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Genentech's Herceptin purification patent fails to pass the acid test

The UK's High Court has decided that Genentech's patent relating to a composition of Herceptin with reduced acidic variant content is invalid.

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 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. The decision regarding the first patent was reviewed in a related article, published here last week. This article focusses on the second patent (EP1308455) at suit in the action. This patent was held to be invalid at the EPO following opposition, and this decision is presently under appeal before the EPO Boards of Appeal.

Following production of trastuzumab in a cell line, the asparagine amino acids in the protein can spontaneously degrade to aspartate (an acidic amino acid). This leads to a mixed population of native trastuzumab and the so-called 'acidic variants' of trastuzumab. Certain acidic variants are less effective than native trastuzumab because they bind to their target (HER2) less tightly. The patent discloses a cationic exchange chromatography method of separating acidic variants and native trastuzumab, using a special 'reverse wash' step. This step increases the yield of native trastuzumab because the acidic variants normally co-purify to an extent with native trastuzumab. The patent's claims are directed to a composition comprising a mixture of an anti-HER2 antibody and one or more acidic variants thereof, wherein the acidic variants make up less than 25% of the mixture.

The parties' arguments and the court's judgment

Novelty

Hospira contended that the claims were not novel over a prior Genentech patent publication describing pharmaceutical compositions of trastuzumab. The publication discloses the separation of native and acidic variants of trastuzumab, and reports that native trastuzumab made up 82% of the protein content of the sample of trastuzumab tested. Hence, the maximum level of acidic variants in this sample was 18%, and so the report of this sample was considered to be a disclosure of a composition according to claim 1.

The judge therefore found that claim 1, and a number of the patent's dependent claims, lacked novelty.

Inventive step

The claims were alleged to lack inventive step over slides presented by a Genentech employee at a conference.

The slides disclosed the fact that trastuzumab was being manufactured on a large scale, disclosed analytical chromatograms showing separation of native and acidic variants of trastuzumab, and noted that the acidic variants were not as effective as the native antibody. The Judge considered that in light of this disclosure it was obvious for the skilled person to seek to reduce the amount of undesirable acidic variants in the composition. Further, he found that it would have been possible to do so because the purification scheme discussed in the slides indicated that the native and acidic forms could be separated.

The slides did not disclose the reverse wash step used in the patent. Genentech's expert had stated that separation of the native and acidic variants of trastuzumab during large-scale production without the reverse wash step would be inefficient and that, as the yield would be so poor, this method would not be used by the skilled person. The Judge considered that this was not relevant; the fact that it would

be technically possible at all for the skilled person to produce a composition which fell within the scope of the claims was what was important, even if to do so was not a commercially sound decision. The Judge also stated that:

> "An improvement in yield might very well provide the basis for an inventive step in the context of a new method for of carrying out an industrial process but it seems to me that it does not confer inventiveness on a product which is defined in such a way that it can be made by any process, whatever the yield."

Accordingly, the Judge found all claims of the patent to be obvious.

Non-infringement

Hospira also requested a declaration of non-infringement, stating that the trastuzumab in batches of their product contained 25-29% acidic variants. The Judge considered that the upper limit of claim 1 of the patent ("less than 25%") was 24.5%, and accordingly found that Hospira's formulations fell outside of the scope of the claims. On this basis, the declaration was granted.

Comment

The patent was revoked for lacking novelty over Genentech's own earlier patent publication, and for lacking inventive step over a conference disclosure by one of its own employees.

In reaching its conclusions, the Court applied the established principles of assessing the subject matter based on the wording of the claim. The arguments by the parties in court included many nuances, including the scale of purification, but at the end of the day the Judge decided that it was possible and obvious to make compositions as set out in the claim. The Judge noted that some methods of making the compositions may be more efficient than others, but what matters is whether it was possible to arrive at the claimed subject matter, not whether or not it would be tedious or commercially sensible to do so.

The consequence of this judgment is to indicate that, provided that it was known or was obvious that particular protein species can be separated from one another, merely reciting the percentage of the purified protein in the resulting composition is unlikely to be found to be inventive. This judgment may therefore obstruct another well-trodden pathway for obtaining follow-on protection in the UK.

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