cetaminopnen (APAP) From Aniline

verall n molar conversion efficiency of:	
(a) Aniline to APAP	).25%
(b) Acetic Acid to APAP	95.0
verall w weight conversion efficiency of:	
(a) Aniline to APAPa	146.5
(b) Acetic Acid to APAPa	239.1
Utilization of:	
(a) Aniline in fermentation broth	2.28 lb/gal
(b) Acetic acid in fermentation broth	1 9/gal
Production of APAP in broth	3.34 lb/gal
Batch volume	33,500 gal
Recovery efficiency	90.0 %
Yield of PAP/batch	100,701 lb
Number of batches/year	100
nnual yi yield of product	10,070,100 lb

verall wt weight conversion of precursor to APAP = molecular wt weight of APAP / molecular weight of precursor x molar conversion efficiency of precursor to APAP

SOURCE: Genex Corp.

APAP involves two steps. The product of the individual reactions for each step represents the overall conversion efficiency. A molar conversion efficiency of 90 percent was assumed for each step. This value is based on a multitude of reports demonstrating similar molar conversion efficiencies for analogous biochemical reactions under actual fermentation conditions.

PRODUCT YIELD

The yield of APAP projected in table I-A-l is based on estimating a ratio of 40 percent weight to volume (i.e., 40 lb per 100 gallons (gal) of fermentation broth prior to 90 percent recovery. Such a high yield is permitted because of the poor solubility of APAP under operating conditions. As a result, high levels of APAP would have no adverse effect on the host micro-organism. Use of insoluble systems in fermentation has in fact been reported in recent years—e.g., in certain microbial transformations of steroids, yields of 40 percent may result due to the insolubility of the product.

[11] Abbott, "Immobilized Cells," in *Annual Reports on Fermentation Processes*, vol. 1, D. Perlman (ed.) (New York: Academic Press, 1977), pp. 205-233.

Economics

PRODUCTION REQUIREMENTS

How the various production requirements would be met during the microbial transformation of aniline to APAP is summarized in table I-A-1 and 2. Aniline and acetic acid would not be added to the fermentation broth all at once but rather step-wise according to their rate of conversion. The plant would contain two 50,000-gal fermenters which in the course of a year would yield 10 million lb of APAP.

PRODUCTION COSTS

The cost for the annual production are summarized in table I-A-3. They are broken down into their major components and are expressed both as annual costs and as unit costs. Detailed budgets for the different cost centers are shown in tables I-A-4 through I-A-lo. Materials and supplies are described in table I-A-4; labor distribution in table I-A-5; utility requirements in tables I-A-6 through I-A-8; equipment in table I-/~-9; and space requirements in table I-A-IO. This analysis reveals the unit cost of APAP equal to $1.05/lb.

Table I-A-2.—Summary of Production Conditions of APAP

Number of fermenters	2
Size of fermenters	50,000 gal
Operating volume	33,500 gal
Cycle	7a
Batches	100

a6-day fermentation, l-day turn around.

SOURCE: Genex Corp.

Table I-A-3.—Summary of Costs of Production of APAP

	Annual cost	Cost/
Materials and supplies	$ 6,133,802	$0.6091
Labor	2,012,140	0.1998
Utilities	630,200	0.0626
Equipment	1,377,590	0.1368
Building	439,399	0.0436
Total	$10,593,131	$1.05/

Annual production - 10,070,100 lb

SOURCE: Genex Corp

Table I-A-4.—Material and Supplies for Production of APAP

Materials	Cost/batch	Cost/year
Fermentation		
Fishmeal (1.5% @ $0.155)	$ 648.68	$ 64,868
Glucose (1.5% @ $0.1535)	642.40	64,240
Lard oil (2.5% @ $0.325)	2,266.88	226,888
Mineral salts (4,215 lb @ $0.05074)	213.77	21,377
Aniline (76,250 lb @ $0.42)	32,027.52	3,202,752
Acetic acid (46,680 lb @ $0.245)	11,436.60	1,143,660
Miscellaneous (10% of basic materials)	377.17	37,717
Subtotal	$47,613.02	$4,761,302
Recovery		
Filter aid (0.2 lb/g @ $13)	$ 871.00	$ 87,1OO
Other chemicals and supplies	1,600.00	$ 160,000
Subtotal	$2,471.00	$ 247,100
Finishing		
Packaging (1,255 bag units at $0.8	$ 1,004.00	$ 100,400
Other (labels, stencils, etc.)	1,004.00	$ 100,400
Subtotal	$2,008.00	$ 200,800
General supplies		
Maintenance (4% of capital investment)		$ 425,900
Other (laboratory office, plant miscellaneous)		498,700
Total		$6,133,802

SOURCE: Genex Corp.

Table I-A-5.-Labor Distribution for Production of APAP

Category	Man-hours per week	Hourly rate	Salary and wage cost: $/week	Salary and wage cost: $/year
Supervision				
General manager	40	20	$ 800	$ 41,600
Superintendents	80	17	1,360	70,720
Managers	80	15	1,200	62,400
Supervisors	320	12	3,840	199,680
Hourly rated employees, services				
Laboratory				
Level I	80	10	800	41,600
Level II	80	8	640	33,280
Level III	120	6	720	37.440
Level IV	40	5	200	10,400
Maintenance and engineering				
Level I	240	10	2,400	124,800
Level II	240	8	1,920	99,840
Level III	240	6	1,440	74,880
Level IV	160	5	800	41,600
Hourly rated employees, production				
Fermentation department				
Level I	200	10	2,000	104,000
Level II	240	8	1,920	99,840
Level III	80	6	480	24,960
Level IV	80	5	400	20,800
Recovery department				
Level I	320	10	3,200	166,400
Level II	400	8	3,200	166,400
Level III	80	6	480	24,960
Level IV	120	5	600	31,200
Subtotal				$1,476,800
Add overtime@ 6% x 1.5				132,912
Subtotal				$1,609,712
Add fringe benefits @25%				402,428
Total salaries and wages				$2,012,140

SOURCE: Genex Corp

Table I-A-6.-Steam Requirements for Production of APAP

Operation	Lb/batch
Sterilization, fermenters, and seed tanks:	
Heating	52,100
Holding	20,000
Sterilization, piping, and equipment (other)	20,000
Heating acetaminophen solution (recovery)	163,500
Drying, turbo dryer	200,300
General purpose usage	50,000
Total	505,900
Cost at $5.00/Mlb:	
Per fermenter batch =$ 2,530	
Per year (100 batches) =$253,000	

SOURCE: Genex Corp.

Table I-A-7.–Electricity Requirements for Production of APAP

Connected load	HP	kW	Units/batch (hours operation)	kWh
Fermenters	200	149	144	21,456
Seed tanks	47.5	35	24	840
Chillers	580	433		4,763
Air compressor	275	205	86	17,630
Harvest tank	100		11	825
Decanter centrifuge	120	90	52	4,680
Process tanks	300	224	19	4,256
Crystallizing tanks	300	224		2,464
Turbo dryer	30	22	23	506
Cooling tower	40	30	144	4,320
Pumps (est. =6@ 7.5)	45	34	144	4,896
Lighting, instruments and general load	25	19	144	2,736
Total kWh				69,372

@O.05/kWh = $3,469 per batch
@100 batches/yr= $346,900 per year

SOURCE: Genex Corp.

Table I-A.8.-WaterRequirements for Production of APAP

	Gal/batch
Fermentation	35,000
Tower makeup	63,000
Process loss	100,000
Chilled water makeup	30,000
Direct cooling	50,000
General use	25,000
Total	303,000 gal

Process Watergate cost = $1.00/M gals
= $303/batch
100 batches/yr = $30,300/year

SOURCE: Genex Corp

Table I-A-9.—Equipment Costs for Production of APAP

Item	Cost
Receiving and batching area	
320,000 gal steel aniline storage tanks, insulated and cooled - @ $47,000	$ 341,000
220,000 gal aluminum acetic acid storage tanks, insulated and cooled - @ $71,300	342,600
110,000 gal steel nitrogen storage tank with controls and instruments	47,000
110,000 gal steel lard oil storage tank, insulated and heated	22,300
110,000 gal stainless steel Batch tank with programmable controller and agitator	59,500
21,700 ft³ stainless steel Hopper bins with conveyors - @ $58,100	116,200
1 Electric forklift truck	11,400
Fermentation and seed area	
1150 gal stainless steel seed vessel, fully instrumented	125,000
12,500 gal stainless steel seed vessel, fully instrumented	169,000
250,000 gal stainless steel fermenters, fully instrumented with central control room - @ $399,000	798,000
Recovery area	
150,000 gal stainless steel process tank, cooled, agitated and insulated	195,000
13,000 gal steel filter aid slurry tank with agitator	11,300
1 Stainless steel continuous decanter centrifuge	167,000
2100,000 gal stainless steel process tanks, insulated with external steam injection heater, pump and agitator- @ $333,000	666,000
120,000 gal stainless steel side-entering surge tank with agitator	$ 56,100
350,000 gal stainless steel crystallizing tanks, insulated with heavy duty cooling coils and top-mounted agitator - @ $195,000	585,000
1 Stainless steel turbo tray dryer	653,000
23,500 ft³ stainless steel hopper bins- @ $66,000	132,000
1 Bagging unit	20,000
4 Stainless steel finished product conveyors- @ $12,000	48,000
Auxiliary equipment	
31,500 c.f.m. reciprocating air compressors - @ $168,000	498,000
Laboratory and office equipment	650,000
Chillers, 500 ton total capacity	575,000
1 Cooling tower, 1,500 g.p.m.	210,000
35 Pumps and motors, various sizes	104,700
2 Dump trucks -$12,000	24,000
Ventilation, general and spot - @ 7.5% of equipment	583,791
Piping, general, materials and installation - @ 7.5% of equipment	583,790
Miscellaneous equipment (hand tools, etc.) - @ 5°A of equipment	389,194
Total	$7,783,875
Annual charge for capital recovery over 10-year period, with 12% interest compounded annually ($7,783,875 x 0.17698)	$1,377,590

SOURCE: 3enex Corn.

Table I-A-10.–Buiiding Requirements for Production of APAP

Area	Gross space ft²/ft³	Unit value[a]	cost
Central office	940	41.00[b]	$ 38,540
Laboratories	4,500	70.00[b]	315,000
Warehouse	2,000/36,000	27.00[b]	54,000
Batching	1,000/30,000	1.75	52,500
Fermentation (including seed)	6,000/320,000	1.75	560,000
Harvest, filter	3,500/169,000	1.75	295,750
Processing, crystallization	8,700/470,000	1.75	822,500
Drying, finishing	5,000/270,000	1.75	472,500
Warehouse, finished product	11,000/200,000	27.00[b]	297,000
Auxiliary equipment	4,300/154,000	1.75	269,500
Maintenance, engineering	11,500/207,000	1.75	362,250
Total			$3,539,540

Amortization over 30 years@ 12% compound interest $439,399[c]

Unit values i in ubic f feet except where noted by b.”
Unit value i in square feet.
Amortization = 0.12414 X otal.

SOURCE: enex Corp.