From Petrochemicals to Pharmaceuticals: Rapid Scale-up of Penicillin by an Academia-Industry Consortium including Shell Development Company during World War II

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Serendipity in Discovery

The accidental discovery by Sir Alexander Fleming in 1928 of the antibiotic action of a contaminant mold *Penicillium notatum* on a Petri disk culture of staphylococcus bacteria is perhaps the most famous example of serendipitous discovery in science.[1] It is also an example of the need for process development beyond initial discovery, as the finding languished for 10 years until Sir Howard Florey and Ernst Chain at Oxford "rediscovered penicillin" after developing a method for isolation and stabilization of very small quantities of impure powder.[2] The three shared the Nobel prize in medicine in 1945, but it was an assistant Norman Heatley who is credited with first isolation (1940) of sufficient quantities to demonstrate clinical effectiveness in treating mice infected with a lethal dose of streptococcus bacteria.[1] A concerted effort at Oxford university (1941) resulted in a "process" that required several months to produce amounts which only allowed testing in 5 – 6 human patients, yielding a drug which failed in initial trials due to low concentrations of actives (0.1%) in the isolated powder.[1] Mold cultures were grown in "every conceivable vessel" including buckets, milk bottles, and bathtubs for production of test quantities.[1]

Penicillin Succeeds via Persistence in Process Development and Scale-up

The U.S. and its allies sought to scale up production and isolation of penicillin in response to needs from the battlefield during World War II. The program became a top-secret project for the U. S. War Production Board.

The scale-up problem was addressed on a number of fronts. Early purification recovered only about one-third the penicillin in active form from dilute fermentation broth. Chemical engineers at Shell Development applied core expertise in solvent extraction to develop a novel countercurrent extraction process using an imposed pH gradient.[4] The new process recovered up to 85% of the penicillin in the fermentation broth, with low losses to deactivation (5%) despite the unstable nature of the penicillin molecule. Development and demonstration via a 200 gallon/day pilot was completed within seven months, in a crash 1943 R&D program.[3-4]

Meanwhile, a team from the Northern Regional Research Laboratory (NRRL) in Peoria, IL identified an improved corn steep liquor medium for fermentation. More productive strains of mold were identified at the USDA, while researchers at the University of Wisconsin used X-ray and UV radiation to genetically modify molds, increasing

production rates more than 1000-fold.[1,4] The consortia of regional and national laboratory, academic, and industrial partners (including Merck, Squibb, Pfizer, Lederle) also addressed the reactor productivity issue. Development of the first large-scale "deep tank" fermentation reactor required innovation in mechanical agitation, antifoaming agents, and use of internal cooling coils, with associated reactor scale-up tests and development work (Merck). Penicillin is inherently unstable in aqueous solution, which required rapid development and commercialization of freeze drying technology (MIT) to improve shelf life.[3,4] War-time production (1943-45) was largely attributed to Pfizer, which scaled up commercial production by a factor of 10^5 in two years.[3,4]

Penicillin scale up and commercialization thus required substantial problem solving and innovation in kinetics of bioconversions, solvent or fermentation media optimization, interfacial phenomena, reactor design including mass and heat transfer, separation, and product stability. In addition to rapid development of an improved extraction process for the penicillin development effort, Shell also spearheaded development and rapid deployment of cumene and catalytic cracking processes to produce high-octane synthetic and refined aviation fuels, and butadiene for synthetic rubber to replace loss of natural rubber supply, [5] all in response to the war-time needs of the US and its allies.

These case histories demonstrate that risk taking and continued problem solving is needed to succeed in technology deployment, beyond the initial idea or project concept phase. The seeds for all of these technologies were laid before the war. Cross-fertilization to apply approaches and best practices from one sub-discipline to another, aided in the rapid innovation and problem solving needed to make "penicillin" a commercial reality.

Reference

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