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“An Error of Principle and Approach” – Birss LJ clarifies the law on breadth of claim and uncertainty insufficiency

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In undoubtedly one of the most important decisions of the year so far, on 24 August 2021, the English Court of Appeal handed down its judgment in *FibroGen v Akebia* (*FibroGen Inc v Akebia Therapeutics Inc [2021] EWCA Civ 1279*), partially allowing FibroGen's appeal, and so finding one of the 'Family A' patents, EP 823, valid and infringed. The judgment is of particular interest for its approach to insufficiency, with the very experienced patents judge, Arnold LJ being overturned on two separate grounds of insufficiency. The judgment aligns UK law on breadth of claim insufficiency with the decision of the German Supreme Court in *Dipeptidyl-Peptidase-Inhibitoren* from 2013 and is more favourable to patent holders than the first instance decision.

FibroGen holds six patents that relate to the use of hypoxia-inducible factor prolyl hydroxylase ("**HIF-PH**") inhibitors for the treatment of anaemia. These patents form two families; Family A (claiming an earliest priority date of 2001) relates to the treatment of chronic kidney disease (CKD) anaemia, whilst Family B (claiming priority from 2004) relates to the treatment of anaemia of chronic disease (ACD). Both families contain broad claims to classes of compounds, and a narrow sub-claim to the same individual compound.

FibroGen has exclusively licensed its patents in the UK to Astellas. Astellas has obtained an MA for its HIF-PH inhibitor product, roxadustat. Akebia and Otsuka (together "**Akebia**") also have a HIF-PH inhibitor, vadadustat, which is in clinical trials for the treatment of CKD anaemia. Akebia applied to revoke the patents, and Astellas brought a claim for infringement, including *quia timet* infringement of the ACD-based Family B patents, with FibroGen joined as patentee.

The case raised a significant number of issues relating to validity and infringement. At first instance, Arnold LJ (sitting in the Patents Court) had held (*Akebia Therapeutics Inc v FibroGen, Inc [2020] EWHC 866 (Pat)*) that:

1. all Family A claims were inventive over the cited prior art, Epstein, and thus the claim to an individual compound was valid;
2. the Family A class of compound claims were implausible and could not be performed across their scope without undue burden, and thus were invalid for insufficiency;
3. Family A claims including the feature "a structural mimetic of 2-oxoglutarate" were uncertain and thus invalid for insufficiency;
4. the Family A single compound claim was not infringed by vadadustat under the doctrine of equivalents;
5. the Family A class of compound claims were infringed by vadadustat;
6. all Family B claims were invalid over WO 997, the published application for the Family A patents; and
7. there was no threat of infringement of the Family B claims.

Therefore, as the only valid claim (the single compound claim in Family A) was not infringed, Akebia emerged as the commercial victor. FibroGen challenged findings ii), iii) and vi) on appeal, and Akebia challenged finding v) by way of respondent's notice.

The lead judgment was given by Birss LJ, with an additional judgment on the insufficiency issue provided by Sir Christopher Floyd. Philips LJ agreed with both judgments.

Insufficiency of Family A claims – Plausibility and Undue Burden

Birss LJ considered there to be two relevant claims, and broke them down according to the table below (the final column is the authors'). This breakdown is very useful in understanding the Judge's analysis and conclusions. As readers will note, Claim 8A is a Swiss form use claim, whereas claim 19A is an EPC 2000 product for use claim, but nothing turned on that distinction.

Integer	Claim 8A of EP 823	Claim 19A of EP 823	Type of Feature
A	Use of a heterocyclic carboxamide compound selected from the group consisting of	A heterocyclic carboxamide compound selected from the group consisting of	Structural
B	pyridine carboxamides, quinoline carboxamides, isoquinoline carboxamides, cinnoline carboxamides, and beta-carboline carboxamides	pyridine carboxamides, quinoline carboxamides, isoquinoline carboxamides, cinnoline carboxamides, and betacarboline carboxamides	Structural
C	that inhibits hypoxia inducible factor (HIF) prolyl hydroxylase enzyme activity	that inhibits hypoxia inducible factor (HIF) prolyl hydroxylase enzyme activity	Functional
D	in the manufacture of a medicament for	for use in	
E	increasing endogenous erythropoietin	increasing endogenous erythropoietin	Functional
F	in the prevention, pretreatment, or treatment of anemia associated with kidney disease	in the prevention, pretreatment, or treatment of anemia associated with kidney disease	
G	wherein the anemia is associated with chronic kidney disease.	wherein the anemia is associated with chronic kidney disease,	
H	–	wherein the compound is a compound of Formula (I) wherein [*chemical Markush formula*]	Structural

As noted in the table above, Birss LJ characterised integers A and B (and H of claim 19A) as structural features, and integers C and E as functional features.

At first instance, Arnold LJ identified a two stage approach to identifying if the claims are sufficient: (i) whether the claims were plausible across their scope, and (ii) whether the skilled person could perform the invention across the scope of the claims without undue burden. The inventive concept of the patent is that HIF-PH inhibitors could be used to increase the production of endogenous erythropoietin to the extent required for the prevention, pre-treatment, or treatment of anaemia. Whilst this concept had been demonstrated for five compounds by the experiments and associated data disclosed in the specification of the patent, Arnold LJ held that it was implausible that substantially all the compounds which satisfy the structural features of the claims would have the required therapeutic efficacy. Arnold LJ defined the test for passing the second hurdle as "*what is required is that the skilled person or team must be able to identify substantially all compounds covered by the claim without undue burden*". As the claims covered an enormous number (estimated at 10^{183}) of compounds, it was impossible to meet this test, and the claims were insufficient.

Birss LJ held that Arnold LJ had construed the claims incorrectly and applied the wrong test. He considered the patent to claim a principle of general application. The UK position on such claims was most recently set out by Kitchin LJ (as he then was) in *Regeneron v Genentech* [2013] EWCA Civ 93: "*it is permissible to define an invention using general terms provided the patent discloses a principle of general application in the sense that it can reasonably be expected the invention will work with anything falling within the scope of these terms*". Birss LJ considered that whether a claim of general application is plausible requires a three step test:

i) what falls within the scope of the claimed class?
ii) what it means to say that the invention works?
iii) is it possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim?

Thus, as Birss LJ observed, in a paradigm case of a Swiss-type claim to the use of a class of compounds defined in a Markush formula to treat a disease, steps i) and ii) will be relatively straight-forward to answer – the compounds contemplated by the Markush formula will fall within the scope of the claimed class and the invention will be said to work if the compounds treat the claimed disease. Step iii) would involve the assessment of whether it is possible to make a reasonable prediction that substantially all the compounds in the claimed class will work to treat the disease. This will depend on the evidence before the Court. The Judge then noted that in addition to the paradigm Swiss-type claims, there were patents with claims containing functional limitations rather than structural limitations and also patents with claims containing both structural and functional limitations but the same three step test should apply in each case.

Birss LJ held that the trial judge had erred in holding that the claim covered all compounds contemplated by the structural features of the claim and that the correct approach to step i) was that it was directed to compounds possessing the relevant structural properties <u>and</u> which satisfy the relevant functional features (i.e. properties C and E as set out in the table above).

In relation to undue burden, Birss LJ turned to *inter alia* the judgment of the German Supreme Court in *Dipeptidyl-Peptidase-Inhibitoren*. The patent in *Dipeptidyl* claimed the use of inhibitors of dipeptidyl peptidase IV ("**DPP-IV**") for lowering blood sugar levels. The German Supreme Court found the claim sufficient, as the patent provided a biochemical rationale as to why it was credible that compounds which inhibited DPP-IV would lower blood sugar. Provided there was no undue burden in identifying compounds which satisfied the DPP-IV inhibition aspect, then such a claim would not be insufficient; it did not matter that the claim covered compounds which had not yet been invented.

Applying this reasoning, Birss LJ held that when assessing a claim with a functional feature or with a mix of structural and functional features, it must be possible, without undue burden, both to identify compounds which satisfy the relevant test and to find out whether any given compound satisfies the test. However, it was not necessary as a matter of law to establish that the skilled person can identify all or substantially all the compounds which satisfy the test.

Given the finding that it was not necessary for the skilled person to be able to identify substantially all compounds falling within the claim, the question remained, how many compounds must the skilled person be able to identify? To assess this issue the Judge considered it helpful to apply a further two-stage test: (i) can the skilled person identify some further useful compounds beyond those named in the patent which are within the claimed class (but with no requirement to identify substantially all those compounds); and (ii) can the skilled person work substantially anywhere within the whole claim?

Turning to the facts of the case Birss LJ held that compounds satisfying structural features A and B (and H) *as well as* functional features C and E fell within the scope of the claimed class. The compounds are for the treatment of CKD (as required by features F and G). From this, the question of step iii) becomes whether it was plausible that compounds which satisfy structural features A and B, *and* functional features C and E, will be useful to treat CKD. As the patent shows that inhibition of HIF-PH can stimulate EPO production at sufficient levels to potentially treat CKD, the claims were plausible.

In relation to undue burden, Birss LJ considered the evidence at first instance. This showed that although it would be a great deal of work, the skilled team, via routine medicinal chemistry work, would be able to find some compounds which were effective. Such work would not constitute an undue burden. Further, although some compounds would be unstable, insoluble or have poor pharmacokinetic properties, this could not undermine the overall conclusion that some useful compounds would be found.

Accordingly, the Family A class of compound claims were considered to be sufficient, and Arnold J's ruling was overturned.

Given the importance of this issue, and the fact that Arnold LJ was being overturned, Sir Christopher Floyd also gave a short judgment, supporting that of Birss LJ.

Insufficiency of Family A claims – Uncertainty

Some other Family A claims required the inhibitor to be "a structural mimetic of 2-oxoglutarate ("**2-OG**")". 2-OG is a co-factor to HIF-PH, and required for its catalytic activity. If a compound is structurally similar to 2-OG it may be able to fit into the binding pocket and prevent HIF-PH from working. Therefore, this claim integer puts another functional limitation on the inhibitor; according to the evidence at first instance, it competes for the 2-OG binding pocket on HIF-PH.

Arnold LJ considered this integer to be conceptually uncertain, as the skilled person would be unable to determine what criterion and test to apply to distinguish between a compound that was a structural mimetic, and one which was not.

Birss LJ disagreed – the skilled person could easily distinguish between competitive and non-competitive inhibitors using well-established enzyme kinetics assays. Akebia also argued that the potency threshold for establishing a competitive inhibitor was unclear. However this fell into the fuzzy boundary (where assessing infringement at the edge of the claim was difficult), rather than true conceptual uncertainty. To demonstrate this, vadadustat infringed this integer, a finding that Akebia had not challenged on appeal.

Infringement of Family A claims

The infringement of the Family A class of compound claims was decided by the interpretation of the Markush formula. Akebia challenged the finding of Arnold LJ that vadadustat fell within the Markush formula, but Birss LJ could not fault Arnold LJ's reasoning, and the finding of infringement was maintained.

Obviousness of Family B claims

At first instance, the Family B claims were found obvious over WO 997, the published application for the Family A patents. At the start of his analysis, Birss LJ noted that findings on obviousness are rarely overturned as the appellant must show that there was an error of principle. FibroGen made five points on appeal, raising, *inter alia*, issues relating to the 'obvious to try' doctrine. However, true to his prediction at the start of the analysis, Birss LJ found that there had been no error of principle, and maintained the finding of invalidity.

Conclusion

With the findings on sufficiency overturned, at least EP 823 in Family A was found to be valid and infringed.

Comment

The patents held by FibroGen were of the sort commonly litigated in the UK and the rest of Europe. It is often the case that claims of medical use patents contain structural and/or functional features which make the scope of the claims broader than the specific compounds disclosed in the patent. Quite often it may be that at the time of filing the application for the patent, the innovator has identified a class of compounds which appear likely, based on the results of *in vitro* or *in vivo* tests, to possess the relevant properties and will have data from those tests for a small number of compounds in the class. However the innovator might not yet have identified the golden goose among the gaggle, so to speak. Under UK law as applied at first instance in *FibroGen*, this would likely have been a problem for the patentee because its broad claims to the class would most likely be held to be unduly broad and its narrow claims might not cover either its or a competitor's product, particularly if the product was developed some time after the patent filing and so would inevitably not have been specifically disclosed in the patent application. The decision from the Court of Appeal means that provided the patentee has disclosed and claimed a class of compounds with a unifying principle, the potential benefits of which can be assessed by reference to functional assays within the patent or the wider art, broad claims covering compounds not disclosed in the application or even contemplated at the time of filing will likely not be held to be unduly broad.

In relation to uncertainty insufficiency, it now appears that it will generally be exceptional cases only that fall on this ground. In *FibroGen*, Birss LJ took the opportunity to align his comments in the *Unwired Planet* [2016] EWHC 576 (Pat) case with those of Floyd LJ in *Anan v Neo* [2019] EWCA Civ 1646: in short, a finding of infringement does not *per se* preclude a finding of conceptual uncertainty but it ought to cause the court to examine what the alleged uncertainty amounts to.

It is not yet known if Akebia and Otsuka will seek permission to appeal to the Supreme Court. Given that Lord Kitchin's 2013 decision (as a Court of Appeal judge) in *Regeneron v Genentech* [2013] RPC 28 was the focus of much attention from the Court of Appeal, and also that several of the UK's most respected and experienced patent judges are in apparent disagreement over the central issues, the authors suspect that

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