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Probing the boundaries of patent law

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Advanced Cell Diagnostics v Molecular Instruments [2024] EWHC 898 (Pat)

On 23 April 2024, Mr Justice Meade handed down his judgment in the dispute between Advanced Cell Diagnostics (ACD) and Molecular Instruments (MI).

ACD is the proprietor of two European patents which relate to *in situ* detection of nucleic acids in single cells. EP (UK) 1 910 572 ("**EP 572**") claims a process for nucleic acid detection, and EP (UK) 2 500 439 B1 ("**EP 439**") claims kits and products for nucleic acid detection. MI, a US-based company, manufactures products in the US which support the *in situ* detection of nucleic acids using various probes. ACD alleged infringement by MI as a joint tortfeasor with its UK customers in respect of both patents and MI counterclaimed for invalidity.

A brief background on the technology used is helpful to understand the issues at play. Hybridisation assays are used to detect particular strands of nucleic acids within a given sample using nucleotide probes (nucleic acid fragments). The probes (or 'capture probes') are designed to be complementary to the target of interest, and if the target is present will hybridise it (i.e. bind to it) to form a stable duplex. Label probes can be used which bind to the capture probes and produce a signal, indicating the presence of the target nucleic acids. Using multiple capture probes confers the benefit of attaching more signal-detecting particles for higher detection sensitivity. Whilst *in vitro* hybridisation methods are applied to nucleic acids which have been extracted from their source, *in situ* hybridisation (ISH) assays provide information whilst preserving the integrity of the cell.

Claim construction – what does 'overlapping' mean?

The patents disclose a method (EP 752) and a kit (EP 439) for detecting nucleic acids using ISH assays. Claim 1 of each patent requires *inter alia* a label probe, and two or more capture probes, for each nucleic acid target. The capture probes must comprise a section which is complementary to (i.e. matches) a non-overlapping section on the nucleic acid target, and a section which is complementary to a non-overlapping section on the label probe (as depicted in Figure 3). This is so the probes do not compete for binding with the same nucleic acid targets which could weaken the connection and cause instability.

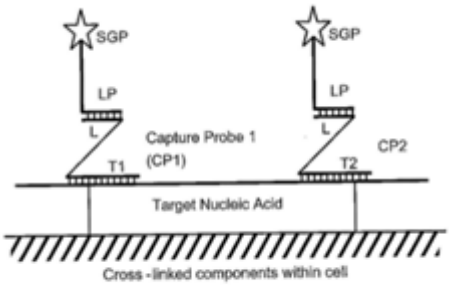

Fig. 3

MI's non-infringement case centred on the fact that in its system the sections overlap, and this makes its system better because it increases specificity. ACD disputed any advantage conferred by the overlap, and argued that in any event MI's system still confers the benefit of using two probes rather than one and therefore infringed. A critical issue for infringement therefore turned on the construction of 'non-overlapping'.

Drawing a parallel with the court's decision in *Catnic*, in which readers will recall a claim to 'vertical' encompassed a small degree of variation which did not impede the weight-bearing function of the product, Meade J found that 'non-overlapping' should not be read as 'completely non-overlapping'. The question was simply whether the two probes could each form stable duplexes so as to get the benefit of two probes rather than one. This was made out on the evidence and therefore on a normal construction claim 1 would be infringed (we come onto validity shortly).

Infringement under the doctrine of equivalence

Should he be wrong in this construction, Meade J also considered the position under the doctrine of equivalence, applying the test from *Actavis v Lilly*. Taking as the 'inventive core' the better specificity achieved by the use of two probes where one would bind unstably, in answer to the first question Meade J considered the variant to achieve substantially the same result (good specificity) in substantially the same way (via two stable duplexes). It follows that, in the knowledge that the variant worked, it must be obvious to the skilled person *how* it worked (question 2). In answer to the third question, Meade J found there is nothing in the patent specifications to require strict compliance with the literal meaning of the claims. Therefore claim 1 would otherwise be infringed by equivalence.

It merits mention that MI relied upon extensive experimental evidence which it had conducted in the normal course of its business, rather than litigation experiments which followed the procedural regime of the Patents Court. The standard of the experiments also fell short of what would have been required for a peer-reviewed publication. Meade J made clear, however, that this was not a criticism of the experimental evidence *per se*, but rather part of the context in which to assess its weight.

Was MI a joint tortfeasor with UK customers?

Regarding joint liability, a distinction was drawn between customers to which MI provided only general and standard directions by way of protocols, and other customers to which MI provided specific troubleshooting tips and tailored advice for their specific needs. Applying the principles set out by the Supreme Court in *Fish & Fish v Sea Shepherd UK*[1], Meade J found the former went no further than "mere facilitation" and thus no joint liability, whereas the latter amounted to

assisting customers pursuant to a common design by working a method which would have infringed EP 572.

Anticipation and obviousness

Turning next to validity, MI's main attack was on anticipation and/or lack of inventive step over the prior art "Collins" alone, or together with the prior art "Kern", a citation in Collins. As readers will know, a much higher threshold applies for combining prior art documents for the purposes of anticipation than obviousness. On these facts the cross-reference to Kern was too general, and the anticipation attack failed (neither document alone contained a clear and unambiguous disclosure). Meade J clarified that whilst there is no absolute rule against combining documents for the purposes of anticipation in UK proceedings, it is a requirement that one document points to the other with "clear and unmistakable directions". Mosaicking was not challenged for obviousness.

On the issue of obviousness, the traditional *Pozzoli* analysis did not easily apply since Meade J found all features of the claims would occur to the skilled person upon reading Collins with Kern. The key dispute instead centred on whether the skilled person would think there were reasonable prospects of success in using the hybridisation assay disclosed in Collins in an *in situ* setting (as claimed). This turned largely on a disputed point of CGK regarding the "mindset" of the skilled person. ACD submitted that whilst there was no *actual* problem in doing so, there was a perception at the time of low or no expectation of success when seeking to take an *in vitro* technique *in situ*, and this was relevant in assessing obviousness. Meade J was not persuaded that this "mindset" formed part of the CGK, not least because there existed techniques which had been taken from *in vitro* to *in situ* with success; it was merely an empirical task which might pose some practical difficulty, but which the skilled person would expect to overcome in due course. In the absence of specific reasoning why the skilled person would *not* have an expectation of success, the claims were held to be obvious. This conclusion was not hindered by the availability of other routes the skilled person could have taken based on the prior art.

Insufficiency

As the case was decided on obviousness, Meade J only made a few remarks on MI's insufficiency attacks, which were maintained as squeezes.

The first squeeze centred around expectation of success of moving from *in vitro* to *in situ*; if ACD maintained that transferring an *in vitro* assay into an *in situ* format would not be obvious to the skilled person due to low/no expectation of success, Meade J found the patents would be insufficient as there is no data to demonstrate that the claimed method or kits work *in situ*. The second (unsuccessful) squeeze went to breadth of claim insufficiency; ACD argued that if a successful ISH assay requires a careful balancing of different parameters, it is not plausible that the invention will work across the scope of the claims. Meade J disagreed; the invention did not require choosing individual sets of detailed conditions and therefore the claims were not about "relevant ranges" in the *Illumina* sense.

The patents were found to be invalid for obviousness, but had they been valid MI would have infringed EP 572 (process) but not EP 439 (product).

Procedural Issues

Also of note are the observations of the court on the instruction of expert witnesses and in

particular the desirability of sequential unmasking. As many practitioners will know, in recent years it has become established practice for potential expert witnesses to be instructed in stages – being first asked about the common general knowledge and then supplied with, and asked to comment on, the cited prior art and then, and only then, being supplied with a copy of the patent in suit. This approach is said to reduce the risk of the expert giving their views with hindsight but in practice it is not always possible because for instance the cited prior art might change quite late in the case. Also, in a niche field, it is sometime inevitable that the expert will guess or have a strong hunch of the subject of the patent given the date on which they are asked to opine on the CGK. Finally, sequential unmasking can lead to a significant increase in costs as the legal team will need to have several calls or meetings with a candidate before asking the crucial questions to discover if the expert is supportive of their client's position. Meade J's comments on this issue in the ACD judgment are typically practical – in essence the message is sequentially unmask where you can but don't get too hung up about it where you can't. The main thing is that the expert must be clear that they have endeavoured to avoid hindsight.

Whilst the decision turned on its facts, the ACD judgment is strewn with various points of interest relating to claim construction, the influence of 'mindset' on the CGK and the mosaicking of documents. It also highlights the difficulty of relying upon 'no expectation of success' as a defence to obviousness in the absence of specific evidence such a prospect is lacking. As well as these comments on the substantive law, the Court's observations on sequential unmasking are also worth noting.

It is not yet known if ACD will seek permission to appeal.

[1] *Fish & Fish v Sea Shepherd UK* [2015] UKSC 10.

This entry was posted on Friday, May 10th, 2024 at 11:30 am and is filed under literally fulfil all features of the claim. The purpose of the doctrine is to prevent an infringer from stealing the benefit of an invention by changing minor or insubstantial details while retaining the same functionality. Internationally, the criteria for determining equivalents vary. For example, German courts apply a three-step test known as Schneidmesser's questions. In the UK, the equivalence doctrine was most recently discussed in Eli Lilly v Actavis UK in July 2017. In the US, the function-way-result test is used.">Equivalents, Infringement, Inventive step, Litigation, Novelty, Patents, Pharma, United Kingdom, Validity
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