

# Alejandro Zaffaroni

## (1923–2014)

Bioentrepreneur who revolutionized drug delivery and screening.

Alejandro Zaffaroni spent some 60 years helping to conduct research that led to the birth-control pill, and co-founded nearly a dozen biotechnology start-ups in California's Silicon Valley. He commercialized innovative ways to get drugs into the body. His adhesive skin patches, implanted devices and controlled-release capsules reduced side effects, boosted efficacy and delivered the correct dose of medicine without complicated schedules.

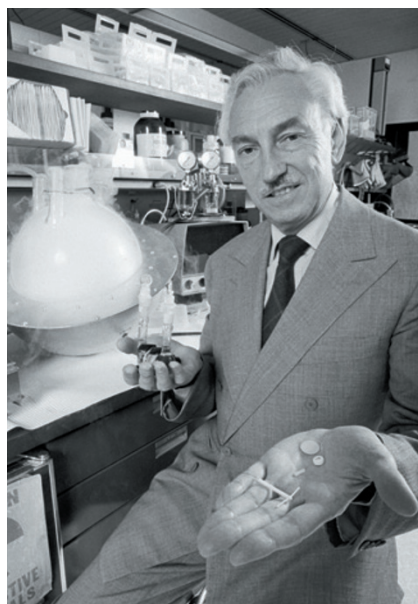
Zaffaroni, who died on 1 March aged 91, was born in Montevideo, Uruguay. He studied for his bachelor's degree there, and in the last days of the Second World War he boarded a military cargo ship to New York, where he gained a PhD in biochemistry at the University of Rochester. He conducted postdoctoral research under a fellowship from the US National Institutes of Health. Zaffaroni adapted a technique known as paper chromatography to purify steroids — the group of chemicals that includes cholesterol and sex hormones. The research led to the first synthesis of the steroid hormone cortisone.

Continuing his work on steroid biosynthesis, Zaffaroni joined Syntex, a small Mexican firm extracting steroid precursors from yams to make therapeutic hormones. He helped to grow Syntex into a pharmaceutical company, and opened a US subsidiary in Palo Alto, California, in 1962. Studying steroid-containing ointments to treat skin disorders, Zaffaroni realized that significant amounts of steroids entered the bloodstream through the skin. He founded the ALZA Corporation in 1968 to control and capitalize on this effect.

Zaffaroni pursued risky businesses and persevered through pitfalls. When a patch for motion sickness was developed at ALZA, the head of marketing protested that it would be difficult to commercialize. But Zaffaroni knew that it would be a springboard; he predicted that the product would gain approval from the US Food and Drug Administration, opening doors to collaborations with deeper-pocketed pharmaceutical partners.

ALZA went on to develop skin patches to help people to quit smoking and to treat pain and high blood pressure, among other conditions. It developed an intrauterine contraceptive; a polymer film that delivered glaucoma drugs without blurring vision; and swallowable capsules that released drugs over many hours. Pharmaceutical giant Johnson & Johnson bought ALZA for US\$12.3 billion in 2001.

The foresight that prompted Zaffaroni to



leave Syntex and start ALZA led to a model for his other companies. First he would articulate a challenge in conversations with industrial and academic scientists. Then he would systematically evaluate existing technologies, competition and potential human impact. When ready to launch a company, he would seek the best advisers and scientific talent to translate basic discoveries into applications.

Zaffaroni did not supervise his scientific teams closely. He empowered people to achieve great things. He paid attention to building design to ensure cross-disciplinary interactions, and he considered colours of furnishings and artwork — all of which he believed would stimulate creativity. More than 40 ALZA employees went on to serve as chief executives of other companies.

The youngest of five children, Zaffaroni credited his mother, a teacher, for his creativity and ability to combine different disciplines. To his father, a banker, he attributed his business acumen and his ability to select, trust and galvanize good people.

The people he tapped would accompany him in pursuits that they had never imagined. In 1970, a phone call from Zaffaroni brought me to Palo Alto from my laboratory at what was then the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts. I knew nothing of the pharmaceutical industry and was not sure what job he was offering. But his passion and commitment inspired me to leave my career in

research for one in pharmaceuticals. Like others, I thought, "If Dr Zaffaroni is leading, I will follow." I did, with not a single regret.

In 1980, Zaffaroni established the DNAX Research Institute of Molecular and Cellular Biology in Palo Alto with three distinguished scientists (two of them Nobel laureates) from Stanford University in California to apply cellular and molecular biology to medicine. This immunology-research paradise fostered the discovery of several signalling proteins used by white blood cells. DNAX was acquired by drug company Schering-Plough in 1982 for \$29 million — reportedly \$1 million for each employee with a PhD.

In his mid-60s, Zaffaroni turned his attention to making drug discovery more efficient, and founded Affymax in 1988. The firm borrowed technology for making computer chips to produce microarrays that rapidly make and test many potential drugs against their protein targets. This was probably the first industrialized biochemical research, and the technique — combinatorial chemistry — is now a component in many major drug-discovery programmes.

The technology behind the chips at Affymax led Zaffaroni to spin out a new company, Affymetrix, in 1991. This was the first company to develop DNA microarrays, which allow rapid analysis of mutations and gene activity. These enabled the rise of genome-wide association studies and are now used widely to detect genetic variants. Subsequent discoveries yielded a string of companies, including Verdia, Avidia, Codexis and Symyx. Mayxgen, for example, worked on 'shuffling' DNA to iteratively improve protein drugs.

The last company that Zaffaroni founded was Alexza in 2000. Its work was inspired by what he identified as the most efficient of all drug-delivery systems: the cigarette. Noting the rapid effect of inhaled nicotine, he sought to apply it to other drugs. Alexza's first inhaled product, for treatment of acute agitation in adults with schizophrenia or bipolar disorder, was approved last year.

As he shaped the industry, Zaffaroni's companies grew, but he remained a famously understated entrepreneur. His impact on biotechnology is immeasurable. ■

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