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HEADLINE: FIRM DID NOT ACT ON AIDS VIRUS WARNING A SCIENTIST SAID ARMOUR'S METHOD DID NOT KILL ALL THE VIRUS IN ITS PLASMA. STRICTER STEPS WAITED 2 YEARS.

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BODY:
In the fall of 1985, **Armour** Pharmaceutical Co. had a **crucial** decision to make. A researcher had told the company privately that the heating process Armour was using to cleanse its blood-clotting medicines was not killing all the AIDS virus.

At a meeting that October, Armour executives discussed several options:

* Immediately spending millions of dollars to improve the heating process.

* Matching their competitors' safety standard, even though the executives believed the other companies' processes weren't 100 percent effective, either.

* Reporting the research findings to the U.S. Food and Drug Administration, and seeking government guidance.

* Keeping quiet for the time being, while continuing to sell the product.

They settled on Option Four.

Not until 1987 did Armour begin using a more rigorous heating process. And Food and Drug Administration officials say there is no indication that Armour told the agency about the 1985 research findings of Dr. Alfred M. Prince.

Armour, a subsidiary of Rhone-Poulenc Rorer Inc. of Collegeville, said in a statement Saturday that it did not make public the Prince findings because "his studies showed inconsistent results."

"Confronted with the facts at the time," the company told The Inquirer, "Armour had no scientific reason to believe that there was anything wrong with its heat-treatment methods, and every good reason to suspect that the Prince results were flawed." (The Armour statement and Prince's are on page A9.)

The company statement noted that Prince said earlier this month that his preliminary Armour findings had been "understandably greeted with initial skepticism" and that Prince did not consider Armour negligent in continuing to sell the blood-clotting medicine.

Prince's Oct. 6 statement also said that he had conducted additional research that confirmed his findings about Armour's blood product. His final report was given to the company in August 1985, two months

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before the Armour executives' r ing.

The October 1985 discussion of problems posed by the Prince research is outlined in company minutes of the meeting, a copy of which was obtained by The Inquirer. The minutes summarize the executives' reasoning:

Mike Rodell, then Armour's vice president for scientific affairs, "noted that it would be unwise to go to the FDA without completing our own work first. Mike pointed out that FDA has not conducted viral inactivation studies and the FDA has not required data on current market products so long as the manufacturer affirms the products are heat-treated."

In other words, once the product was licensed, the FDA did not require updates on the effectiveness of the heating process.

The minutes describe the executives' overriding focus as concern about losing ground to the competition.

A marketing official, Anita Bessler, "stressed the absolute need to duplicate the data of our competitors because we are in danger of losing a large part of our market share to our competitors," the minutes state.

Or, as Rodell is quoted in the minutes: "The issue is not one of regulation, but rather marketing."

Even after Armour switched to a higher temperature and longer heating time in early 1987, it continued to sell what remained of the less-heated medicine, mostly in Canada.

By then, several hemophiliacs in Britain, Canada, the United States and elsewhere had contracted the AIDS virus from the Armour product, made from pooled human plasma and known by the brand name Factorate.

Heat-treating, it had been hoped, would mean that no more hemophiliacs would become infected by the medicines they took to prevent uncontrolled bleeding. In the early 1980s, before the products were heated, thousands of hemophiliacs contracted the AIDS virus from the plasma-based drugs.

The Armour minutes, combined with interviews and documents that are sealed by U.S. courts but recently were made public by investigators for the Canadian government, portray a company that fought to keep its share of the lucrative clotting-drug market while discounting, and sometimes concealing, information about Factorate's safety.

As The Inquirer reported on Oct. 5, Prince, head of the virology laboratory at the New York Blood Center, told the company in August 1985 that the Armour heating method resulted in "little or no inactivation" of the AIDS virus. Armour invoked a confidentiality clause in Prince's contract that forbade him to publish his final report.

Armour termed the Inquirer article "inaccurate and misleading," saying on Oct. 6 that it had not wanted Prince's final report published "in isolation," given "the confusion surrounding the issue."

In the minutes of the Armour meeting, Prince's data are referred to as "preliminary results." It would be "unwise" to tell the FDA about Prince's findings, the minutes say, until scientists at Armour's research affiliate, Meloy Laboratories Inc., completed their studies.

Two days after the executives' 1985 meeting, the chief of the Meloy researchers wrote in a preliminary report that they, too, had found "infectious doses" of AIDS virus in Factorate after heat-treating.

In March 1986 - seven months after Prince submitted his report to Armour and five months after Meloy's preliminary findings - company officials in England claimed that live AIDS virus "has never been isolated from heat- treated Factorate."

The Armour minutes describe one official, Alain Schreiber, as urging that the company gear up production immediately for a higher temperature and longer heating period, to make the product safer. Other executives were said to feel that it would take too long for the company to change its process, and would cost millions of dollars while "we're losing markets everywhere each month that there's a delay."

Plans were already set for 1986 production; contract bids had to be submitted in Canada and France; and, according to the minutes, "we're going to lose them, as well as those in the U.S. because we lack the viral

inactivation data of our competi" "

Switching to a higher-heat process would require FDA approval and cost in the range of $6-20 million," and "we have at least $6 million in sales at risk in 1986," said the minutes, drafted by Joseph G. Perpich, a doctor and lawyer who was vice president for planning and development.

The minutes also recount a discussion on whether Armour should use standards less stringent than those in the Prince research. Prince's standard was that there should be no virus present after heat-treating. Some competitors allowed for minute levels of virus, which they believed could not transmit the disease.

Referring to Bessler, the marketing executive, the minutes state: "In her view, if we could establish that our heat treatment meets the claims of our competitors, at least we could compete on the market while we continue work to determine if, indeed, there is detectable virus at the lower cutoff."

The minutes continue: "We now know that the standard used by our competitors is not sensitive enough and their product may have detectable virus." If Armour used the competition's statistical method, "then we could inform the FDA that we met current industrial standards, but these standards may be insufficient."

In addition to the minutes, other documents and interviews show:

* Armour not only refused to allow Prince to publish his research, but the company also did not share it with the FDA, according to government officials. In response to a request filed by The Inquirer under the federal Freedom of Information Act, the FDA said it found no reference to the Prince report in its files.

* Meloy Laboratories eventually concluded that, at least on the basis of what the company called "arbitrary" statistical standards, all the AIDS virus in Factorate should be killed by Armour's heating process. Those data were presented to the FDA and to foreign regulators as proof that the Armour process worked, the Armour documents show. It is unclear whether the regulators were told that Meloy, like Prince, still found live virus in the product, even after testing at a standard more stringent than the "arbitrary" one.

* As Prince was completing his research on Factorate, Armour sought another outside opinion - and found it in Germany, where a scientist at the Paul
Ehrlich Institute assured Armour in February 1986 that Factorate contained no live AIDS virus. Armour presented the Ehrlich data to regulators in the United States and Britain, but doubts soon arose. Dr. William Terry, head of Meloy, thought the Ehrlich study was poorly executed and its conclusions overstated. Terry wrote in a May 1986 internal Meloy memo: "To spend approximately $120,000 for experiments that do not follow the required protocol and that are reported in a misleading manner does not seem to be in the best interests of the corporation."

* In August 1986, an Armour official paid a visit to a doctor who was described as Israel's major prescriber of clotting medicines. During the visit, an Armour official said the company was switching to a more intense heating process "specifically in response to regulatory and commercial pressures, rather than any evidence that our current process was inadequate," according to an internal company memo. The Israeli physician "said that before my visit he had doubts about the Armour product, but since our meeting he was satisfied regarding potential safety," the memo says.

* An Armour official also visited Germany, where physicians had declared they would not use "dry-heated" products such as Factorate. Meeting in Bonn in September 1986, the Armour representative presented data from Meloy - and
from the Ehrlich Institute study, previously discredited by Armour's own research lab. According to an Armour memo describing the visit, the Germans' refusal to use dry-heated product "seemed to soften," and they promised to reevaluate before deciding what to prescribe in 1987.

The Inquirer asked Armour for comment on the October 1985 company minutes and the other documents.

Armour's reply characterized the Prince findings as at variance with a study conducted about the same time as Prince's for the federal Centers for Disease Control by J.S. McDougal.

The McDougal study, Armour said, "showed no detectable virus" in blood clotting medicines that had been heated either at 68 degrees Centigrade for 24 hours or 60 degrees Centigrade for 20 hours. "At the time, Armour heated its factor concentrates at 60 degrees Centigrade for 30 hours," the company noted.

The McDougal study did not inc any of the Armour medicine.

At the time of the October 1985 meeting, Armour's major U.S. competitors who used the dry process were heating their products at higher temperatures, or for longer periods, or both. Baxter Healthcare Corp., which in March 1983 became the first company to reach the U.S. marketplace with a heat-treated clotting drug, used 60 degrees centigrade for 72 hours. Miles Inc. used 68 degrees for 72 hours.

Beth Leahy, Armour's spokeswoman, said Saturday that the Perpich document - labeled "Recombinant DNA Steering Committee, Minutes of the Seventh Meeting" - was "not minutes but a running narrative of one person's recollection of the meeting."

*

If government regulators in the United States and elsewhere were not fully informed by Armour of all its research findings on Factorate, there still was ample reason for them to ask questions.

In June 1985 - two months before Prince gave his report to Armour - scientists from the University of California and Cutter Laboratories wrote in The Lancet, a British medical journal, that live AIDS virus was detectable in clotting medicines even after heating at 68 degrees Centigrade for 34 hours.

In 1986, Prince repeated his studies with clotting medicine from his own lab at the New York Blood Center. He got the same results.

In May of that year, he published his new findings in The Lancet. Prince's account did not mention Armour or indicate that he had ever tested Factorate for the company. But he included what appeared to be an oblique warning about the 60-degree process Armour was using. Saying he did not mean to suggest that all dry-heated products were unsafe, Prince wrote: "Some products are heated above 60 degrees C."

In the same issue of The Lancet, Ralph Rousell, a scientist from Cutter Laboratories, noted that physicians in North Carolina and the Netherlands had written recently to The Lancet about patients who had tested HIV-positive after using heat-treated clotting products. Rousell called for "details of the duration of heat treatment and the temperature," because "heating at a lower temperature or for a shorter duration is less efficient than heating at a higher temperature for longer."

Rousell's letter was republished the following month.

In February 1986, British pediatrician Peter Jones, director of a hemophilia treatment center in Newcastle-upon-Tyne, went public with his fears about Factorate. He told a medical conference there was evidence that some hemophiliacs had contracted the AIDS virus from Factorate.

"I thought they were hiding something," he said of Armour in a telephone interview. "I was censured by our chief medical officer for even suggesting this."

In a letter to Jones in March 1986, and in a so-called defense statement issued to counter other critics, Armour officials in England wrote that live AIDS virus "has never been isolated from heat-treated Factorate." They wrote as well that Meloy scientists believed Armour's process "likely" eliminated any living virus.

Seven months later, Armour relinquished its licenses to sell Factorate in Britain after two hemophilic children who had used the medicine tested positive for HIV, the AIDS virus.

At a meeting in October 1986 with British regulators, Armour officials said there were no laboratory data to suggest the company's heating process was ineffective against HIV, according to a corporate memo summarizing the meeting. "On the contrary, three studies have indicated that the Armour process inactivates virus in excess of" the theoretical maximum, the memo recounts.

The company met with the FDA soon afterward, and the agency concluded there was insufficient evidence that the product should be withdrawn.

Factorate stayed on the U.S. market for another 14 months. It was withdrawn in December 1987, after news that six Vancouver-area hemophiliacs who had used the product - five of them children - had tested

positive for HIV.

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