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Less is more, but still not enough, for Genentech's dosing schedule patent

The High Court has decided, in a single judgment, that Genentech's patents relating to a dosage regimen for Herceptin and a purified composition of non-acidic variants of Herceptin are invalid. This article focuses on the dosage regimen patent.

Background

Herceptin is the world's tenth best-selling drug, with sales of US$ 6.9 billion. Genentech held a (recently expired) patent protecting the monoclonal antibody trastuzumab, the active ingredient in Herceptin. The supplementary protection certificate (Europe's mechanism for patent term extension for pharmaceutical products) based on this patent and protecting trastuzumab expires on 28th July 2014.

Hospira aims to sell a generic of Herceptin in Europe after this date (it has already obtained approval for the generic in South Korea, so Hospira appears well prepared to roll it out in Europe). Genentech, however, also owns two further Herceptin patents with later expiry dates, which were at suit in this action. EP1210115 relates to a dosage regimen, and EP1308455 relates to certain purified compositions. Here, we review the decision in respect of the first patent, '115. The patent was held to be invalid at the EPO following opposition, and is presently under appeal before the EPO Boards of Appeal.

The '115 patent contains Swiss-type and EPC2000 second medical use claims specifying an initial dose of 8 mg/kg of Herceptin, followed by maintenance doses of 6 mg/kg every three weeks, for treating breast cancer. Further dependent claims recite co-administration of a chemotherapeutic agent, in particular, paclitaxel.

The known schedule for Herceptin involved weekly administration. Paclitaxel was a well known cytotoxic drug used in chemotherapy, which was administered once every three weeks for the treatment of metastatic breast cancer. Herceptin had previously been approved by the FDA in the US for use in combination with paclitaxel (with the two drugs being administered according to different dosage regimens).

The parties' arguments and the Court's judgment

Hospira contended that the claimed dosage regimen was obvious in light of the FDA's previous approval of Herceptin co-administered with paclitaxel, in particular, based on the FDA's label for Herceptin. Hospira also argued that if the claimed subject matter was inventive over the label, then the patent was insufficient instead. This is because it did not disclose the results of any human testing performed using the claimed dosage regimen.

Genentech argued that the label did not render the claimed subject matter obvious, on the basis that a clinician would never think of switching from once weekly to dosing every three weeks. It also argued that, in contrast to the prior art, the patent would have given the reader sufficient confidence to conduct a clinical trial of the proposed regimen.

Inventive step

The Judge assessed the difference between the FDA label and the claims to be that the label did not disclose the claimed dosage regimen, nor state that such a regimen would be effective for the treatment of breast cancer. To him, the question was therefore whether the claimed dosage regimen would have occurred to the skilled person, and if so, whether they would have decided

to test the claimed dosage regimen in a clinical trial. In this case, the skilled person was assessed to be represented by a team consisting of a clinician and a pharmacokinetics expert.

The Judge considered that the skilled team would have investigated the claimed dosage regimen, noting the inherent advantage of less frequent dosing:

> "The idea of three weekly dosing arises because the treatment is combined with paclitaxel which is itself three weekly. It would be entirely obvious that a three weekly schedule for Herceptin, if it is safe and efficacious, would deliver immediate and concrete convenience and quality of life benefits. [...] The clinician at this stage will not know whether a three weekly dosing schedule for Herceptin would indeed be safe and efficacious, but I am satisfied it would occur to skilled clinicians to think about it."

The Judge considered that the pharmacokinetics expert in the skilled team, on reading the FDA label together with further papers discussing the half-life of trastuzumab, would understand that it would be possible to use a less frequent dosage regimen. This was deemed achievable simply by administering a greater dose of Herceptin, particularly in light of Herceptin's known safety at higher doses.

Accordingly, the recited dosing interval of three weeks was considered to be obvious. Once the Judge had made this finding, he considered that the specific doses recited in the claims would also be obvious.

Sufficiency

The Judge agreed with the reasoning put forward by Hospira that the disclosures of the patent and the FDA label would carry equivalent weight, because the patent contained no results in relation to dosing every three weeks, although it did propose an outline for a trial. The Judge thus considered that in the event that the FDA label did not render the claimed subject matter obvious, then the examples of the patent still did not reflect a sufficient teaching of the claimed subject matter:

> "... on that hypothesis the patent would not render the claimed effect plausible and the patent would be invalid for insufficiency."

Priority

Although not a point that was fundamental to the decision following his finding of obviousness, the Judge also analysed the priority claim of the patent, as Genentech admitted that the patent would be invalid if priority was lost. Here, the Judge agreed that there was disclosure in the priority document of once every three weeks dosing regimens. He considered, however, that the priority document was not an enabling disclosure, as the priority document was insufficient for the same reasons as the patent, and so the priority claim was not valid.

Comment

This judgment relates to an important issue in the field of dosage regimen patents. It highlights the importance of meeting the requirements for sufficient disclosure for claims based on dosage regimens, and the difficulty of obtaining the information required in clinical trials which can be long and expensive affairs (echoing the Court's earlier judgment, finding insufficiency, in Hospira v Novartis [2013] EWHC 516 (Pat).

This latest attempt of the Court to grapple with dosing schedules indicates that it is willing to consider seriously under inventive step the additional steer provided by the dosing of a coadministered treatment, which could lead to problems for patents of this nature, at least before the UK courts. It will also raise concerns regarding the amount of information required in the application to render a dosage regimen claim sufficiently described, particularly in light of the added worry that the now seeming need for human data could potentially only come from clinical trials which are subsequently judged to be prior art disclosures of the subject matter. The trend towards increased openness of clinical trial data is not going to make life any easier for those attempting to secure follow-on protection for their products.

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This briefing note was first published in the IAM IP Newsletter.