Legislation on vitamin D patent makes waves

■ Lawyers may be the beneficiaries
■ Wisconsin U. pinch-hits for courts

London

A CASE heard in the Chancery Division of the British High Court last Tuesday (8 March) has drawn attention to a long-standing battle over patents for processes to manufacture the active principle of vitamin D, 1α,25-dihydroxycholecalciferol, but observers differ in their interpretation of the judgement by Mr Justice Whitford, which has not yet been made public.

The patent dispute is significant not merely for the costs which have accumulated over almost fifteen years and the importance of a means of synthesizing the active principle of vitamin D (formed in the liver and kidneys by the successive conversion of the natural vitamin), but for the distinction of those responsible for the two alternative processes — Sir Derek Barton, now at the University of Texas at Austin, who was at Imperial College London when he won the Nobel Prize for chemistry in 1969, and Dr Hector DeLuca, professor of biochemistry at the University of Wisconsin.

The litigants in the long-standing suit are not the inventors of the two processes, but the organizations to which the inventors assigned the patent rights. The Wisconsin patent (based on E.J. Semmler, M.F. Holick, H.K. Schnoes and H.F. DeLuca, *Tetrahedron Lett.* **40**, 4147; 1972) has been assigned to the Wisconsin Alumni Research Foundation (WARF), originally constituted in 1925 by Dr Harry Steenbock, who was among the first to demonstrate the value of vitamin D in the treatment of rickets. Last year, WARF contributed more than $11 million to the university's research fund.

The Barton patent (D.H.R. Barton, R.H. Hesse, M.M. Pechet & E. Rizzardo *J.Am. chem. Soc.* **94,** 9518; 1973) is assigned to the Boston-based company Research Institute of Medicine and Chemistry (RIMAC), of which Pechet is the chairman. The US patent applications were lodged in the early 1970s, since when the two holders were in litigation until their dispute was settled out of court last summer.

The terms of the agreement were 'sealed' by the US courts, but include an agreement that the litigants will not in future attack each others' patent rights to the active principle of vitamin-D and the payment of an undisclosed sum by WARF to RIMAC.

Quite apart from the duration of the litigation, the way in which it has been punctuated by personal charges against the Wisconsin group has made the case unusually bruising. DeLuca said on the telephone last week from Wisconsin that he had been so resentful of some of the charges that he had asked the University of Wisconsin early last year to institute a formal inquiry by outside people.

Dr Bernard C. Cohen, vice-chancellor for academic affairs at the university, said on Monday this week that DeLuca's request last spring had been delayed because the university had been hoping that the suit then current in the US courts would clear the air. The out-of-court settlement meant that the issues did not come to trial.

During the past few weeks, Cohen said, he has learned that recruiting a panel of people sufficiently knowledgeable about laboratory work and the field concerned, but sufficiently detached from the participants "is not as easy as I had hoped, but as difficult as I had feared".

Part of the contention in the case stems from the detail in which the discovery process built into US patent law has enabled the RIMAC side to inspect the Wisconsin laboratory notebooks, from which it appears to have emerged that the Wisconsin synthesis as published would not have worked as described.

Dr M.F. Holick, a graduate student in DeLuca's laboratory at the time and a participant in the synthesis on which the WARF patent was based, acknowledged on Monday the truth of one of the charges made in litigation by RIMAC that one of the fourteen stages in the process, the purification of a pair of isomers (only one of which was needed for the later steps), would normally yield only the unwanted isomer, because of the unexpected difference of the diffusion constants of the two isomers.

Holick also confirmed this week a point made by RIMAC in the litigation that the published synthesis is now known to have been successful because one of his colleagues, Dr Eric J.Semmler, having broken a flask and spilled the output from the chromatography column on the floor, returned the contents to the top of the column for repurification, whereupon the two isomers eluted together.

It has also been an important issue in the litigation that DeLuca first learned of the Barton synthesis when asked to act as a referee for its first publication in the communications section of the *Journal of the American Chemical Society*, and that the Barton process was used as the means of making small quantities of the active principle of vitamin D available for tests of biological efficacy.

DeLuca said on the telephone last week that he had given the Barton manuscript a favourable and prompt report (contrary to suggestions during the trial) and that it was in no sense improper to use another's published processes for the purposes of research, which is of course generally accepted.

Despite the out-of-court settlement between RIMAC and WARF, litigation nevertheless continues. Last week's hearing in London was an appeal by WARF against an order by a British patents examiner last November that the files in the case should remain open, allowing the British Patent Office to continue brooding about the validity of the original WARF patent. WARF may yet appeal.

But one set of documents has been returned to WARF's representatives. WARF seems also to have won the point that the amendment of its patent does not, of itself, impugn its validity.

Meanwhile, RIMAC, according to its London lawyers, is distressed that WARF is disputing the RIMAC patent in New Zealand (where WARF has no patent) despite last year's settlement in the United States.

John Maddox

Stanford still on top

Berkeley

Stanford University has received over $6 million in royalty income from patents in 1986–87, up $1 million from the previous year. The sum was more than that received by Harvard, the Massachusetts Institute of Technology (MIT) or the University of California (UC), and possibly higher than any other US university, according to Kathy Ku of Stanford's technology licensing office.

For the first time, Stanford's leading earner was the 1980 patent by Stanley Cohen of Stanford and Herbert Boyer of the University of California at San Francisco on recombinant DNA.

Stanford shared the royalty income with UC. The Cohen–Boyer patent brought $1.7 million to Stanford, surpassing the former leader, a 1971 patent on the FM synthesizer chip, invented by music professor John Chowning, and used in Yamaha music synthesizers.

Included in last year's income total was $700,000 from the settlement of a patent infringement lawsuit with Coulter Corporation of Hialeah, Florida. In addition to the $700,000, Coulter will pay royalties for its use of phycobiliproteins, patented jointly by Stanford and UC as a fluorescent label for cell sorting.

Marcia Barinaga