

rt admits he did not full access to data

THE TIMES HIGHER OCTOBER 12 2007



One of the world's leading bone experts has confirmed that he signed an incorrect declaration for a research paper that presented some erroneous findings about a leading osteoporosis drug.

Almost two years after *The Times Higher* first reported concerns about the validity of a paper by Richard Eastell on the effects of Procter & Gamble's multi-million-pound drug Actonel, the Sheffield University professor has published a peer-reviewed letter addressing the concerns raised.

In a letter to *The Journal of Bone and Mineral Research (JBMR)*, which published the original contested paper in 2003, Professor Eastell this week accepted that he had incorrectly signed a declaration stating that he and other authors had had "full access" to the Actonel drug-trial data held by P&G.

The data analysis for the paper was carried out by P&G, which paid for the research and which did not release the data to Professor Eastell.

In the letter, published by the *JBMR* following an independent analysis of P&G's drug-trial data, Professor Eastell also conceded that the original article to which he put his name contained "some errors and some poor practice".

The editor-in-chief of the *JBMR*, John Eisman, said in the journal this week that as a result of the case, the American Society for Bone and Mineral Research (ASBMR) had agreed new publication procedures.

These insist that "authors sign that they have had full access to the underlying data for all manuscripts", which "should help reinforce the independent role of the academic researcher" in working with pharmaceutical companies.

The Times Higher was the first to report concerns about the work in November 2005, after a whistleblower in Professor Eastell's Sheffield team raised the alarm.

Aubrey Blumsohn was suspended and threatened with the sack by Sheffield for co-operating with *The Times Higher*, but he later agreed a settlement understood to be worth six figures.

The work of Professor Eastell, who runs Sheffield University's Bone Metabolism Research Unit, had helped to change the understanding of the treatment of osteoporosis.

P&G's Actonel and its market rival Fosamax both reduce the risk of bone fractures by increasing bone density and reducing the "turnover" of bones — the rate at which they break down and regenerate. It had been generally understood that Fosamax was more effective at doing this.

But Professor Eastell's research suggested that Actonel's inferior potency did not mean that it was less effective at reducing the risk of fractures. He had suggested that there was a "threshold effect" — a point beyond which any further reduction in bone turnover did not affect fracture risk.

Professor Eastell reported this threshold effect in an article published in June 2003 in the *JBMR*: "Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate [Actonel's generic name]."

On the paper, a declaration by the authors confirmed that Professor Eastell had received research funding from P&G and that two co-authors were full-time employees of P&G, but it concluded with the statement that "all authors had full access to the data and analyses".

Professor Eastell writes in his letter to the *JBMR*: "In the original paper one of the authors, a

statistician working for P&G [Ian Barton] had full access to all data." He said that P&G applied pharmaceutical industry guidelines at the time, which restricted the release of original data to investigators.

He added that the P&G statistician "worked closely with all of the authors of the original report on the data analysis... and responded to all requests for further analyses. Thus, the authors had full access to the analyses they had requested... but not all had direct access to the raw data.

"At the time of writing (2002-03), not all the original authors were given access to the raw data."

An e-mail exchange between Professor Eastell and P&G's statistician Ian Barton, seen by *The Times Higher*, shows Professor Eastell's requests for the raw data were rejected by P&G.

In May 2002, Professor Eastell wrote that a colleague "was really surprised when I told him that all the analyses" for a presentation of research findings "were done by P&G employees".

"I think that to avoid criticism in the future it would be good if we could say that we had done the analyses independently," he said. But P&G declined, saying that while this would "add an extra layer of external credibility" to the research, the data itself was the result of an investment of "hundreds of millions of dollars" and belonged to the company.

Professor Eastell's letter to the *JBMR* also acknowledges that the independent analysis of the data "identified some errors and some poor practice" in the original paper published under his name.

An incorrect statistical test had

been used and, in particular, a graph in the original paper had been "cropped extensively and in an asymmetric manner".

"In the original paper we should have given a rationale for the approach used in cropping [lines on a graph], and stated how much data were cropped. However, we were unaware that the cropping procedure was carried out in an asymmetric way at the time we wrote the original manuscript and therefore that was not indicated." The original graph "excludes between 34 per cent and 49 per cent" of the data.

Dr Blumsohn said this week that the new independent analysis of the data showed that all his concerns had been validated. He added that "the authors have been unable to replicate the analysis as originally reported" now that they have all the data.

But Professor Eastell said the conclusion of the original *JBMR* paper that there was "a level of bone turnover reduction below which no further fracture benefit is observed" — the so-called threshold effect — could "still be supported based on the new analysis".

He told *The Times Higher* that his letter was "the final word on the topic" and had been through a thorough scientific peer review.

A spokesman for P&G said: "We agree with the corrections noted by the independent researchers... and we are pleased that the re-analysis supports the original conclusions drawn in 2003. While the mistakes in the original paper did not affect the scientific conclusions, we recognise the need for consistent and robust scientific analysis.

"It is important to note this work was not related to the safety, efficacy or approval of Actonel. This research also did not directly involve clinical research in patients."

phil.baty@thes.co.uk

Professor Eastell's letter to the JBMR acknowledges that the independent analysis of the data "identified some errors and some poor practice"