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Race to Deliver Nicotine's Punch, With Less Risk

By BARRY MEIER DEC. 24, 2014

NEUCHÂTEL, Switzerland — Deep inside a modernist research center on the edge of a mountain lake here, automated smoking machines sample the future of nicotine.

Scientists at Philip Morris International are experimenting with ways to deliver nicotine — Big Tobacco's addictive lifeblood — that are less hazardous than cigarettes but still pack the drug's punch and smoking's other pleasures. The smoking carousels, stuffed with burning cigarettes or glowing electronic devices, are among dozens of high-tech instruments being used.

The rush by Philip Morris and other tobacco companies to develop new ways of selling nicotine is occurring as more consumers are trying e-cigarettes, devices that heat a nicotine-containing fluid to create a vapor that users inhale.

While only a small percentage of smokers have switched to the devices — experts say early e-cigarettes did not deliver enough nicotine to satisfy a smoker's cravings — major tobacco companies are deploying their financial resources and knowledge in a bid to dominate a potentially huge market for cigarette alternatives.

In recent months, several tobacco companies have ramped up nicotine levels in their e-cigarette brands, while others, like Philip Morris International, are starting to introduce slender, tubelike devices that will give users as much nicotine as the real thing by heating, not burning, tobacco. A few months ago, another cigarette maker, British American Tobacco, won approval from British drug regulators to market an inhalable nicotine spray.

“Our efforts are guided by two objectives,” said Dr. Patrick Picavet, the director of clinical assessment for Philip Morris International. “To develop a range of products that can be scientifically substantiated to reduce risks and that are acceptable substitutes for smokers who can't or aren't willing to quit.”

The entry of Big Tobacco into the e-cigarette business has set off alarm bells. Public health advocates, pointing to the industry's documented history of deception about the risks of smoking, question whether cigarette makers want to develop devices to help smokers quit or find new ways to sell nicotine to young people who have never smoked.

“Developing products that satisfy a smoker's addiction will increase the risk that they will be highly addictive to nonsmokers,” said Matthew L. Myers, the president of the Campaign for Tobacco-Free Kids, an advocacy group in Washington, D.C.

These are not Big Tobacco's first efforts at mitigating tobacco's considerable health risks. Beginning in 1980s, Philip Morris and R.J. Reynolds Tobacco made stabs at introducing "safer" cigarettes designed to produce fewer carcinogens. But those products never caught on, and the tobacco industry was seemingly caught flat-footed when upstart companies started selling e-cigarettes, mostly made in China.

The new e-cigarette industry is still tiny, with global sales this year of \$5 billion compared with more than \$800 billion for tobacco products, according to estimates by Wells Fargo Securities. Still, cigarette companies have hedged their bets by acquiring e-cigarette makers or stepping up their own research efforts.

Along with replicating important sensory aspects of smoking, like taste, the biggest hurdle for the new devices, experts say, is delivering nicotine with the efficiency of a cigarette.

Within seconds of taking a drag, a smoker feels the nicotine's soothing effects because compounds that are produced when tobacco burns are perfectly sized to carry nicotine deep into the lungs allowing the drug to quickly reach the brain. Those same compounds, which are collectively known as tars, also cause cancer and other diseases.

By comparison, the type of vapor generated by e-cigarettes, experts say, is a less efficient carrier of nicotine than smoke. "There is more deposition in the mouth," with vapor, said Jeffrey S. Gentry, the chief scientific officer of R.J. Reynolds, a division of Reynolds American.

A study published last year showed that one e-cigarette brand, Njoy, produced levels of nicotine in a user's blood significantly lower than the amount produced by a cigarette like a Marlboro. As a result, e-cigarette users have frequently turned to larger devices known as vape pens that have bigger batteries that can produce more heat. But more heat to increase nicotine levels may also result in higher levels of toxins and carcinogens, experts say.

Tobacco companies have rushed to increase nicotine levels in their vapor devices.

About a year after Altria, which sells Marlboro, introduced the MarkTen e-cigarette brand, it increased the concentration of nicotine by about 65 percent. Blu eCigs, which is owned by Lorillard, has raised the nicotine output of its latest device by 50 percent through a variety of changes such as increasing its nicotine concentration and incorporating a larger battery to produce higher heat. Njoy, which only makes e-cigarettes, is using a pharmaceutical ingredient in a new version of its device that is supposed to increase vapor absorption in the lung and elevate nicotine delivery to about 70 percent of a cigarette, according to company data.

At Philip Morris International's research center here, where about 300 scientists work, the nicotine chase is headed in several directions. The company says it has spent about \$2 billion since 2008 researching cigarette alternatives with much of that effort focused on devices that use tobacco, but heat it, rather than burn it. Though the "safer" cigarettes that Philip Morris and R.J. Reynolds introduced decades ago were also heat-not-burn devices — and flopped with smokers — the new products, Philip Morris officials say, are more technologically advanced.

Last month, Philip Morris International began test marketing the first of these new devices, called iQOS, in Japan. The device has three components; a pocket-size charger, a heating element and a short stick containing tobacco and other ingredients. The tobacco sticks are heated to a point below combustion, producing an aerosol-like vapor that has about same amount of nicotine as a cigarette.

The company plans to introduce another heat-not-burn device in 2016; the heating element of that device can be lit with a match, like a cigarette, but the tobacco stick does not burn.

Some public health researchers are critical of heat-not-burn products, saying that even heating tobacco produces carcinogens. Philip Morris International officials, like Dr. Picavet, counter that the safest nicotine delivery system has little value unless smokers want to use it. Heat-not-burn products, they argue, give consumers what they want with what appear to be lower health risks.

Company scientists are trying to quantify those risks through experiments that use a traditional cigarette as the toxic yardstick. The smoking machines in a laboratory here are used to draw on cigarettes and heat-not-burn devices and then send the resulting smoke or vapor through a series of tubes to a machine in an adjoining room. Cells resembling those found in the human lung are grown in the machine. After the smoke or vapor hits the cells, they are cultured and taken to other laboratories in the building where researchers examine them for biological or genetic changes.

Company officials report that the test results show far less cell damage with heat-not-burn-devices than with cigarette smoke — though they emphasize that laboratory tests do not translate into less disease in humans. To try to get at that risk, Philip Morris is also running clinical studies to measure the level of toxic compounds in the blood and urine of people who use the new devices.

The first study, conducted in 2013 in Poland, showed that levels of some of the most toxic contaminants in tobacco smoke were substantially lower in users of the iQOS heat-not-burn device than in smokers, though they were somewhat higher than in those who abstained. That study, however, lasted only five days. Scientists have not yet published results from a second study, which involved 160 people and lasted three months, company officials said. A third study, which is

expected to last six to 12 months, has yet to begin, they said.

Assuming positive results from the human studies, Philip Morris International says it expects to eventually apply to the Food and Drug Administration for agency support for a claim that iQOS poses a “modified risk” to smokers when compared with a cigarette. If the device is approved, Altria will market it in the United States. (Philip Morris International was once part of Altria and the companies have an agreement that allows them to sell each other’s products.)

R.J. Reynolds is poised to release Revo, a rebranded version of its heat-not-burn device originally called Eclipse and first marketed in 1996. Last year, a Vermont state judge ordered the cigarette maker to pay \$8.3 million in fines after a finding that the company had misleadingly claimed in marketing that the device could lower a smoker’s risk of contracting cancer, emphysema and other diseases. Those claims were made before the F.D.A. gained regulatory oversight of tobacco-related health claims. A spokesman for R.J. Reynolds, David Howard, said it plans to initially claim only that Revo “offers less cigarette smoke smell and no ashes” when compared with a cigarette. He declined to say whether the company plans to eventually seek a modified health risk claim with the F.D.A. for Revo.

Despite the proliferation of cigarette alternatives, industry critics fear that Big Tobacco, given its mastery of nicotine, will manipulate drug levels in new devices so that smokers end up using them, not as quitting aids, but as a way to get nicotine where smoking is prohibited. Public health experts also fear the devices will create a new generation of nicotine addicts.

Cigarette makers dismiss such suggestions. But the newest nicotine delivery devices hitting the market suggest the shape of things to come. Several years ago, Philip Morris International bought the rights to a novel form of inhalable nicotine. The idea was developed by outside researchers including Dr. Jed Rose of Duke University, the an inventor of the nicotine skin patch.

In the past, smoking replacement products like gums and patches have generally failed because they released nicotine too slowly or in amounts too low to satisfy smokers. And on one point, both cigarette industry executives and their critics appear to agree. If the newest alternative products are to succeed from both a financial and a public health standpoint, they will have to deliver nicotine at levels comparable to a cigarette.

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