

Many companies and government laboratories, assisted by many universities, took up the challenge. Particularly prominent were Merck, Pfizer, Squibb, and the USDA Northern Regional Research Laboratory in Peoria, Illinois.

The first efforts with fermentation were modest. A large effort went into attempts to chemically synthesize penicillin. This effort involved hundreds of chemists. Consequently, many companies were at first reluctant to commit to the fermentation process, beyond the pilot-plant stage. It was thought that the pilot-plant fermentation system could produce sufficient penicillin to meet the needs of clinical testing, but large-scale production would soon be done by chemical synthesis. At that time, U.S. companies had achieved a great deal of success with chemical synthesis of other drugs, which gave the companies a great deal of control over the drug's production. The chemical synthesis of penicillin proved to be exceedingly difficult. (It was accomplished in the 1950s, and the synthesis route is still not competitive with fermentation.) However, in 1940 fermentation for the production of a pharmaceutical was an unproved approach, and most companies were betting on chemical synthesis to ultimately dominate.

The early clinical successes were so dramatic that in 1943 the War Production Board appointed A. L. Elder to coordinate the activities of producers to greatly increase the supply of penicillin. The fermentation route was chosen. As Elder recalls, "I was ridiculed by some of my closest scientific friends for allowing myself to become associated with what obviously was to be a flop—namely, the commercial production of penicillin by a fermentation process" (from Elder, 1970). The problems facing the fermentation process were indeed very formidable.

The problem was typical of most new fermentation processes: a valuable product made at very low levels. The low rate of production per unit volume would necessitate very large and inefficient reactors, and the low concentration (titer) made product recovery and purification very difficult. In 1939 the final concentration in a typical penicillin fermentation broth was one part per million (ca. 0.001 g/l); gold is more plentiful in sea water. Furthermore, penicillin is a fragile and unstable product, which places significant constraints on the approaches used for recovery and purification.

Life scientists at the Northern Regional Research Laboratory made many major contributions to the penicillin program. One was the development of a corn steep liquor–lactose based medium. This medium increased productivity about tenfold. A worldwide search by the laboratory for better producer strains of *Penicillium* led to the isolation of a *Penicillium chrysogenum* strain. This strain, isolated from a moldy cantaloupe at a Peoria fruit market, proved superior to hundreds of other isolates tested. Its progeny have been used in almost all commercial penicillin fermentations.

The other hurdle was to decide on a manufacturing process. One method involved the growth of the mold on the surface of moist bran. This bran method was discarded because of difficulties in temperature control, sterilization, and equipment size. The surface method involved growth of the mold on top of a quiescent medium. The surface method used a variety of containers, including milk bottles, and the term "bottle plant" indicated such a manufacturing technique. The surface method gave relatively high yields, but had a long growing cycle and was very labor intensive. The first manufacturing plants were bottle plants because the method worked and could be implemented quickly.

However, it was clear that the surface method would not meet the full need for penicillin. If the goal of the War Production Board was met by bottle plants, it was estimated