Cohen-Boyer patent

Licensees ponder weaknesses

Washington

IN the aftermath of the long-awaited grant of the Cohen-Boyer patent in September, it is becoming increasingly clear that serious questions about the patent's validity remain unresolved. The opening of the complete file has in fact brought to light new questions, and Stanford University may now be reluctant to enforce its patent in the courts for fear of opening these issues to new scrutiny, possibly leading to judicial invalidation of the patent.

The September patent, which covers recombinant DNA molecules used in the cloning process developed by Stanley Cohen and Herbert Boyer, was issued to Stanford University and the University of California after a prolonged negotiation with the Patent Office. Stanford, which had initially waived its right to secrecy during this process, abruptly reversed course in November 1982 after the Patent Office tentatively rejected the claim and began asking uncomfortable questions.

It now turns out that shortly after asking that the file be closed to public scrutiny, Stanford's attorney, Bert Rowland, was told by the Patent Office that the case would be turned over to its fraud examiners; the examiners in spring 1984 concluded that Rowland and the applicants had committed a "clear violation of their duty to disclose to the Office information they are aware of which is material to the examination of the application". Because these violations were found to be the result of something less than bad faith or "gross negligence", however, they did not affect the ultimate issue of the patent.

The violations concern a scientific paper published by Cohen in 1977 that contradicts the earlier patent application description of how to make the key cloning vector pSC101, a plasmid. The Patent Office learned of the article only in June 1982, just as it was preparing to approve the patent; and the source of the information was press accounts of a critical article by Albert Halluin, now a patent attorney for Cetus Corporation. In the autumn of 1982, Rowland admitted to the Patent Office that he had known about the 1977 article when it had appeared, but had "no recollection" of why he failed to bring it to the Patent Office's attention. The fraud examiners' investigation further revealed that Rowland had written to Stanford's patent administrator in 1977 suggesting that the Cohen article might render the patent's description of how to make pSC101 "non-enabling" and asking whether they should revise the application accordingly.

Another apparent inconsistency is that in response to questions from the fraud examiners, Cohen early this year stated to the Patent Office that he had not appreciated the significance of the 1977 article with respect to the patent "until the

significance was explained to me at the time of my preparation of my declaration of April 20, 1983". In August 1982, however, Cohen denied reports in *Nature* (see 298, 595; 1982) and elsewhere that the 1977 paper admitted an error in the patent description. Rowland's declaration in autumn 1982 admitted to the Patent Office that pSC101 "could not be prepared in accordance with the working example" in the patent.

The real question for Stanford now is how many companies will continue to pay the \$10,000-a-year licence fee for the patent, due next February. Sixty-six companies are currently enrolled. The weakness of the patent is clearly weighing on the licensees' minds. An appellate court decision within the past month has con-

siderably toughened the definition of fraud, and if this standard had been applied to the Cohen-Boyer patent, it would probably not have been issued. The new tough standard would be applied by the courts now in any legal challenge to the patent's validity.

It is thought very unlikely that any company will go to the expense of mounting such a challenge. But Stanford itself would be opening the door if it goes to court to enforce the patent in an infringement action. It is thus likely that some companies may choose simply to ignore the patent, in effect daring Stanford to respond.

And even on the face of the patent claims, Stanford's position is not so strong as it would like it to be. The patent is limited to prokaryotes. And the admitted flaws in the pSC101 description remain in the earlier patent covering the cloning process, thereby raising doubts about that patent's validity.

Stephen Budiansky

Dangerous pathogens

Illegal US bug trade halted

Washington

TWO Canadians were arrested by Federal Bureau of Investigation (FBI) agents in Buffalo, New York State, last week as they attempted to collect botulinum and tetanus cultures that they had ordered under an assumed name from the American Type Culture Collection (ATCC). Neither of the two is a scientist, a fact that has fuelled speculations of a possible extortion scheme or terrorist plot.

The incident has also served to highlight the virtual absence of regulations governing the sale and acquisition of highly infectious or toxic agents. Federal regulations restrict only the importation or transfer of foreign microorganisms; indigenous microorganisms can in principle be sold freely to anyone. The two Canadians in fact obtained a tetanus culture from ATCC in September without incident.

It was only after they placed a second order that ATCC officials apparently became suspicious and approached FBI. The bureau found that the name and address used by the men were fictitious, and asked ATCC to process the order, substituting inert samples for live cultures. The Canadians were presumably going to carry the material across the border themselves, avoiding the customs problems of a direct shipment to Canada. When they attempted to pick up their order, FBI agents were waiting for them.

The only crime the two men have been charged with is wire fraud, for having used a false name in placing the order over the telephone. According to the FBI office in Buffalo, the men did not attempt to pass themselves off as scientists, although they did tell ATCC that they wanted the material for unspecified "research". FBI has identified the men as a Bell Canada employee and an Ontario Industrial Develop-

ment Corporation employee. No motive has been established.

ATCC is the major germ-plasm reference bank and supplies culture materials to researchers at or below cost; according to Pierre Daggett, acting director of ATCC, an internal safeguard system screens out people who are not qualified researchers and ensures that they do not receive infectious material. ATCC distributes 60,000 cultures per year. The regulations governing foreign microorganisms, which are administered by the US Department of Agriculture and the Public Health Service, require researchers to obtain a permit.

Both tetani and botulinum owe their lethality to toxins that they produce while growing under anaerobic conditions. Tetanus toxin is not normally harmful when ingested; botulin is a potent toxin when ingested or inhaled.

Toxin experts said last week that a botulinum culture of the type supplied by ATCC would probably be a mixture of spores and live cells, and possibly a small amount of toxin. Anyone with a basic knowledge of microbiological techniques, however, would have little difficulty in growing larger cultures and producing considerable quantities of toxin. On the other hand, any microbiologist would also have little difficulty in isolating botulinum or tetani from the environment.

Dr Michael Gill of Tufts University discounted the possibility that botulin could be used as a terrorist weapon: "The old scenario of putting it into a reservoir is not going to work". The bacteria would not grow in oxygenated water. But speculation is now centring on a possible extortion scheme, in which commercial products would be contaminated, or perhaps merely the claim made that this had been done.

Stephen Budiansky