#SPECIAL REPORTS

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Special Report: Scientists describe problems in Philip Morris e-cigarette experiments

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A man smokes iQOS at a restaurant in Tokyo, Japan November 2, 2017. Picture taken November 2, 2017. REUTERS/Kim Kyung-Hoon

TOKYO/NEUCHATEL, Switzerland (Reuters) - The U.S. Food and Drug Administration is weighing whether to approve a potentially path-breaking smoking device by Philip Morris International Inc (PM.N). With a decision expected next year, former employees and contractors have described to Reuters a number of irregularities involving clinical trials that underpin the tobacco giant's application to the agency.

By heating tobacco instead of burning it, the company says the device, known as iQOS, avoids subjecting smokers to the same levels of carcinogens and other toxic substances found in a regular cigarette. The company has spent more than $3 billion developing new smoking platforms like iQOS. As part of that initiative, Philip Morris has published extensive scientific findings, based in part on clinical studies.

Tamara Koval, who worked at the company from 2012 to 2014 and helped coordinate clinical trials for the device, questioned the quality of some of the researchers and sites contracted to carry out those experiments. Koval was a co-author of the company's protocol used to run the studies globally. When she highlighted an irregularity in one of the studies, Koval said, Philip Morris excluded her from meetings.

Reuters also found irregularities during interviews with some of the principal investigators contracted to conduct the trials for the company. One principal investigator said he knew nothing about tobacco. Philip Morris had to jettison the experiment that investigator performed after it emerged he hadn't followed a basic procedure for obtaining informed consent from participants during clinical trials.

A second investigator submitted urine samples that exceeded what a human being is capable of, according to two former company employees, and then initially refused to acknowledge there was a problem. A third said he doesn't hold such company-sponsored clinical trials in high regard, describing them as "dirty" because their purpose is more commercial than scientific.

After reviewing Reuters' findings, Philip Morris said in a statement that "all studies were conducted by suitably qualified and trained Principal Investigators." The company said it understands that "FDA inspectors have already audited some facilities" involved in the trials. Philip Morris also said it had taken steps to address "any reported irregularity in our studies."

“Our policies encourage speaking up about suspected violations of law or our policies and we do not tolerate retaliation against those who speak up,” the company said.

In addition to former Philip Morris employees involved with the iQOS program, Reuters interviewed six of the 11 principal investigators who were responsible for five of eight clinical trials the company submitted to the FDA. Reuters also reviewed hundreds of pages of publicly available Philip Morris study reports and FDA filings.

That reporting identified shortcomings in the training and professionalism of some of the lead investigators, as well as their knowledge of the study results.

A group of tobacco research and policy experts reviewed detailed summaries of Reuters’ reporting and Philip Morris’ response. The experts, including a former head of the FDA and two former scientific advisers for the agency, said those findings raise concerns about Philip Morris’ clinical trial program.

“Taken as a whole, it’s clear they do not have the sophistication to carry out adequate and well-controlled clinical trials,” said David Kessler, the FDA’s commissioner from 1990 to 1997, referring to the company. “I am not inferring any malicious intent here, just that they lack sophistication, because this is not their bread and butter.”

If the FDA has already audited some of the trial sites used by Philip Morris, the agency “should carefully review its audits and possibly expand them,” said Kessler, a former dean of the medical school at Yale University.

‘THE FDA SHOULD AUDIT’

Tom Eissenberg, who served on the FDA’s tobacco products scientific advisory committee until earlier this year, said: “The FDA should audit.”

Reuters did not find any evidence that the outcome of the experiments presented by the company to the FDA was manipulated or falsified.

The new insights into the company's clinical trial program for iQOS come at a crucial time for Philip Morris. The world's largest publicly traded tobacco company by market value and maker of Marlboro cigarettes has applied to the U.S. FDA to be able to sell iQOS in America, and also for permission to market it as a modified-risk tobacco product. That designation could mean that Philip Morris is allowed to market iQOS as presenting less harm or risk of disease to users than traditional tobacco.

For now, the FDA is evaluating the company's studies. Reuters outlined its findings about the iQOS trials to the agency. The FDA said it cannot comment on a pending application.

Philip Morris says the device, which heats small tobacco inserts, is meant for smokers who would not otherwise quit. Its chief executive officer, Andre Calantzopoulos, has told investors and media alike that he intends to one day replace cigarettes with products like iQOS. So far, iQOS makes up a fraction of the company's $75 billion revenues and Philip Morris continues to market conventional cigarettes across the globe.

Internal Philip Morris documents reviewed by Reuters show the significance of iQOS goes beyond its profit potential. The device is now sold in more than two dozen nations after it was first launched in Japan and Italy during late 2014.

The company has a 10-year plan for what it calls "normalization" of the tobacco industry, according to a 2014 strategy document. The industry has been shunned over the past two decades for producing and marketing products that kill people and previously lying about it. Under a section on "strategies and actions" to achieve that goal, the document lists, among other things, new smoking devices such as iQOS and the scientific research involved in developing them.

Told about that document, Philip Morris said: "The suggestion that the purpose of our development of IQOS and our scientific research program is to 'normalize' the tobacco industry is false."

That previously undisclosed document and others can be found in a searchable repository published by Reuters, The Philip Morris Files. (reut.rs/2sT51xF)

'I JUST DON'T READ THEM'

As part of its submission to the U.S. FDA, the company said the results of its research showed the device significantly reduced the level of certain harmful substances that users were exposed to compared with cigarettes, and satisfied their nicotine cravings. “In fact the level of reduction is so considerable, it approaches 95% of the levels measured in smokers who quit altogether,” the company said in a statement to Reuters.

Taken along with the company’s laboratory studies, Philip Morris said, the research program “in its entirety demonstrates that IQOS is likely to reduce the risk of smoking related diseases.”

Philip Morris is responsible for the majority of the science that has been published about iQOS. “Those who criticize us should probably look at our science,” said Tommaso Di Giovanni, a company spokesman, during a tour of Philip Morris’ research and development headquarters in March.

The eight clinical experiments that Philip Morris submitted to the FDA were conducted between 2013 and 2015. For one study, scientists in Texas and Florida did not respond to messages left by Reuters. Other scientists, in Belfast and Tokyo, declined to talk. Half of the eight studies were done in Japan.

FDA guidelines for conducting clinical studies say a trial should adhere to standards such as Good Clinical Practice. That best-practices document says investigators “should be qualified by training and experience and should have adequate resources” to properly conduct a trial.

Masayuki Sugimoto, the principal investigator who oversaw testing at one facility used by Philip Morris to conduct a trial, said his Tokyo clinic is “heavily in the red.”

Sugimoto said he generally has little confidence that all the participants in experiments like the one he ran for Philip Morris on nicotine tell the truth about their smoking history – that is, whether they smoke.

Speaking about the final study report from the Philip Morris trial, Sugimoto said in an interview that he generally doesn’t have time to read such things in detail. He said he probably signed a document indicating he had received the final report. Sugimoto gestured with his thumb and forefinger to indicate a thick document: “I just don’t read them.”

Philip Morris said that it "did not receive any such comments or statements from the PI," or principal investigator. Sugimoto's study, it said, was completed "without any issues." The company said the study data was reviewed and discussed with the investigator throughout the trial.

The Japanese company hired to monitor studies in the country, CMIC Holdings Co Ltd (2309.T), said in a statement that researchers confirmed that trial participants were smokers by using urine tests.

Asked about the tests, Sugimoto said he thought they would prevent non-smokers from joining the trial but added, "I don't know whether they were done that rigorously."

Told of Sugimoto's doubts about the honesty of study participants, Eissenberg, who served on the FDA's tobacco products scientific advisory committee from 2011 to 2017, said "it raises a great deal of concern."

A principal investigator "is required to make sure that the participants meet the inclusion-exclusion criteria that are in the protocol," said Eissenberg. He was referring to the fact that clinical trial subjects' backgrounds – such as whether they are smokers – should meet the parameters of the experiment for the data to be valid. "And a PI should have confidence in that," he said.

DATA DISCARDED

At another laboratory in Japan, issues with how the study was carried out were so acute that data from 56 participants was thrown out, raising questions about the competence of the principal investigator. Philip Morris halted the study at that location.

In the company's study documentation released by the FDA, Philip Morris recorded the reason for discarding the data as non-compliance with good clinical practices, specifically "failure of the site to meet sample collection procedures and data recording procedures."

Slideshow (8 Images)

Kishor Lad, who was Philip Morris' data manager on the study, said the site crossed a line of what's allowed during such trials: It collected samples before getting informed consent forms signed by the volunteers. "Completely a no-no in the GCP world," Lad said, using the acronym for good clinical practice.

Philip Morris confirmed to Reuters that "informed consent was not obtained prior to execution of a study procedure" – specifically, the collection of urine samples. The problem was identified by CMIC, the contract research group, during a routine monitoring visit, Philip Morris said. A subsequent round of audits, it added, "led to prompt discontinuation of the study at the Seishukai Clinic." The incident, the company said, was properly logged in the study report and the submission to the FDA.

"It suggests the investigator had no idea, did not understand or just didn't care what his responsibilities were in conducting the study," said Greg Koski, a former director of the U.S. federal Office for Human Research Protections, which advocates for research subjects. "This is such a flagrant violation, that investigator shouldn't be doing clinical studies."

Mamoru Oki was the principal investigator at the time at the facility, the Seishukai Clinic in Tokyo. Reached by phone, Oki said: “My specialty is urology and I don’t know anything about tobacco, so I cannot talk.”

Told of that remark, Philip Morris said: “Dr. Oki was qualified and trained specifically on the product.”

Dorothy Hatsukami, a member of the FDA’s tobacco products scientific advisory committee from 2010 to 2013, said a principal investigator’s professed lack of knowledge about tobacco is not ideal.

“For any tobacco-related clinical trial, an investigator with a background in tobacco product research would have better qualifications to evaluate the study results than a novice,” she said.

The study continued at a parallel site, the Tokyo Heart Center.

During an interview at the center, principal investigator Masahiro Endo said repeatedly that he had no idea what the results were from his study.

“We did medically safe and accurate blood samples, but were not told the results. So even if we are asked questions, we won’t be able to answer,” he said. “We were paid, it ended there.”

But in a statement signed last year and submitted by Philip Morris to the FDA, Endo said he had read the clinical study report from the company and confirmed “that to the best of my knowledge it accurately describes the conduct and results of the study.” Principal investigators in all of the Philip Morris clinical trials signed the same statement.

A day after speaking with Reuters, Endo sent an email clarifying that after checking his records he saw that he’d signed a receipt saying he received a report on the results and acknowledging that he’d be listed as the principal investigator. He had spoken during the interview “with a fuzzy memory,” Endo said.

‘LESSER OF TWO EVILS’

Clinical trial experts interviewed by Reuters said it's not uncommon for principal investigators to be unaware of test results sent to a third party specialty laboratory for analysis. But they also emphasized that if companies want better science, they need the investigators to be more involved with all aspects of a study.

"It seems like the investigator here is in the role of a technician, not as a principal investigator," said Kessler, the former FDA commissioner.

Kessler said it's hard to understand how such investigators could have signed off on the clinical study report "when they clearly were not versed in the study results."

Other principal investigators described their work differently.

Fumimasa Nobuoka, a principal investigator on one of the trials in Japan, said he read the Philip Morris study report: “I thought it was well done, well written.”

James Borders, who was the principal investigator for a study held in Lexington, Kentucky, said the experiments in his trial were done ethically and followed sound scientific practice.

Borders, who became chief medical officer at the Baptist Health Lexington hospital, said such studies help consumers make an informed decision. His decision to be involved with the study, he said, hinged on the proposition that a device like iQOS could be the “lesser of two evils.”

Philip Morris said that while it sponsored the clinical trials, the experiments were “performed by reputable research facilities” and monitored by contract research organizations – companies used to oversee such studies. It hired U.S.-based Covance Inc to serve as its global contract research organization, according to an internal Philip Morris 2013 assessment plan. Covance, a unit of Laboratory Corporation of America Holdings (LH.N), declined to comment.

CMIC, the company hired to monitor the Japan studies, said in a statement: “All the clinical trials you referred to were conducted in accordance with GCP guidelines” – good clinical practices – “and we believe that the results of the trials are scientifically trustworthy.”

As part of her job coordinating between Philip Morris and those contracted to run its clinical trials, Koval, the former company scientist, conducted medical safety training across the world for principal investigators and others involved with the iQOS studies.

During one study training session in Tokyo, Koval said, she realized some of the researchers could not speak English well and she was unable to communicate with them. Koval said she does not speak Japanese and there was no interpreter present.

“I was like, Jesus, what are we doing here?” she said. At dinner later, Koval said, she saw two of the men, and they were unable to describe in English what their jobs were.

When asked about Koval’s session, Philip Morris said it was a meeting with its contract research organization and others. It added that “all PIs and team members with active roles in the study were fluent in English.”

But Sugimoto, one of the Japanese principal investigators, told Reuters in an interview, “I can’t speak English.”

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And Endo, another of the lead researchers, said that when Philip Morris executives visited his site someone was present who helped translate “questions like whether to cut the crusts off bread” when giving food to study subjects.

CMIC said, “All the principal investigators received adequate training in Japanese before the trial began.”

URINE SAMPLES

In Poland, some urine samples collected as part of one Philip Morris clinical study exceeded the limits of what a human being is capable of producing in a single day, according to Koval and Lad, the former clinical data manager.

Lad, who worked at Philip Morris from 2012 to 2015, said he didn’t think anything “malicious” had happened. Maybe urine samples were swapped or there was a mistake with the containers used to collect the urine, he said.

But when the principal investigator for the Polish site was asked about the results, she would not admit there was a problem, Lad and Koval said. Instead, they said, the scientist explained that the test subjects were large Polish men.

Philip Morris said that “a few participants” in an early stage of the trial “produced unusually large volumes of urine.” Because medical tests showed no problems with the subjects, the company said, the investigator did not initially consider the samples to be “adverse events.”

After discussion with the medical monitors of the study as well as Philip Morris, the investigator "ultimately decided to mark these incidences as adverse events," the company said. An investigation at the site confirmed that researchers had followed study protocol and good clinical practices, the company said.

The principal investigator running the study in Poland for Philip Morris, Katarzyna Jarus-Dziedzic, declined to discuss what happened with the urine case at her site, citing confidentiality.

Koval said that after she raised concerns about the Polish study with Philip Morris executives in Switzerland she was excluded from meetings.

Philip Morris said in a statement that Koval was "part of the team" that followed up on the urine samples. In fact, the company said, she was "an active member" of the group that finalized the data set from the studies for further analysis.

Koval confirmed that she was part of the team and involved with the data set. But she stood by her account that she was shut out of conversations and meetings about the urine samples.

In 2014, Philip Morris terminated her contract, Koval said. She said she returned to the pharmaceutical industry a few months later and now works for Swiss drugs giant Novartis AG (NOVN.S).

After leaving Philip Morris, Koval was given a certificate of service that said, "Tamara drove clinical program development activities." It said she had demonstrated "professionalism" and "unwavering commitment" in her work.

Additional reporting by Ari Rabinovitch in Jerusalem, Joe Brock in Johannesburg, Anna Koper in Warsaw, Amanda Ferguson in Belfast, Hyunjoo Jin in Seoul and Kate Kelland in London; Editing by Peter Hirschberg

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