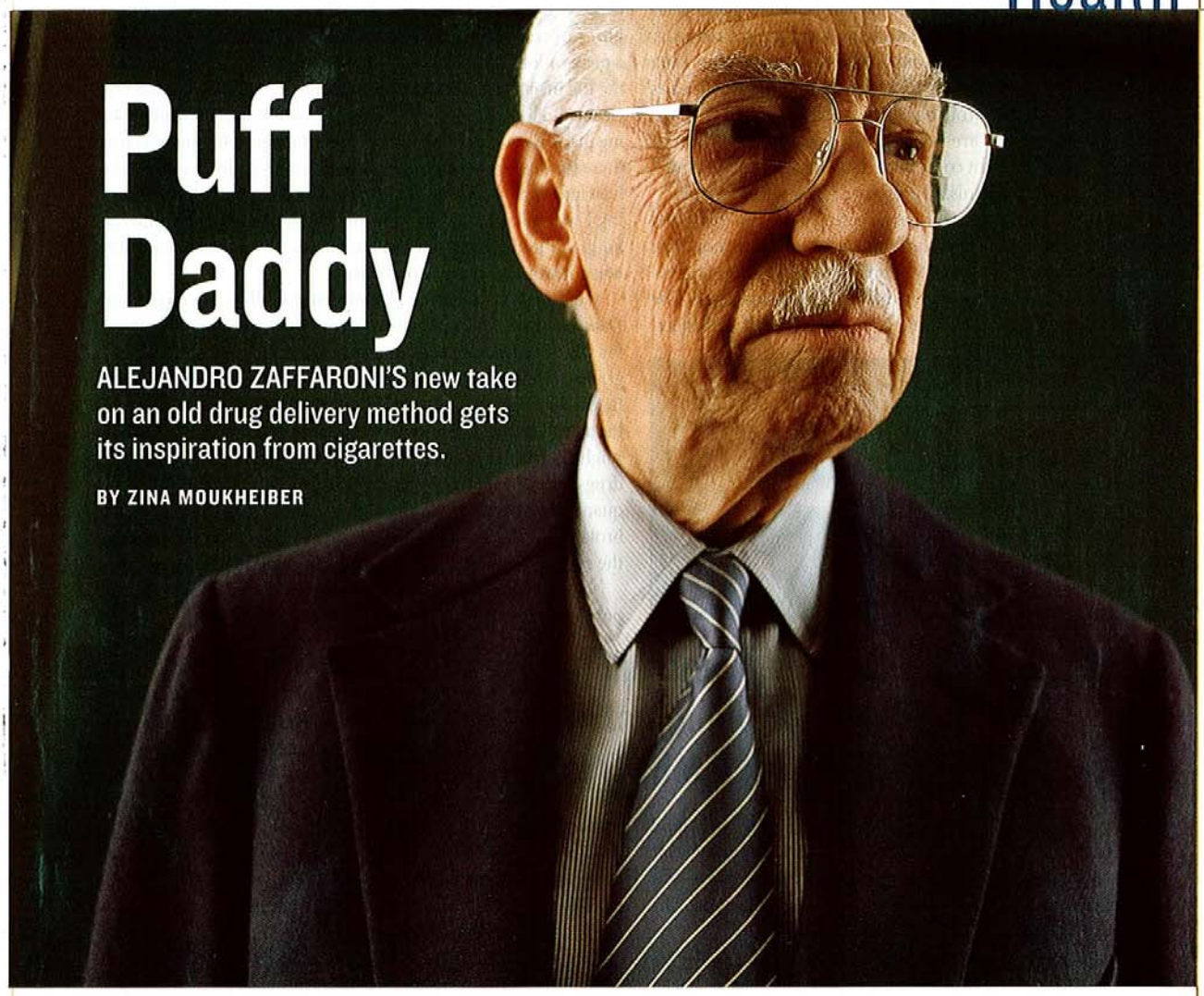
Puff Daddy

ALEJANDRO ZAFFARONI'S new take on an old drug delivery method gets its inspiration from cigarettes.

BY ZINA MOUKHEIBER



THOMAS BROCKING FOR FORBES

ALEJANDRO ZAFFARONI, A DEVOUT NONSMOKER AND one of the world's most successful biotech entrepreneurs, has always been fascinated with the cigarette. Not by its romance or dangers, but by its efficiency. "It is an amazing delivery system; one puff and the nicotine goes to the brain in 15 seconds," says Zaffaroni. "Why not do this for drugs?"

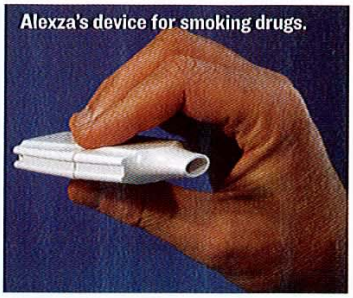
It was a question he asked himself a few years ago, while reading about nicotine addiction. This summer he will move one step closer to an answer. Alexza Molecular Delivery Corp., the latest Zaffaroni startup (it's his fourteenth), will begin human trials of a migraine drug to be inhaled through a device that looks like a flat whistle. Add heat and—poof!—the drug vaporizes into an odorless microparticular mist that passes quickly through the lungs into the bloodstream in order to, it is hoped, deliver instant relief.

The idea of inhaled medicine goes back to German experiments with insulin in 1925 and continues with Inhale Therapeutic Systems, which went public in 1994 (recently renamed Nektar Therapeutics). The small stampede of companies working this mine includes Aerogen and Aradigm, which are exploring aerosolizing injectable liquid drugs such as insulin and certain painkillers; and Alkermes and Nektar, which are working on drug powders to be inhaled.

What sets Alexza apart is its counterintuitive scheme to apply heat to turn pills or liquids into a fast-acting smoke. Chemists consider it heresy to heat up a drug, because heating increases the rate of its degradation, potentially rendering it impotent; it also introduces the risk that carcinogenic or otherwise toxic by-products could lodge in the lining of the throat and lungs. "We don't want to go there," says John S. Patton, Nektar's founder and chief scientific officer.

Leave it to Zaffaroni to try. He has astonished the scientific community before. Now 81, the Uruguyan-born biochemist has fathered such groundbreaking biotechs as Alza (of nicotine-patch fame and now part of Johnson & Johnson), DNA-chip king Affymetrix and gene-breeder Maxygen. Along the way he has amassed a fortune that probably exceeds $300 million. "He has a vision of where things are going in science, and he's smart at putting together the right combination of business and science," says noted Stanford chemistry professor Harden McConnell.

Alexza, in Palo Alto, Calif., is targeting ailments that need rapid relief, such as pain, insomnia and erectile dysfunction. The four-year-old startup has spent $30 million so far developing a vaporization method and an experimental inhalation device. The migraine drug, if approved, could compete very well against existing treatments such as Merck's Maxalt and GlaxoSmithKline's Imitrex. In pill form, these medications typically take two hours to kick in and a half hour via injection. Zaffaroni wants to provide relief in 60 seconds. In animal trials Alexza conducted in 2002, an inhalable version of Maxalt constricted blood vessels in dogs within a minute, compared with 15 minutes by injection. For its human trials due to begin this summer Alexza has chosen a generic migraine drug that doesn't have the cardiovascular risks associated with Maxalt or Imitrex.


Alexza's device for smoking drugs.

It takes 2 HOURS for a migraine pill to kick in, 30 MINUTES via injection, and potentially LESS THAN A MINUTE via inhalation.

Zaffaroni admits he had no idea before he started Alexza whether heating drugs would work or not. In 2000 he began bouncing the idea off his vast network of eminent-scientist friends, including Stanford's Harden McConnell. "I thought it was crazy," says McConnell.

Zaffaroni was determined to give it a try, putting up so far $9.2 million of his own money. McConnell suggested he hire one of his doctoral students, Joshua Rabinowitz, a 32-year-old physician with a talent for solving difficult chemistry problems.

As a first stab Rabinowitz picked the antihistamine Benadryl and set about figuring out how to turn this powder into pure, medicinally potent smoke. He tried heating it up at different temperatures on a piece of metal foil and succeeded only in turning the drug into piles of stinky tar. He then sparked a small fire when he tried to heat it up quickly before it could disintegrate. After six months Rabinowitz was frustrated, but he remembered Zaffaroni's words: "We're going to fail, and fail again, until we succeed."

One Saturday evening in early 2001 Rabinowitz mixed the drug with a solvent, transforming the mound of powder into a film 1 micron thick (that's a thousandth of a millimeter) coating a piece of foil. Then he switched on an electric current to heat up the foil instantly to 600 degrees Fahrenheit. In a flash the foil was clean, and a clear mist hung in the air without any burning taking place. By augmenting the drug's surface area, Rabinowitz had increased its exposure to air, allowing it to quickly escape the heat and vaporize without burning. The drug particles, measuring 1 to 3 microns across, were just the right size to pass into the lungs without getting stuck in the throat. "It was an amazing day when it worked," says Rabinowitz.

He leafed through the pharmaceutical bible, the *Physicians' Desk Reference*, and selected 300 drugs to test, culling only those for which fast-onset was a necessity, including medicine for migraines (Imitrex), allergies (Claritin) and depression (Prozac). Before blowing them up Rabinowitz first stripped the drugs of the additives that give pills structure, taste and shelf life but which might harm the lungs if inhaled. As it turned out, 160 of the drugs came through the vaporization process with sufficient dose quantity and purity and the right particle size. The rest either broke down because of the heat or lost their strength because the surface of the foil couldn't hold enough of a dosage.

Now Alexza needed a device that could replicate the lab vaporization. A chemist formerly at Alza who knew of Zaffaroni's project put him in touch with a firm called Molecular Delivery in nearby Pleasanton. Its founder, Stephen Schneider, had developed a device the size of a small shoebox to heat up pure tetrahydrocannabinol, or THC, the active ingredient in marijuana. It was intended for medicinal use as a nausea reliever or appetite stimulant for those unwilling to smoke plant material. The THC project was deprioritized when, in late 2001, Alexza merged with Molecular Delivery.

Though biotech was suffering one of its worst downturns in 2002, venture funds were more than willing to throw money at the next Zaffaroni venture. Alexza raised $45 million from investors including Versant Ventures and Frazier Healthcare Ventures and in 2003 hired Thomas King to be chief executive.

King puts the potential market size for heated-up, smokable drugs at $15 billion a year. Besides developing the migraine drug, he aims to find larger pharma firms eager to vaporize their patented compounds. Alexza is still fiddling with the shape of its device, to be powered by batteries and other means. King says the device should cost no more than $2 to make.

Plenty of questions remain. Alexza's human trials may fail to replicate the success of the earlier animal study. And the company may struggle to overcome fears of smoking harmful chemicals. The device can't be used to deliver all drugs; Rabinowitz had to rule out almost half of the first 300 he tested because they came out too weak or decomposed. But there are enough worthy candidates for Zaffaroni to make a business out of it. **F**