# INDUSTRIAL USE OF ENZYMES

## Technical and Economic Barriers

Edited by
Bernard Wolnak
and
Marvin Scher

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**Bernard Wolnak and Associates, Inc., Chicago, Illinois**

Printed by Johnson Graphics, Decatur, Michigan

*Library of Congress Cataloging-in-Publication Data:*

Industrial use of enzymes: technical and economic barriers/edited by Bernard Wolnak and Marvin Scher.

Proceedings of a conference sponsored by Bernard Wolnak and Associates, held in Chicago, May 9 – 11, 1990.

Includes index.

1. Enzymes – Industrial applications – Congresses. 2. Enzymes industry – Congresses. I. Wolnak, Bernard. II. Scher, Marvin. III. Bernard Wolnak and Associates (Chicago).

TP248.E5I62 1990 615.19 90-070727

ISBN 0-9626769-0-X



Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED BY JOHNSON GRAPHICS, DECATUR, MICHIGAN, USA

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# PART I

# INDUSTRIAL ENZYMES

# FORTY YEARS ATTACKING BARRIERS - ENZYME COMMERCIALIZATION PAST, PRESENT AND FUTURE THE PARADOX AND THE PROMISE

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## INTRODUCTION

In May of 1978, we organized a conference on a closely related subject, namely, enzyme economics. Now twelve years later, we are again assembled to discuss this challenging and exciting area of enzymes, and we are focusing again on the frustratingly slow growth of industrial markets for enzymes.

We are immensely pleased that so many of you have come from all parts of the world to attend this conference and to become part of these meetings and discussions. We look forward to a successful conference, successful not only in the technical and professional aspects, but also successful in its social and cultural aspects as well. If there is anything we can do to make your stay here in Chicago more enjoyable, please contact either me or other members of our staff. I would also like to note that we are hopeful that another twelve years will not elapse before we hold a third conference; we are looking tentatively at holding such a third conference two years hence in Chicago in May, 1992. Any thoughts you have regarding the time, location, theme and content for this third conference would be appreciated.

To begin with, let me define an enzyme, an entity which will occupy our attention for the next three days. Most of you have seen this definition many times and in many different forms; to those who are working in enzymology this information is elementary. Because the definition and properties of enzymes are the focal point of the conference, I include them here. Everything said from here to the conclusion of the conference, one way or another, will be impacted by these properties.

By our definition, an enzyme is an organic chemical or molecule of biological origin, proteinaceous in nature of comparatively high molecular weight and can, under certain conditions, act as a catalyst significantly accelerating the rate of a specific chemical reaction.

What are some of the advantages and disadvantages which accrue when using enzymes? First, the advantages of enzymes are as follows:

1. Operate at ambient temperatures.
2. Operate in aqueous solution.
3. Operate at neutral of physiological pH.
4. Have a very high specificity.
5. Require low concentrations to produce the desired effect.
6. Usually produce a comparatively rapid reactions.
7. Usually have a low level of toxicity to mammals.

Some of the important disadvantages of enzymes are as follows:

1. Difficult and often expensive to prepare, particularly in pure forms.
2. Comparatively sensitive or unstable molecules which require a degree of care and expertise in their use.
3. Operate best in aqueous solution wherein the substrate is present in dilute solution.
4. Extremees of pH and temperature often limit activity levels.

In this conference we shall be restricting our discussion to the activities, uses, economics and properties of single, well-defined enzymes. Although we would very much like to include multi-enzyme systems, whicha re the basis for fermentation processes, I believe that we cannot and should not dilute our discussions by including thee related and important unit processes.

As a point of departure, I would like to discuss briefly the historical development of the enzyme business in the United States. In so doing, I would like to identify some of the important developments which have led to the barriers which we will discuss during this conference.

## HISTORICAL DEVELOPMENT AND PRESENT MARKETS

The enzyme business in the United States started fairly early in the twentieth century. In this early period, three prominent names come to mind. One is that of Dr. Takamine;

it was in the early 1900's that Dr. Takamine established a production unit in Clifton, New Jersey to provide enzymes for the food industry. The second name is Dr. Otto Haas, the founder of the Rohm and Haas Company, who developed the use of pancreatic enzymes in leather production. And third, there was Leo Wallerstein, who, in 1911, began the commercial production of papain for use in the beer industry.

This rather inauspicious beginning established the enzyme business in the United States, which during the succeeding eighty years, has grown slowly but steadily. Thus, by 1960, sales of enzymes in the United States, at the manufacturer's level, reached about $25 million. In 1977, sales were at about $115 million, and in 1989 sales had reached barely $200 million.

In Table 1, the sales levels for the major enzymes used in the U.S.A. are listed for the period 1975 to 1989.

Table 1
Market Summary for Important Enzymes
in the United States(a)(b)
1975-1989
Dollars not Adjusted for Inflation

| Enzyme | Estimated Annual Sales, $MM 1975 | 1980 | 1989 |
|---|---|---|---|
| Alpha Amylase | 5.5 | 11.6 | 20.9 |
| Amyloglucosidase | 6.0 | 14.3 | 26.5 |
| Beta Amylase | 2.5 | 3.2 | 4.5 |
| Glucose Isomerase | 15.0 | 40.0 | 36.0 |
| Glucose Oxidase | 0.7 | 1.1 | 1.5 |
| Invertase | 0.3 | 0.3 | 0.3 |
| Lipase | 0.5 | 0.8 | 6.5 |
| Cellulase | 0.3 | 0.4 | 1.0 |
| Pectinases | 2.0 | 2.7 | 7.0 |
| Papain | 10.1 | 14.9 | 21.0 |
| Bromelain | 1.0 | 1.3 | 1.6 |
| Pancreatin | 4.6 | 5.9 | 7.5 |
| Pepsin | 3.5 | 4.5 | 6.0 |
| Rennins | 14.9 | 19.9 | 31.0 |
| Bacterial Proteases (Detergent enzymes) | 4.7 | 6.2 | 27.5 |
| Fungal Proteases | 0.9 | 1.1 | 1.4 |
| Total | 72.5 | 128.2 | 200.2 |

(a) BWA estimate
(b) Excludes captive production

On an absolute dollar basis, the increase in the sales of enzymes from 1975 to 1989 was at 176%, a respectable value. However, if we adjust the 1989 values for inflation and redo Table 1 in constant 1975 dollars, we obtain the following picture.

Table 2
Market Summary for Important Enzymes
in the United States
1975-1989
Dollar Values Adjusted for Inflation

| Enzyme | Estimated Annual Sales, $MM | |
|---|---|---|
| | 1975 | 1989[a] |
| Alpha Amylase | 5.5 | 9.1 |
| Amyloglucosidase | 6.0 | 11.6 |
| Beta Amylase | 2.5 | 2.0 |
| Glucose Isomerase | 15.0 | 15.7 |
| Glucose Oxidase | 0.7 | 0.7 |
| Invertase | 0.3 | 0.1 |
| Lipase | 0.5 | 2.8 |
| Cellulase | 0.3 | 0.4 |
| Pectinases | 2.0 | 3.0 |
| Papain | 10.1 | 9.2 |
| Bromelain | 1.0 | 0.7 |
| Pancreatin | 4.6 | 3.3 |
| Pepsin | 3.5 | 2.6 |
| Rennins | 14.9 | 13.5 |
| Bacterial Proteases (Detergent enzymes) | 4.7 | 12.0 |
| Fungal Proteases | 0.9 | 0.6 |
| Total | 72.5 | 87.3 |

[a] In 1975 dollars

The previous increase in sales volume of almost 130 million dollars now shrinks to an increase of only 14.8 million dollars, only 20%. For a 14 year period, this increase is not impressive.

The industrial enzyme market may be divided as follows, Table 3.

Table 3
Market Summary for Enzyme Groups
in the United States

| Enzyme Group | Estimated Annual Sales 1989 | % of Total |
|---|---|---|
| Amylases | 87.9 | 44.0 |
| alpha-Amylase | | |
| beta-Amylase | | |
| Glucose isomerase | | |
| Amyloglucosidase | | |
| Proteases | | |
| Bacterial (detergent enzymes) | 27.5 | 13.7 |
| Other | 29.4 | 14.7 |
| Rennins | 31.0 | 15.5 |
| Lipases | 6.5 | 3.2 |
| Pectinase | 7.0 | 3.5 |
| Others | 10.9 | 5.4 |
| Total | 200.2 | 100.0 |

## PRESENT MAJOR PRODUCERS

What U.S. companies are involved in the production and sale of enzymes in the U.S.A.? These are given in Table 4 with the estimated % of the market and corresponding sales level:

Table 4
Market Segments Held by the Major Enzyme
Marketers in the U.S.A., 1989

| Company | % of U.S. Market | Estimated Dollar Volume |
|---|---|---|
| Novo-Nordisk | 40 | 80.1 |
| Gist-Brocades | 15 | 30.0 |
| Miles/Bayer | 20 | 40.0 |
| Hansen | 5 | 10.0 |
| DFL/Sanofi | 2 | 4.0 |
| Genencor | 5 | 10.0 |
| Finnsugar | 2 | 4.1 |
| Enzyme Development Co. | 5 | 10.0 |
| Others | 6 | 12.0 |
| Total | 100 | 200.2 |

It should be noted that Finnsugar and Genencor recently merged with the Kodak group to form a new consortium, Genencor, International. The "Others" in the Table are Pfizer, Amano, PMP Products, and the Rohm group of Germany.

The other major producing segment of the enzyme industry is present in Europe. Here, the major producers of industrial enzymes are Gist-Brocades in Delft, Holland and the Novo-Nordisk group in Copenhagen, Denmark. As in the U.S.A., there are a significant group of producers of varying size spread through the many countries of Europe. Some of these producers are:

- Novo-Nordisk, Denmark
- Gist-Brocades (RNFI), Holland
- Associated British Malsters (AMB), U.K.
- Miles, Seravac, U.K.
- Boehringer-Mannheim, W. Germany
- Bayer, West Germany
- Rohm, West Germany
- Ciba-Geigy, Switzerland
- Kali Chemie, West Germany
- Biochemie, Austria

The Japanese situation is interesting. Although the Japanese have been very prolific researchers in enzymes and have published extensively, commercial enzyme operations are much more limited in Japan, as compared to the U.S.A. or Europe. The most important determinant factor in this situation comes from the fact that there is essentially no corn wet milling industry in Japan and the dairy business, i.e., cheese production, is very limited. The enzyme fortified detergent industry has become significant only comparatively recently. The major commercial activity in enzymes in Japan revolves around the production and sale of digestive-aid enzyme preparations. These enzymes are prepared in large part by using Koji tray processing as opposed to the submerged culture processes used in the U.S.A. and Europe. This medical use for enzymes is not to be dismissed lightly since the market for these products is in excess of 250 million dollars per year. A similar, but somewhat smaller market, exists in Europe. Only a very small market for digestive enzymes exists in the U.S.A. because the FDA does not recognize their efficacy, and thereby prevents advertising these products.

The major producers of industrial ezymes in Japan are:

| | |
|---|---|
| Ajinomoto Co. | - Proteases |
| Amano Pharmaceutical Co. | - Varied |

| | |
|---|---|
| Dawai Kasei | - Varied |
| Meiji Seika Kaisha, Ltd. | - Cellulase, protease, amylase |
| Nagase and Co. | - Varied |
| Toyo Jozo Co., Ltd. | - Cellulase, lipase, research enzymes |

## BARRIERS

Inspection of the data presented in the preceeding tables shows that the enzyme industry today is not a growth industry. Consider, for a moment, a highly technologically based industry founded some eighty-five years ago which has reached a U.S.A. market value of only 200 million dollars and a worldwide market of barely 500 million dollars. I do not believe this is representative of a dynamic growing industry. If we accept this statement, then the question arises as to what are the important factors which have prevented the enzyme markets from being an order of magnitude, greater, say in the range of three to five billion dollars? In addition, what factors and forces are present and operating which are working to maintain the enzyme industry as a comparatively low growth industry?

The important question is: What are the barriers which have prevented and continue to prevent the enzyme industry from being a growth industry?

Let me take this opportunity to begin to develop some of the answers to this complex and difficult question.

As an example, let us assume that there is a situation wherein your company and your R&D organization sees a marketing opportunity which may be amenable to a new enzyme system. By developing this enzyme system, with certain definable properties and capabilities, your company can enter into the production and sale of a new enzyme product on a profitable basis. To reach this goal, what important factors have to be considered and what barriers need to be overcome?

It is in answering these questions that we hope the papers and discussions to be presented at this conference will begin to give us some useful answers.

Having previously briefly described the enzyme industry on an historical and economic basis, what factors can we identify as barriers to the growth of the enzyme industry? This list of factors which I have identified are summarized in Table 5 and will be discussed in the following sections.

Table 5
Barriers to Enzyme Market Growth

1. Enzyme Pricing
2. Profitability
3. Creation of New Markets
4. Patents
5. Time and Funding Requirements for Enzyme Research and Development
6. The Decision-making Process
7. Impact of Low Profits
8. Facilities and Personnel
9. Problem Identification
10. Capital and Technology Requirements
11. Technical Service Requirements
12. Locked-in Customers
13. Lack of Mechanisms for Technology Transfer

## 1. Enzyme Pricing

We believe that a major reason for poor growth of the enzyme industry has been the pricing policies of the major enzyme producers during the past decade. During this decade, increasing competition has developed in the sale and marketing of amylases, glucamylase, and glucose isomerase enzymes. These starch processing enzymes constitute a large part of the industrial enzyme market. To protect and maintain their market position, producers lowered prices of these enzymes drastically, their goal being either, at the extreme, to drive their competition out-of-business, or minimally, to maintain their market position. To date, this pricing policy has had little success in driving out competition. One small, new entry into the business, Enzyme Technology Corp. of Ashland, Ohio, was forced out of business, in large part because of this competition, but insofar as the majors were concerned, this policy resulted only in a significant loss of profits for all the enzyme-producing companies concerned. Pricing now is at an improved level, but enzyme sales are still not very profitable.

Another aspect of this barrier to enzyme market growth is that enzymes used in industrial processes do not add very much to the cost of the final product. In many processes, the cost of enzyme used is less than 1% of the cost of the end-product. As an example, the cost of the amylase and the glucamylase enzymes, used to convert corn starch to glucose, costs the producer about $0.20 per 100 lbs of glucose produced; this cost for the two enzymes amounts to about 0.4

cents per kilogram of glucose produced. Using the enzyme, glucose isomerase, to convert this glucose to high fructose corn syrup (HFCS) will add another 0.5 cents per kilogram of product produced. The total enzyme cost for conversion of one kilogram of starch to one kilogram of high fructose corn syrup solids is less than one U.S. cent per kilogram.

If one looks at those industry segments and those industries wherein enzymes are used to a significant extent, e.g., in starch conversion, in the production of wine, cheese, beer etc., we see only very high volume industries. One can conclude that high-volume industries today represent the only industries wherein viable enzyme markets can develop. A further conclusion is that significant enzyme sales are created only when the low enzyme cost per unit of product can be multiplied by a high volume of production thus ultimately requiring large amounts of enzyme units.

To illustrate the effect of low enzyme cost, we have developed the calculation shown in Table 6.

Table 6
Calculation of Potential Enzyme Sales

| | Scenario 1 | Scenario 2 |
|---|---|---|
| End-product sales | $1,000,000,000 | $100,000,000 |
| Mfgr. cost of goods 50% of sales[a] | $ 500,000,000 | $ 50,000,000 |
| Enzyme sales 1% of COG[b] | $ 5,000,000 | $ 500,000 |

[a] The ratio of the end-product cost-of-goods to sales value is 50%, a value which is high for a high volume business.

[b] Enzyme costs are 1% of the cost-of-goods, also a high probable value.

Table 6 shows that end-product sales of $1 billion generate enzyme sales of only about $5 million, assuming an end-product cost-of-goods-sold-to-sales ratio of 50% and enzyme expenditures of 1% of cost of goods. But when end-product sales are at $100 million, enzyme sales of only $500,000 are generated, a market size which may be only marginally economical for the enzyme manufacturer. Thus, if the above scenario is valid, major enzyme markets are developed almost exclusively where billion dollar markets of the end-product are produced.

This assumption was tested by looking at five major product areas using enzymes. In Table 7 we have listed these product areas.

Table 7
End-Markets for Enzymes in the United States 1989

| End-Market | Volume of Output ($\times 10^6$) M.T. | Mfgr. Sales ($ $\times 10^6$) |
|---|---|---|
| High-fructose corn syrup | 6,800 | 3,500 |
| Detergents | 3,600 | 11,000 |
| Cheese | 3,000 | 8,000 |
| Beer | 25 | 13,000 |
| Wine | 2.5 | 2,800 |

In addition, these large volume products, while showing growth at varying rates during the past decades, are now growing only at comparatively low rates. The impact on the existing enzyme industry is to allow for only correspondingly low rates of growth for the existing enzymes being produced and marketed.

If enzyme sales are indeed tied only to very high volume products, finding these products to expand enzyme markets is now, and will continue to be, difficult. Here then, in the pricing and sales volume relationship of enzymes, I believe we have an example of a very important barrier.

2. Enzyme Profitability

Gross profit margins in enzyme manufacture can be very high, reflecting the oligopolistic competitive structure of the industry, wherein pretax-gross income profits may be as high as 20% to 25% for the major producers. However, calculation of such gross profits in this enzyme business are misleading because several important factors lower this gross profit rapidly and drastically.

First and foremost, there is a continuing and large expense involved in customer technical service, which the enzyme producer must supply to purchasers and users of enzymes. This technical service is actually demanded by the enzyme user, particularly in the food industry. Needless to say this is an expensive obligation and removes a large amount