

## CASE COMMENTS

# THE PATENTABILITY OF BIOSCIENCE INVENTIONS: *LILLY v HGS* IN ITS BROADER CONTEXT

**PAUL ABBOTT AND CHRISTOPHER STOTHERS**

Arnold & Porter (UK) LLP\*

Eli Lilly's challenges to Human Genome Sciences' Neutrokine- $\alpha$  patent in both the European Patent Office and the UK courts have been widely reported and discussed. This article places the most recent decisions of the UK courts in their broader context: first, against the background of the numerous other patent and regulatory filings concerning Neutrokine- $\alpha$ ; and second, in the wider context of bioscience inventions more generally.

### The Race to Patent Neutrokine- $\alpha$

At the very highest of levels, the dispute in relation to the Human Genome Sciences ('HGS')<sup>1</sup> patent EP 0 939 804 ('the HGS Neutrokine- $\alpha$  patent') comes down to a question of how early in the development of a bioscience invention one should be permitted to file for a patent. This was the emphasis of the submissions made by the BioIndustry Association ('the BIA') in the Supreme Court proceedings, as quoted by Lord Neuberger in his judgment:<sup>2</sup>

*If the application is filed early ... [t]he company will be left with no patent protection, but would have disclosed its invention in the published patent application to competitors. If the application is filed late, there is a risk in such a competitive environment*

*where several companies may be working on the same type of research projects, that a third party will already have filed a patent application covering the same or a similar invention, in which case the company may not be able to gain any patent protection for its work and by continuing their programme they may risk infringing that third party's patents. In both cases, the company will have lost much of the benefit of its costly research and development.*

In the present case, it is clear that the competitive risk was a real one. There was a drive in the late 1980s/early 1990s to identify new members of the TNF ligand superfamily of cytokines ('the TNF family'), driven particularly by the discoveries that the first identified member of the TNF family (TNF- $\alpha$ ) had various effects on different cell types which could potentially be exploited for pharmaceutical purposes. By 1996, at least eight other members of the TNF family had been identified.

The HGS Neutrokine- $\alpha$  patent was filed on 25 October 1996 and relates to a new member of the TNF family. The application did not publish until 7 May 1998, by which time three competitors of HGS had also filed applications relating to the same cytokine (known under various alternative names including TALL-1, xTNF4, THANK, BAFF, Kay Ligand and BlyS):<sup>3</sup>

- Biogen: a US provisional application 60/058,786 filed on 12 September 1997 which was used as a (part) priority claim for at least three later European Patent applications (EP 1 012 270 and EP 1 027 431, neither of which proceeded to grant, and EP 1 012 282, which concerns novel receptors in the TNF family and was granted in 2007 and was not opposed at the EPO);
- Schering Corporation: a US provisional application filed on 17 December 1996 and the subsequent PCT application filed on 16 December 1997 (later published as WO 98/27114; no European patent application proceeded to grant from it), the latter being used as a priority filing for a granted European Patent (EP 1 003 861) and two divisional applications derived therefrom (EP 1 798 286, granted, and EP 1 798 287, refused).
- SmithKline Beecham: two US applications, 60/041,797 filed 2 April 1997 and 08/984,396 filed 3 December 1997, and a subsequent European Patent application EP 0 869 180 filed on 1 April 1998 (later withdrawn).

\* Arnold & Porter (UK) LLP, Tower 42, 25 Old Broad Street, London EC2N 1HQ. Address for correspondence: paul.abbott@aporter.com. The views expressed in this article are the authors' own and do not necessarily represent the views of Arnold & Porter.

1) HGS was acquired in August 2012 by GlaxoSmithKline.

2) [2011] UKSC 51, at paragraph 97.

3) This information is largely derived from Teva's Grounds of Opposition against HGS's follow-on patent EP 1 294 769, and that submission itself relies upon HGS's Grounds of Opposition against Biogen's patent EP 1 146 892.

At the time the HGS Neutrokin- $\alpha$  patent was filed, no ultimate commercial use for products relating to Neutrokin- $\alpha$  had been identified. Instead, the specification of the HGS Neutrokin- $\alpha$  patent described the varying (and sometimes contradictory) functions of the other members of the TNF family and suggested that the uses of Neutrokin- $\alpha$  would likely be the same. However, the HGS Neutrokin- $\alpha$  patent was the first to describe this novel member of the TNF family.

## Subsequent Neutrokin- $\alpha$ Patent Filings

After publication of the application for the HGS Neutrokin- $\alpha$  patent, numerous further patent applications were made, including by Regeneron, University of Washington, Biogen, Eli Lilly, Chiron, ZymoGenetics, Glaxo, the US Department of Health & Human Services, and HGS itself, all relating in some way to the same cytokine, Neutrokin- $\alpha$  (claiming, for example, specific antibodies to Neutrokin- $\alpha$ ). Some of these patents have proceeded to grant:

- ZymoGenetics' EP 1 141 274 (opposed by Genentech and Biogen<sup>4</sup> at the EPO and maintained following appeal).
- Biogen's EP 1 146 892 (which Biogen asserted against Eli Lilly in the UK; however, following a Technical Board of Appeal hearing on 9-10 October 2012 concerning an opposition brought by Merck Serono<sup>5</sup>, this patent has now been revoked).
- Glaxo's EP 1 141 283 (unopposed).
- HGS's EP 1 294 769 (opposed by Teva, no date for oral proceedings at the Opposition Division yet having been appointed).

But regardless of whether the subsequent patent filings themselves relate to patentable advances or not, the HGS Neutrokin- $\alpha$  patent has a position at the top of the tree. Aside from claiming an isolated nucleic acid molecule comprising a polynucleotide sequence encoding a particular Neutrokin- $\alpha$  polypeptide, the HGS Neutrokin- $\alpha$  patent also covers *inter alia*:

*13. An isolated antibody or portion thereof that binds specifically to:*

*(a) the full length Neutrokin- $\alpha$  polypeptide [as defined by an amino acid sequence]; or*

*(b) the extracellular domain of the Neutrokin- $\alpha$  polypeptide [as defined by an amino acid sequence comprising part of the sequence in (a)]*

*18. A pharmaceutical composition comprising ... the antibody or portion thereof of ... [claim 13] and optionally, a pharmaceutically acceptable carrier.*

*19. A diagnostic composition comprising ... the antibody or portion thereof of [claim 13].*

From a commercial perspective, it is these claims which are most relevant, since the drug products being developed by various different companies (discussed later in this article) concern antibodies that bind specifically to Neutrokin- $\alpha$ . These were the claims at issue in the most recent Court of Appeal decision.

## Brief Background to the UK and EPO Proceedings

The history of the *Lilly v HGS* litigation is well documented. In short:

- After oral proceedings in June 2008, the EPO Opposition Division held the HGS Neutrokin- $\alpha$  patent invalid on the basis that the claimed invention lacked any inventive step and constituted a claim to an arbitrary member of the TNF family without a known function. Written reasons were not handed down until December 2008. HGS appealed this decision.
- In July 2008 (after a trial in December 2007 and January 2008), Kitchin J<sup>6</sup> held the HGS Neutrokin- $\alpha$  patent invalid as a whole on the basis that (1) none of the claims were susceptible of industrial application, and (2) the patent constituted mere speculation and was therefore obvious in the *AgrEvo* sense. Further, whilst the claims to the isolated polynucleotide sequence for Neutrokin- $\alpha$  and isolated antibodies which bind specifically to Neutrokin- $\alpha$  (claim 13 above) were sufficient, the claims to pharmaceutical and diagnostic compositions comprising such antibodies (claims 18 and 19 above) were not. HGS appealed the decision and Lilly cross-appealed on some of the sufficiency issues found adverse to it.

4) Corixa and HGS were also opponents but withdrew on 25 September 2007, just two days before the Opposition Division hearing.

5) HGS were also an opponent at first instance but withdrew from proceedings on 19 November 2008, apparently on agreeing a licence which

gave Biogen a royalty stream for HGS and GlaxoSmithKline's lupus drug BENLYSTA – a royalty stream Biogen have since (in September 2012) sold to DRI Capital.

6) [2008] EWHC 1903 (Pat).

- In October 2009, following accelerated proceedings, an EPO Technical Board of Appeal overturned the Opposition Division's decision and ordered the patent maintained on the basis of certain amendments filed during oral proceedings. Written reasons were delivered on 1 December 2009.<sup>7</sup>

- The Court of Appeal (Jacob and Hallett LJ, Lewison J) heard HGS's appeal later in December 2009 and in his leading judgment delivered in February 2010, Jacob LJ upheld Kitchen J on the industrial application issue and did not go on to consider the other issues.<sup>8</sup> HGS appealed.

- In November 2011, the Supreme Court (Lords Hope, Walker, Neuberger, Clarke and Collins) overturned Kitchen J and Jacob LJ, holding the patent susceptible of industrial application and the claims to the isolated polynucleotide sequence for Neutrokine- $\alpha$  sufficient.<sup>9</sup> The remaining open issues were remitted to the Court of Appeal for determination.

## The Court of Appeal Decision of 5 September 2012

As Lilly had (perhaps surprisingly) conceded that the *AgrEvo* obviousness point stood or fell with industrial applicability, the only issues left open for determination concerned claims 13, 18 and 19 (set out above). Kitchen J had held claim 13 sufficient but claims 18 and 19 insufficient.

Delivering the leading judgment,<sup>10</sup> Sir Robin Jacob (with whom Hooper and Lewison LJ agreed, the latter adding some comments of his own) recognised that claim 13 was commercially the most important claim of the patent (at paragraph 6). Lilly did not challenge Kitchen J's finding of fact that it would not have required undue effort to make and identify specific antibodies to Neutrokine- $\alpha$ . Instead, Lilly's case was that claim 13 should be read as confined to antibodies which have a valuable use and, although one could make and isolate individual antibodies without undue burden, nearly all would be useless – hence undue effort was required to find out which of the millions of possibilities would, in fact, have a practical use. Mr Waugh QC (appearing for Lilly) used the analogy of identifying which of a large pool of tadpoles was a tadpole that would develop into a frog that when kissed would turn into a prince.

Sir Robin Jacob rejected Lilly's submissions. In the light of the Supreme Court's decision, every member of the large class of antibodies had to be regarded as being susceptible of industrial application. That an antibody would specifically bind to Neutrokine- $\alpha$  was, in itself, its potential utility. Further, as a matter of construction, claim 13 contained no limitation to 'useful' antibodies (even when considered alongside claims 18 and 19 which, in any event, were later held to be sufficient in their own right). Claim 13 was, therefore, valid.<sup>11</sup>

In relation to claims 18 and 19, HGS submitted that Kitchen J had been wrong to construe these claims as being directed to compositions with immediate practical use as a pharmaceutical or diagnostic. In the light of the generality of the disclosure, the claims should be construed as compositions which could be formulated as *suitable for* administration as a pharmaceutical or *suitable for* use as a diagnostic. Sir Robin accepted that submission. Claims 18 and 19 were, therefore, sufficient.

## What Does This All Mean in the Wider Context?

The Court of Appeal's decision means that the ultimate result of the UK proceedings<sup>12</sup> was exactly the same as that of the EPO Technical Board of Appeal. It was clear in the reasoning of the Supreme Court that such a conclusion should be very much the norm, save where a difference in assessment of the evidence could validly justify different conclusions being reached.<sup>13</sup>

It remains to be seen whether the UK courts will tend to become more patentee-friendly in the light of the result in *Lilly v HGS*. One thing is clear: the status quo has been restored and the requirement that an invention be susceptible of industrial application will now catch out very few patents.

The key point to draw from *Lilly v HGS* concerns the vexed question of how early in a research and development project one should file for patent protection. The answer seems to be as early as possible, even in the absence of firm results confirming any kind of practical utility, so long as some plausible (even if speculative) utility can be proposed.

7) T 0018/09 *Neutrokine/Human Genome Sciences*. The decision refers to the acceleration of proceedings at the request of the UK court. The EPO Appeal proceedings were completed a mere 16 months after the Opposition Division's decision. This record was recently bettered in T 1839/11 *Enzyme granules/Novozymes* (12 months).

8) [2010] EWCA Civ 33.

9) [2011] UKSC 51.

10) [2012] EWCA Civ 1185.

11) Lilly also unsuccessfully raised a question of claim broadening in relation to claim 13 (which was amended following grant).

12) However it is understood that Lilly is now seeking permission to appeal the Court of Appeal's latest ruling to the Supreme Court.

13) Lord Neuberger at paragraph 128.

Provided the patent disclosure is at a similar level of generality as the HGS Neutrokin- $\alpha$  patent, neither the requirement of capability of industrial application nor that of sufficiency of disclosure is likely to impede the maintenance of the patent.

For bioscience innovators this is particularly important. The Neutrokin- $\alpha$  situation could easily be replicated many times over: multiple players all investigating in the same field all making the same discovery at around the same time, without necessarily knowing whether that discovery will ultimately yield any commercial benefit. If, however, it does give such a benefit (even where getting that benefit requires substantial further innovative work), then whoever files first will be in a position to require royalties and/or cross-licences from everyone else working on the same biomolecule.

Should this be the case? The Supreme Court's decision was driven by two policy reasons: first, that the UK courts should, so far as possible, be in agreement with EPO jurisprudence; and second, that the patent system should not provide a barrier to investment and innovation in the bioscience industry. Both reasons are fundamentally sound. However, there are problems with where the line has been drawn, which we explore further below when discussing Lilly's ongoing follow-up claim against HGS in relation to Supplementary Protection Certificates (SPCs). Only time will tell whether the position of the UK courts in fact promotes or hinders innovation in this field.

Finally, from a legal perspective, it is interesting to consider where the *AgrEvo* ground of invalidity now fits in UK law. Although it is not entirely clear from the Supreme Court's ruling, Lilly conceded that in this case the *AgrEvo* ground stood or fell with the industrial application ground. Typically, the *AgrEvo* ground can be regarded as a species of insufficiency or as relevant to inventive step, the latter being where it fits in the EPO jurisprudence. For example, in the recent case of *Generics (UK) Ltd (t/a Mylan) v Yeda Research and Development Co Ltd & Anor*,<sup>14</sup> Mylan pleaded obviousness for want of technical contribution and insufficiency on the basis of excessive claim breadth based on the same evidence. From a practical point of view, *AgrEvo* should probably be introduced as a stand-alone ground of invalidity to avoid a gap between traditional insufficiency and traditional (UK) obviousness.

## 'Downstream' Products

Sir Robin Jacob mentioned, in paragraph 8 of his judgment, the commercial question of what developers of 'downstream' products (themselves possibly being patentable in their own right) should pay by way of tribute to HGS because it has the 'master claim' to all Neutrokin- $\alpha$  antibodies. This is important as a number of companies do have such antibodies in the pipeline.

- HGS itself has developed a product (with GlaxoSmithKline) called belimumab, marketed as BENLYSTA. This drug is approved in the United States for the treatment of patients with active, autoantibody-positive Systemic Lupus Erythematosus and in Europe as an add-on therapy for adult patients with the same disease who still have a high degree of disease activity despite standard therapy. BENLYSTA is the first new lupus drug approved for more than 50 years. Clinical trials are ongoing for other indications, including *inter alia* treatment of Rheumatoid Arthritis.
- Lilly has a product in development called tabalumab (LY2127399). Phase III trial results for treatment of Systemic Lupus Erythematosus have been published, and there are ongoing clinical trials for treatment of Rheumatoid Arthritis and Multiple Myeloma.
- Merck Serono's product atacicept (originally developed by ZymoGenetics) is in clinical trials for treatment of *inter alia* Systemic Lupus Erythematosus, Rheumatoid Arthritis, and Optic Neuritis.
- Anthera's product blisibimod (originally developed by Amgen) is in clinical trials for treatment of Systemic Lupus Erythematosus.

Sir Robin referred, in passing, to the compulsory licence scheme under the Patents Act 1977 indicating, perhaps, his view that a high-level early-stage patent such as HGS's should not entitle its holder to seek substantial royalties or injunctions. This comment does not form part of the ratio of the Court of Appeal's decision but gives an indication of what the court may do should HGS seek to assert its patent in court proceedings.

A number of companies appear already to have entered into licences with HGS relating to the Neutrokin- $\alpha$  patent. The licensing agreement entered into between HGS and Biogen

14) [2012] EWHC 1848 (Pat), see further the Case Comment in Vol 12 Issue 5 BSLR 192-196.

which gave Biogen a royalty stream from BENLYSTA and which led to HGS withdrawing from its opposition of Biogen's EP 1 146 892 has been mentioned above. In addition, both Merck Serono and ZymoGenetics were originally opponents of the HGS Neutrokine- $\alpha$  patent, but both withdrew from the opposition in October 2007, presumably on agreeing a licence relating to their jointly developed product atacicept.

Companies that have not yet having reached settlements with HGS include Lilly (more on the ongoing dispute below) and also Teva, who are opposing HGS's follow-on patent which protects BENLYSTA.<sup>15</sup> The latter suggests that Teva have a biosimilar of BENLYSTA in development. So even with the completion of proceedings over the patentability of HGS's Neutrokine- $\alpha$  patent, there is plenty more scope for battle over Neutrokine- $\alpha$ -related patents.

### Further Court Proceedings in the United Kingdom: Supplementary Protection Certificates

The Court of Appeal's decision is not the end of the story even in relation to the HGS Neutrokine- $\alpha$  patent. Eli Lilly has brought further proceedings against HGS seeking a declaration that any SPC which might be granted to HGS in respect of the HGS Neutrokine- $\alpha$  patent based upon any marketing authorisation (MA) obtained by Lilly for its product tabalumab would be invalid.

Lilly is concerned that, if it was to be granted an MA for tabalumab before the HGS Neutrokine- $\alpha$  patent expires in October 2016, HGS as a holder of a basic patent which covers tabalumab (under, at least, claim 13) could be entitled to obtain an SPC based upon tabalumab. This would leave Lilly in the position either of having to pay a royalty to HGS for the duration of the remaining patent term and SPC term, or of being prevented from exploiting tabalumab at all.

In August 2012 HGS unsuccessfully sought to have Lilly's claim struck out as raising purely hypothetical questions and being subversive of the statutory procedure under which grant of and challenge to SPCs is to be made. Warren J concluded that the court had jurisdiction to entertain Lilly's

claim, and the powerful commercial reasons for Lilly bringing the claim outweighed all other factors, meaning that the court should exercise its discretion to hear the claim.<sup>16</sup>

In the same hearing, Lilly sought an immediate reference to the European Court of Justice on the interpretation of Article 3 of the SPC Regulation.<sup>17</sup> Two issues were raised:

- First, whether a holder of a basic patent can make an application for an SPC in reliance on an MA granted to a third party having no connection of any sort with that holder ('the third party SPC issue');
- Second, what express words need to be found in a basic patent in order to enable the grant of an SPC relating to an active ingredient within the scope of the patent ('the specification issue').

Warren J held that, on the third party SPC issue, the law is sufficiently clear to allow him to exercise its discretion to decline making a reference to the CJEU (although not necessarily *acte clair*, i.e. not so reasonably clear and free from doubt that a national court of last resort would not be obliged to make such a reference). Moreover, the judge saw the law as being against Lilly: there is no requirement that the holder of a basic patent and the holder of an MA be connected.

On the specification issue, Warren J referred to the earlier decisions of Arnold J in *Novartis Pharmaceuticals v MedImmune*<sup>18</sup> and the Court of Appeal in *Medeva v Comptroller General of Patents*<sup>19</sup> in holding that, despite the reasoning of the CJEU in the *Medeva* and *Queensland* cases<sup>20</sup>, the answer to this question remained unclear. At that time, Warren J declined to make an immediate reference to the CJEU, holding that only once a sufficient factual context was agreed or decided at a trial should questions be referred to the CJEU.

However, in a further decision handed down on 10 October 2012<sup>21</sup> and with the agreement of both parties, Warren J has now agreed to refer the specification issue to the CJEU. It is notable that, since Warren J's initial decision, Arnold J has made a reference to the CJEU on the same issue in *Actavis Group v Sanofi Pharma Bristol-Myers Squibb*<sup>22</sup>: "What are the

15) EP 1 294 769, upon which HGS have obtained a Supplementary Protection Certificate (SPC/GB12/005) based on BENLYSTA.

16) [2012] EWHC 2290 (Pat).

17) Council Regulation 469/2009.

18) [2012] EWHC 181 (Pat).

19) [2012] EWCA Civ 523.

20) Case C-322/10 *Medeva v Comptroller General of Patents*; Case C-630/10 *University of Queensland v Comptroller General of Patents*.

21) [2012] EWHC 2857 (Pat).

22) [2012] EWHC 2545 (Pat).

criteria for deciding whether ‘the product is protected by a basic patent in force’ in Article 3(a) of the Regulation?”

However, Warren J maintained his view that he should not make a reference in relation to the third party SPC issue, even though he had indicated in his earlier judgment that it would make sense to refer that issue at the same time as the specification issue to eliminate any possible uncertainty. Instead the judge ordered that proceedings in relation to the third party SPC issue alone should continue toward a trial to be listed by the end of 2013 (rejecting Lilly’s request that the trial of the third party SPC issue be expedited). The two issues have thus been bifurcated by the English court. The judge did recognize the possibility that a reference may need to be made on the third party SPC issue once the facts had been decided at trial, although his views on the clarity of the law on that issue are clear from both of his judgments.

So, although the main proceedings relating to the patent are complete (subject to Lilly’s application for permission to appeal to the Supreme Court), the SPC proceedings will now carry on in both the English court and at the CJEU, the two courts considering two different issues. The story, it seems, never quite comes to an end.

## Conclusions

Although the *Lilly v HGS* dispute is interesting from a legal perspective, it is even more intriguing when considered in the wider context.

There can be no argument that the discovery of Neutrokine- $\alpha$  has ultimately led to the development of a number of potentially blockbuster pharmaceutical products for largely ignored diseases such as lupus. The upholding of the HGS Neutrokine- $\alpha$  patent, particularly the commercially relevant claim 13, gives HGS a degree of control over all other companies working to develop pharmaceuticals related to that cytokine. Some companies, such as Biogen and Merck Serono, appear to have already agreed licences/cross-licences with HGS. Some, like Lilly and Teva, choose to fight on in the courts and at the EPO.

However, Neutrokine- $\alpha$  is not the end. It is perfectly possible that the same kind of situation could be repeated in the fast-developing innovative bioscience sector. The race is on to make discoveries and be the first to file a patent application. The line drawn by the UK courts seems to encourage earlier filing; it remains to be seen whether the consequences of *Lilly v HGS* will ultimately promote or stifle innovation and/or the benefits of pharmaceutical developments to patients.