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CORRESPONDENCE

PHENYLALANINE FUSS

To the editor:

I am writing in response to your article "Building for Success in Phenylalanine," in the April issue.

One of the most effective yet simple ways to compare the economics of different processes is by their raw material contribution. Although the article uses this method of comparison, its oversights lead to incorrect conclusions. The raw materials of Synthetech's process (cinnamic acid and ammonia) are—and will always be—significantly cheaper than Purification Engineering's (phenylpyruvate and aspartic acid). Furthermore, cinnamic acid is generally available in quantity, whereas phenylpyruvate is not. This *forces* a back integration of the phenylpyruvate, and attendant capital outlays.

Phenylpyruvate's precursors are hydantoin and benzaldehyde. Cinnamic acid's precursors are benzaldehyde and acetic anhydride. Therefore, back integrated to the same level, Synthetech's raw materials are benzaldehyde, acetic anhydride, and ammonia. PEI's are benzaldehyde, hydantoin (which is twice as expensive as acetic anhydride) and aspartic acid (which is 15 times more expensive than ammonia).

In addition to this substantially greater raw material efficiency, Synthetech's process has other fundamental advantages. For example, assuming 100 percent conversion in the bioreactor, PEI's process still has 50 percent byproducts on a mole basis where Synthetech's process has no byproducts.

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PURIFICATION ENGINEERING RESPONDS

To the editor:

When entering any area of research, the cost of raw materials must be carefully considered. An adequate assessment of scale-up process economics cannot be made, however, without equal consideration being paid to yields, isolation of the desired product, and waste stream disposal. When these are considered, we believe, the phenylpyruvate route to phenylalanine becomes superior to the cinnamic acid route.

Back integration for the production of phenylpyruvic acid allows Purification Engineering Inc. (PEI) to use this material in its aqueous state: we save the cost of isolation and shipment. Since similar equipment is used to prepare phenylpyruvate and cinnamic acid, the capital cost should be comparable. Also, the production of cinnamic acid and phenylpyruvate proceed in equivalent yield[1]. Thus—with the money we save through back integration—the cost advantage for this phase goes to phenylpyruvic acid.

In addition, hydantoin is not the only possible precursor to phenylpyruvate. Rhone-Poulenc, Ethyl, and Dynamit Nobel all have commercial processes and patents for the production of phenylpyruvate from benzylchloride via biscarbonylation[2–4]. Soon this process should significantly lower the cost of phenylpyruvic acid. The price of cinnamic acid in the grades necessary for use in the production of phenylalanine has dropped to $2.50/lb. But this still places cinnamic at a cost *disadvantage* when compared to phenylpyruvate prepared either by biscarbonylation or by the hydrolysis of 5-benzylidine hydantoin.

Finally, it is always dangerous to assume 100 percent conversion of any chemical in a bioreactor. Chibata and his co-workers have shown that the conversion of cinnamic acid to phenylalanine proceeds in 70 percent yield at a pH of 10.5 and an ammonium ion concentration of 7.5M. This requires paying for the disposal of 7.5M ammonium ion in an eluent stream contaminated by cinnamic acid. Phenylpyruvic acid may be converted to phenylalanine in 98 percent yield[6].

Purification problems are also reported to significantly add to the cost of the cinnamic acid process[7].

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AGAROSE ADVOCATE

To the editor:

In "Scale-Up: The Next Hurdle" (May, 1985) on page 421, the statement was made: "The scientists discovered that conventional agarose-based columns, routinely used for bench scale operations were not suitable for large scale processing." I would like to point out that 75-liter columns of agarose immunosorbents have been used in production. In addition, new improved crosslinking of Sepharose® (agarose) has made possible flow rates of up to 500 cm per hour.

The article states that beaded cellulose disintegrated at low pH. But it omitted to state that silica disintegrates at pH of 7.5 and above, making cleaning with sodium hydroxide—the most widely accepted method for cleaning and maintaining aseptic conditions in chromatography—impossible.

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