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Plausibility post G2/21 – Apixaban in the UK

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On 4 May 2023, a mere two weeks after the conclusion of the hearing, the Court of Appeal handed down its decision in *Sandoz and Teva v BMS*. The appeal decision is centred on the question of plausibility and comes hot on the heels of the Enlarged Board of Appeal's decision in *G 2/21*. Indeed, it is the first time that the Enlarged Board of Appeal's decision has been considered in an English judgment. As such, it is of great relevance to practitioners interested in the evolution of this legal concept.

The facts

BMS's patent (EP (UK) 1 427 415 B1, the "**Patent**"), which benefits from a SPC, is titled "*Lactam-containing compounds and derivatives thereof as Factor Xa Inhibitors*" and claims a compound called apixaban. Claim 1 of the patent as granted was to the compound *per se*. Claim 7 is to the use of apixaban for treating a thromboembolic disorder. Apixaban is a factor Xa inhibitor marketed by BMS to treat thromboembolic disorders. Sandoz and Teva argued that the Patent was invalid for lack of inventive step and insufficiency as the Patent did not make it plausible that apixaban would have any useful factor Xa inhibitory activity. The parties agreed that plausibility should be assessed by reference to the application for the Patent (the "**Application**") as if the Patent as granted rendered the claims plausible but the Application did not, then the Patent would be invalid for added matter.

The Application discloses a large number of compounds as "*Preferred Embodiments*", by way of Markush formulae and lists of compounds. Apixaban is specifically disclosed as one of 74 compounds in one of the embodiments and one of the claims. Apixaban was also one of 140 examples where synthesis data was provided (there were many thousands of representative examples). Importantly, the section on the synthesis of apixaban discloses that 3.5 g was produced and that a double-crystallisation purification was performed.

The Application contains various statements of utility. In particular, it states that the compounds of the invention "*are inhibitors of factor Xa*" and that the effectiveness of compounds as factor Xa inhibitors "*was determined*" by means of a particular assay. The Application does not contain any specific data for any one compound. However, it does state, *inter alia*, that "*Using the methodology as described above, a number of compounds of the present invention were found to exhibit a K_i of ? 10 µM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.*"

At first instance, Meade J held that the Patent was invalid for lack of plausibility and lack of technical contribution over the prior art.

BMS' grounds of appeal

Lord Justice Arnold gave the leading decision and summarised BMS' grounds of appeal as being that Meade J:

1. Erred in law because, in the case of a claim to a single chemical compound, it is sufficient that the specification discloses the structure of the compound and a method of synthesis and contains an assertion of potential utility for the compound, provided that that assertion is not manifestly speculative or wrong – the specification need not make it plausible that the compound is useful.
2. Erred in law because he applied the standard of plausibility laid down by the majority in *Warner-Lambert* when he should have applied the minority's standard, or the standard of the majority but less strictly.
3. Erred in law because he wrongly held that it was not enough for the specification to encourage the skilled person to test the efficacy of the claimed compound and to identify simple tests which the skilled person could carry out for that purpose and which, if carried out, would confirm that the compound was likely to have the efficacy claimed for it.
4. Erred in law or principle because he failed to stand back and consider whether the claimed invention fulfilled the "*patent bargain*".
5. Erred in principle because he should have held that the Application contained an implicit disclosure that apixaban had a nanomolar K_i against factor Xa or had a K_i which made it suitable for therapeutic use (which was found at first instance to be CGK to require a nanomolar K_i, making the points essentially the same).
6. Was wrong to hold that the disclosure of two particular sections in the Application taken together did not make it plausible that apixaban was an effective factor Xa inhibitor.

The Court of Appeal's findings

Lord Justice Arnold first dealt with grounds 1-4 together on the basis that they were essentially alternatives. Rejecting all four grounds, he confirmed that the Court of Appeal is bound by the majority judgment in *Warner-Lambert v Actavis* (the Supreme Court's decision in the pregabalin case). He disagreed with BMS' argument that the decision in *Warner-Lambert* was not binding on compound patent claims. The Court found that whilst the concept of plausibility may have originated from claims covering broad classes of compounds, and though *Warner-Lambert* concerned a second medical use claim, it applies equally to claims to a single compound *per se*, as seen in the case law relied upon by the Supreme Court. Notably, the G2/21 decision from the Enlarged Board of Appeal (the "**EBA**") also considered existing EPO case law where plausibility was addressed for a product claim. The Court went on to note that all these types of claims are united by the same underlying principle – namely that the scope of a patent monopoly must be justified by the patentee's technical contribution to the art. On this, the judge noted that it does not matter if the technical effect is an explicit feature of the claim language, or whether the claim is to a compound *per se* and the assertion of utility is found in the specification only. That is, there is "*no invention in merely identifying a new chemical compound, invention can only lie in identifying the utility*." Further, the patent bargain requires sufficient disclosure in the specification and subsequent data cannot be a substitute to such disclosure.

On ground 5, Lord Justice Arnold agreed with Sandoz and Teva's objection that this ground raised

a new unpleaded case which BMS could not now argue on appeal. He noted in any event that the Application could not have impliedly disclosed that apixaban had been tested and found to have nanomolar K_i given that the judge was correct to find that the Application did not impliedly disclose apixaban to have been tested and found to have micromolar K_i.

Finally, Lord Justice Arnold rejected ground 6 also. He found that Meade J had made no error in his assessment of the significance of the Application's disclosure on the synthesis of apixaban (in particular the fact that 3.5 g had been made). He agreed with the first instance judge's conclusion that whilst promising early results were one possible reason why the skilled team would think the patentee created a relatively larger quantity, there were other possible reasons for this. Whilst Meade J did not mention the disclosure about recrystallization of apixaban, and whilst this step does increase the compound yield, it does not add anything to the disclosure of the quantity of apixaban being synthesised. Additionally, Lord Justice Arnold found that contrary to BMS' argument, Meade J did consider the combined effect of the passages disclosing the apixaban compound and its synthesis.

Concluding, Lord Justice Arnold held that in the absence of any theory based on apixaban's structure or any data in the specification, by way of example, there was nothing in the Application supporting the assertion that apixaban is a factor Xa inhibitor at all. As such, the assertion is not plausible because the Application gives the skilled team no reason for thinking that there is a reasonable prospect that the assertion will prove to be true.

G 2/21

The Court of Appeal provided some interesting *obiter* observations on the EBA's decision in *G 2/21*:

- First, Lord Justice Arnold opined that the majority approach in *Warner-Lambert* corresponds to the "*ab initio* plausibility" test identified in the referral decision underlying *G 2/21* (T 116/18 *Sumitomo*), whereas that of the minority corresponds to the "*ab initio* implausibility" test. He noted that the *Warner-Lambert* decision illustrates that the two approaches do not necessarily lead to the same result, contrary to the EBA's suggestion that they were reconcilable.
- Second, he observed that the EBA's harmonised approach is more akin to "*ab initio* plausibility" than the alternative.
- Third, he noted that the EBA's observation that plausibility is a criterion for the reliance on a purported technical effect, rather than a condition of validity in itself, is in accordance with the majority decision in *Warner-Lambert.*
- Fourth, he commented that, in respect of sufficiency, the EBA's reference to "*a claimed therapeutic effect*" is to an effect which is asserted as the basis for a second medical use claim.
- Finally, and perhaps most importantly, Lord Justice Arnold observed that the core question for inventive step is whether the technical effect relied upon by the applicant or patentee was derivable from the application at the filing date in the mind of the skilled person with the CGK.

Where do we go from here?

As Lord Justice Arnold pointed out, the concept of plausibility features in neither the Patents Act 1977 nor the European Patent Convention. Notwithstanding this, its role in the analysis of the validity of patents at national and EPO level has persisted and in this case, it is the very hurdle upon which invalidity has been determined. The Court of Appeal decision confirms that there are

not different standards of plausibility for different types of claim. Whether the claim is in the form of second medical use or to a single compound, the same standard applies, namely the approach of the majority in *Warner-Lambert*.

In *G 2/21*, the EBA attempted to more clearly define the parameters of the analysis, whilst simultaneously downplaying the distinction between *ab initio* plausibility vs implausibility. However, as Lord Justice Arnold observed, these approaches do not always lead to the same end result. Additionally, the EBA eschewed use of the word "plausibility" in its final characterisation of the analysis to be undertaken, but by its own admission, the characterisation it proffered (that the skilled person would consider the technical effect as being "*encompassed by the technical teaching and embodied by the same originally disclosed invention*") is not free from abstractness. Fortunately, this will not be the final word on the matter in the UK as the Supreme Court is due to consider this and other points in the *Fibrogen v Akabia* appeal, currently scheduled to be heard in March 2024. It also remains to be seen whether BMS applies for permission to appeal to the Supreme Court in this case.

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