FIBROGEN v AKEBIA: A CLASH OF PRINCIPLES BETWEEN THE JUDGES IN THE COURT OF APPEAL

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The Court of Appeal, led by Birss LJ, has overruled[1] the approach of Arnold LJ in the Patents Court[2] to construction of patent claims that are limited by functional features. The Court of Appeal has applied a more lenient and patentee-friendly construction to such claims, with the effect that they are considerably more likely to satisfy the requirement in the Patents Act 1977 that the specification discloses the invention clearly enough and completely enough for it to be performed by a person skilled in the art.

In this article, rather than attempting to summarise each technical and legal issue raised in the case, the author seeks to produce a 'quick read', whereby the principles decided which are of general applicability to the assessment of sufficiency of claims limited by functional requirements can be understood without having to delve into the detail of the specific patents under consideration.

Unusually, Arnold LJ was sitting as a first instance judge in the decision which has been overturned. The decision therefore puts the two patent specialists in the Court of Appeal at odds as to construction of such patents. The implications of this will also be considered in this article.

Background

The case concerns a family of six patents owned by FibroGen and licensed exclusively to Astellas. The key principles in the case can be understood by looking at two of the claims from a single patent, EP(UK)1,463,823. The breakdown of the claims, as set out by Birss LJ, is shown in Table 1 (the categorisation of the integers in the right-hand column is as proposed by Birss LJ, and will be explained later in the article).

As can be seen, the claims are substantially similar, with claim 8A being drafted in the so-called 'Swiss form' and claim 19A in the EPC2000 product for use form. The parties were agreed that nothing turned on the differences between the claims, with which Birss LJ agreed.

The patent specification provides details of five specific compounds, falling within the claims, which have the desired therapeutic effect. However, the structural features specified in integers A and B define an extremely large class of compounds: Arnold LJ at first instance stated that it covers around 10^{183} compounds, and Birss LJ on appeal described it as an 'essentially infinitely large class'. It is worth noting that current estimates are that there are between 10^{78} and 10^{82} atoms in the known, observable universe, and therefore a number many orders of magnitude larger than that is, as Birss LJ says, effectively infinitely large for practical purposes.

Integers C and E introduce two functional limitations. The technical detail is interesting, and is set out in detail in Arnold LJ's judgment, and more briefly in Birss LJ's judgment.

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1) [2021] EWCA Civ 1279.
2) [2020] EWHC 866 (Pat).

Table 1

Integer	Claim 8A	Claim 19A	Categorisation
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	Step One Functional
D	in the manufacture of a medicament for	for use in	
E	increasing endogenous erythropoietin	increasing endogenous erythropoietin	Step One Functional
F	in the prevention, pre-treatment, or treatment of anaemia associated with kidney disease	in the prevention, pre-treatment, or treatment of anaemia associated with kidney disease	Step Two Functional
G	wherein the anaemia is associated with chronic kidney disease.	wherein the anaemia is associated with chronic kidney disease,	Step Two Functional
H	–	wherein the compound is a compound of Formula (I) wherein [Markush formula]	Structural

However, it is not necessary to understand it at anything other than a very high level in order to glean the underlying principles. At a very high level, it is only necessary to understand that:

- Anaemia is a disease in which there is a deficiency in the number of red blood cells.
- Erythropoietin is a naturally occurring protein which stimulates production of red blood cells.
- Hypoxia inducible factor (HIF) causes erythropoietin to be produced, which in turn causes more production of red blood cells.
- HIF prolyl hydroxylase enzyme (HIF-PH) is an enzyme which breaks down HIF.
- Consequently, by inhibiting HIF-PH, HIF levels are increased, erythropoietin levels are increased, and more red blood cells are produced.

Integers F and G define the disease to be treated – anaemia associated with chronic kidney disease.

Finally, integer H, which appears only in claim 19A, sets out a type of chemical formula called a Markush formula. The details of it were relevant to the issue of infringement, but are not relevant to sufficiency and will not be further discussed in this article.

Akebia contended that the patent claims were insufficient on three grounds. First, the breadth of each claim was excessive because it was not plausible that substantially all the compounds falling within it would have the desired therapeutic effect. Secondly, the breadth of each claim was excessive because the claims cannot be performed across their scope without undue burden. There was a third ground which relates to uncertainty of a term – 'structural mimetic of 2-oxoglutarate' – which appears in certain of the claims. This ground does not raise the matters of general importance raised by the first two grounds, and will not be discussed further in this article.

Decision at First Instance

At first instance, Arnold LJ proposed a two-stage enquiry as to sufficiency: first, is the claim plausible, and, secondly, could the skilled person identify substantially all compounds covered by the claim without undue burden?

He held that the claims are insufficient for lack of plausibility. In essence, as Arnold LJ saw it:

> *… the patent is implicitly promising that substantially all compounds which satisfy the structural definitions in the claims in issue will have the claimed therapeutic efficacy. Otherwise, the skilled team would be faced with a situation where the structural definition covers around 10^{183} compounds (or a little less or even more), but the specification only demonstrates that five compounds, namely Compounds C, E, F, J and K, satisfy the criteria for therapeutic efficacy. That would amount to no more than an invitation to the skilled team to find the other compounds covered by the claim which work. It would not involve an inventive step, because it would not solve the technical problem of identifying compounds which have the desired activity, and it would not sufficiently disclose the invention, because it would leave most of the work to the reader.*[3]

Furthermore, and irrespective of the above, he held that the claims are insufficient on the undue burden basis as well:

> *Taking all of the evidence into account, the conclusion I reach is that the invention cannot be performed across the scope of the claims in issue without undue burden. It would require a substantial research project to identify any compounds other than those specifically identified in the specification which met the criteria for efficacy, and success would not be guaranteed. While it is probable that, if sufficient resources were thrown at the project, the skilled medicinal chemist would be able to identify some compounds falling within Formula (I) (and more which constituted Carboxamides) which were effective, they would not be able even in many lifetimes of sustained effort to make and test more than a tiny fraction of such compounds, and a substantial proportion either could not be made or would not work. This is not only setting the skilled team a research project and claiming the results, it is a never-ending one. Accordingly, on this ground also I conclude that the claims in issue are insufficient.*[4]

To understand Arnold LJ's decision, and to compare it to Birss LJ's decision, it will be helpful to consider the following simplified hypothetical patent claim: 'a compound falling within structural definition X, which displays biological activity Y, for use in treating disease Z'.

In essence, Arnold LJ construes such a claim, for the purpose of assessing sufficiency, as a claim that substantially all compounds within structural definition X will have the desired therapeutic effect against disease Z. Arnold LJ does not regard the middle integer – 'which displays biological activity Y' – as having any relevance to the question of sufficiency (the reason for Arnold LJ's view will be explained in the 'Discussion' section below).

Clearly, unless the class of compounds falling within structural definition X is fairly small, the skilled person is unlikely to consider it plausible that substantially all will have the claimed therapeutic efficacy, and any such claim will therefore be invalid for want of plausibility. Similarly, unless either the class of compounds is small, or there is some principled means, taught by the patent, of identifying the specific compounds likely to have the desired therapeutic effect, such a claim is likely to be insufficient on the undue burden basis as well.

Decision on Appeal

Early in his judgment Birss LJ gives a foretaste of his reasoning and his disagreement with Arnold LJ:

> *Returning to the claim, feature C requires that the compound must inhibit HIF-PH. There is an important issue of claim construction which arises here. The*

3) Paragraph 376.

4) Paragraph 399.

> *question can be posed by asking – what compounds are within the claim? Is the patent (and the claim) directed to each and every heterocyclic carboxamide of the claimed structure and then, by feature C, asserting that they will be inhibitors of HIF-PH? Or is the patent here only claiming those heterocyclic carboxamides of the claimed structure which are themselves inhibitors of HIF-PH? Looking ahead, if the right construction of the patent is the latter, then a compound which is a heterocyclic carboxamide of the claimed structure but is not an inhibitor of HIF-PH is not an example of a claimed compound, nor is its existence evidence that part of what is claimed does not work.*[5]

Using the hypothetical patent claim example set out in the above section, this can be simplified further. Birss LJ's two alternatives are:

1. Does the patent claim that each and every compound falling within structural definition X *will* display biological activity Y?

2. Or does the patent claim only those compounds falling within structural definition X which *do actually* display biological activity Y?

The first alternative is that preferred by Arnold LJ. The second alternative would clearly be far more likely to satisfy the requirements of plausibility and undue burden, provided of course that the skilled person would consider it plausible that there is a connection between biological activity Y and treatment of disease Z.

Birss LJ provides a helpful and detailed account of the English decisions relevant to the law of sufficiency,[6] including a review of the principles established in *Warner-Lambert v Generics* and *Regeneron v Genentech*. At paragraph 53, he proposes a three-step test for assessing plausibility (which he prefers to call 'reasonable prediction'):

> *First one must identify what it is which falls within the scope of the claimed class. Second one must determine what it means to say that the invention works. In other words what is it for? Once you know those two things, the third step can be taken: to answer the question whether it is possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim.*

At paragraph 56, he introduces the concept of two types of functional features for determining scope of a claim:

- 'step one functional features', such as 'inhibits hypoxia inducible factor (HIF) prolyl hydroxylase enzyme activity', and
- 'step two functional features', such as 'treatment of anaemia associated with kidney disease'.

In essence, 'step one functional features' are functional features that delineate the claim (and hence are relevant to the first step of the above test), whereas 'step two functional features' relate to the ultimate purpose for which the compounds are to be used (and hence are relevant to the second step). Using the hypothetical claim set out above, 'displays biological activity Y' would be a step one functional feature, whereas 'treating disease Z' would be a step two functional feature.

Birss LJ's dual categorisation of functional features is critical to understanding the decision in this case. In fact, as explained in the 'Discussion' section below, it is the key factor which led him to overturn Arnold LJ's decision.

At paragraphs 66 to 77, Birss LJ considers a decision of the German Supreme Court in *Dipeptidyl-Peptidase-Inhibitoren*. In that decision, the patent claim in question was:

1. The use of inhibitors of the enzyme activity of dipeptidyl peptidase IV (DP IV)

2. for lowering the blood glucose level below the glucose concentration characteristic of hyperglycaemia in the serum of mammals with diabetes mellitus.

It was therefore in the form 'Use of compounds with biological effect Y for treatment of disease Z', that is, in contrast to FibroGen's patent claims, it did not include a structural

5) At paragraph 21.

6) At paragraphs 49 to 65.

limitation at all. Again, applying Birss LJ's categorisation of functional features, 'inhibitors of the enzyme activity of dipeptidyl peptidase IV' would be a step one functional feature, and 'lowering the blood glucose level below the glucose concentration characteristic of hyperglycaemia in the serum of mammals with diabetes mellitus' would be a step two functional feature.

The German Supreme Court upheld the validity of the claim, and Birss LJ's characterisation of its reasoning is set out at paragraph 73:

> *… the BGH is reiterating the important point that it is not acceptable simply to claim 'everything which works' without telling the skilled person how to achieve success. However the BGH clearly did not think that that was what was happening in the case before them, and it is easy to see why not. A claim simply to the use of any compound for achieving the therapeutic efficacy feature would fall foul of that principle. That would be a claim to anything which satisfied the step two functional feature, in other words a claim to everything which works. However a claim to the use of any compound which has the step one functional feature (of being a DP IV inhibitor) for that step two therapeutic purpose does not simply claim everything which works. The skilled person must be able to identify such compounds with the step one functional feature without undue burden, but that is a different issue. Moreover the fact the claim would cover compounds which may not have been invented yet is not a problem either.*

Finally, at paragraphs 78 to 94, Birss LJ reviews the relevant EPO decisions. He concludes at paragraph 95 that most of the EPO decisions do not support Arnold LJ's approach. Instead:

> *The right test is as follows. If one has a claim with a functional feature which defines the claimed compounds, or a mix of such 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 is not necessary as a matter of law, for sufficiency (or for* Agrevo*), simply because a claim contains functional features (or a mix of functional and structural features) to establish that the skilled person can identify all or substantially all the compounds which satisfy the test.*

Birss LJ therefore proposes a two-step test for assessing undue burden:

1. It must be possible for the skilled person, without undue burden, to identify *some* compounds beyond those named in the patent, which are within the claimed class and therefore are likely to have therapeutic efficacy.

2. Furthermore, it must also be possible for the skilled person to work substantially anywhere within the whole claim – it must be possible for the skilled person, given any sensible compound within the structural class (or substantially any), to apply the tests without undue burden and work out if it is a claimed compound.

Pausing for a moment, and turning back to the hypothetical patent claim posited above ('a compound falling within structural definition X, which displays biological activity Y, for use in treating disease Z'), Birss LJ construes it, for the purpose of assessing sufficiency, as a claim that substantially all compounds within structural definition X *and* which display biological effect Y will have desired therapeutic effect against disease Z. It is permissible, therefore, to take into account 'step one functional features' when determining the scope of the claim for assessment of sufficiency, but not the 'step two functional features' – taking the latter into account would in effect allow the patentee to 'claim everything which works'.[7]

Having established the above, Birss LJ turned to Arnold LJ's decisions on plausibility and undue burden. With regard to plausibility, he held that Arnold LJ had essentially asked himself the wrong question. It was not correct to ask whether it is plausible that substantially all the compounds which satisfy the structural definitions will have the claimed therapeutic efficacy. Rather, the judge should have asked whether it is plausible that compounds which satisfy *both* the

7) Paragraph 73.

structural definitions and the step one functional features will have the claimed therapeutic activity. On Arnold LJ's findings on the basis of the expert evidence before him, the answer to that correct question is 'yes'. Therefore, Birss LJ held that the patent claims satisfy the plausibility requirement.

As for undue burden, Birss LJ was satisfied that:

> *… although it would be a great deal of work, the skilled team would be able to find some compounds which were effective. The judgment does not expressly state that this result would be reached without undue burden but I believe that is the only answer. It would take a great deal of work but it would be routine for the medicinal chemist and iterative in nature.*[8]

Additionally, on the evidence, there was no indication that there are particular regions of the claim scope which cannot be tested, and accordingly the second requirement identified by Birss LJ is also satisfied.

Discussion

As a first point, it is worth noting that a reader will look in vain in the Patents Act 1977 (or the EPC for that matter) to find references to plausibility, undue burden or even the word 'sufficiency'. As pointed out by Birss LJ at paragraph 49 of his judgment, the 1977 Act requires only that to be valid the specification must disclose the invention 'clearly enough and completely enough for it to be performed by a person skilled in the art'. This corresponds to Article 83 EPC. All the concepts mentioned above are judge-made, developed in response to specific issues that have arisen over the years.

By way of recap, Birss LJ proposes a three-step test for assessing plausibility/reasonable prediction:

1. Identify what it is which falls within the scope of the claimed class, taking into account structural and step one functional features.

2. Determine what it means to say that the invention works. In other words what is it for? The step two functional features will be determinative of this step.

3. Ask whether it is possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim.

For assessing undue burden, he proposes the following two-step approach:

1. Can the skilled person, without undue burden, identify some compounds beyond those named in the patent, which are within the claimed class and therefore are likely to have therapeutic efficacy?

2. Furthermore, can the skilled person work substantially anywhere within the whole claim – is it possible for the skilled person, given any sensible compound within the structural class (or substantially any), to apply the tests without undue burden and work out if it is a claimed compound?

Why, then, did Birss LJ reach such a dramatically different conclusion to Arnold LJ? The reason can be found in paragraphs 369 to 381 of Arnold LJ's judgment, which merit close reading. In essence, though, Arnold LJ considered that he was bound by the Court of Appeal's decision in *Idenix v Gilead*,[9] in which a decision of his in the Patents Court[10] was upheld. In *Idenix*, the patent claim in question was on its face a pure compound claim based on a Markush formula which embraced a very large number of compounds. The parties agreed at trial, however, that the validity of the claim should be assessed on the basis that it was to be construed as a claim to compounds which had a particular therapeutic effect (specifically, anti-*Flaviviridae* activity, *Flaviviridae* being a type of RNA virus). Arnold J (as he then was) held the claim to be insufficient for want of plausibility, as he put it:

> *Otherwise the patentee would have been saying, in effect, ' I claim those compounds which are among the billions covered by the structural definition which happen to have anti-*Flaviviridae *activity, but I make no promise that any of them do, and you, dear reader, can go and find out which if any do have such activity'. That would not have involved an inventive step, because it would not have solved the technical*

8) Paragraph 142.

9) [2016] EWCA Civ 1089.

10) [2014] EWHC 3916 (Pat).

> *problem of providing compounds which did have anti-*Flaviviridae *activity. Equally, it would have meant that the specification did not sufficiently disclose the invention, because it was leaving the task of finding compounds which had anti-*Flaviviridae *activity to the reader.*

The Court of Appeal upheld that reasoning.

Birss LJ has not sought to overturn *Idenix*, but rather has distinguished it by categorising functional features into step one and step two functional features. Using that terminology, the feature in *Idenix* would be a step two functional feature, and hence cannot be used to limit the scope of the claim for sufficiency purposes. Presumably, had the claim in *Idenix* been in the form 'a compound falling within structural definition X, which inhibits protein Y, for use in treating *Flaviviridae* infections', Birss LJ would have regarded the requirement 'which inhibits protein Y' as a step one functional feature. He would therefore have regarded the claim as being potentially valid, provided that protein Y is associated with *Flaviviridae* and the skilled person would regard it as plausible that a protein Y inhibitor will display anti-*Flaviviridae* activity.

Conclusion

In the author's view, the disagreement between Arnold LJ and Birss LJ, whilst one of principle, is ultimately a matter of policy. Should the courts take account of the difficulties faced by a patentee who has developed a new class of therapeutic compounds, identified a small number of specific compounds within the class which display therapeutic effect, but seeks a wider degree of protection than those specific compounds (Birss LJ's approach)? Or should they resist efforts by patentees to posit a line of research for others to undertake, the fruits of which the patentee then seeks to claim (Arnold LJ's approach)? There are of course pros and cons to both approaches, and whereas the pharmaceutical industry may welcome the wider protection provided by Birss LJ's approach, they may also be mindful of the uncertainty it produces.

In any case, however, this is unlikely to be the last word on the subject, for at least two reasons. First, Birss LJ's categorisation of functional features into two categories is likely to lead to disputes. As Birss LJ said, 'It will be a matter of construction to work out what sort of functional features one is dealing with'.[11] The author can envisage scenarios in which the categorisation is less straightforward than in this instance, which will therefore require determination by the court.

More fundamentally, though, it is apparent that there is a substantial divergence of approach on this important issue between the two patent specialists in the Court of Appeal. The pathway of the case was unusual, with Arnold LJ hearing the case at first instance despite already being a Court of Appeal judge. Inevitably, therefore, when the case reached the Court of Appeal, Arnold LJ was precluded from participating, meaning that Birss LJ's approach prevailed. Under the English courts' rules of precedent, Birss LJ's approach will be binding on Arnold LJ (should another similar case be appealed to the Court of Appeal), unless Arnold LJ can establish one of the exceptions to the rule that the Court of Appeal binds itself.[12]

In the author's view, it is somewhat unfortunate that both judges were unable to contribute to the decision. The author understands that whereas the Court of Appeal refused permission to appeal, permission has now been sought directly from the Supreme Court, and the author hopes that the Supreme Court will agree to consider this dispute (or another future case in which the same issue arises), in order to provide a definitive ruling on the issue.

11) At paragraph 56.

12) These are:

1. Where the decision of the Court of Appeal conflicts with a later decision of the Supreme Court the Court of Appeal must follow the Supreme Court;
2. Where there are two earlier conflicting decisions of the Court of Appeal then the later Court of Appeal in a third case must choose between them;
3. Where an earlier decision of the Court of Appeal was made *per incuriam*, that is, the earlier Court of Appeal overlooked something that was binding on it such as a statute, the later Court of Appeal is not bound to follow its earlier decision.