"An ingenious attempt to exploit a loophole":

High Court rejects generic manufacturer's JR of marketing authorisation refusal

R (Teva B.V.) v Secretary of State for Health [2018] EWHC 228 (Admin)

Biogen Idec Ltd was an interested party

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Paragraph numbers are references to the judgment.

Overview

On 13 February 2018, the High Court (Jay J) dismissed an application for judicial review brought by Teva BV ("**Teva**") challenging the refusal by the UK's Medicines and Healthcare Products Regulatory Agency ("**MHRA**") to validate Teva's abridged application for a marketing authorisation ("**MA**") for its generic version of Tecfidera, a drug used to treat multiple sclerosis. Teva relied on Tecfidera as its reference medicinal product but sought to challenge indirectly the scope of the earlier marketing authorisation that had been granted to Tecfidera by the Commission in 2014 under the centralised procedure

Teva's argued that the MHRA was not bound by a conclusion, appearing in a recital to the Commission Decision granting the MA to Tecfidera, as to the extent of its "global marketing authorisation" ("GMA") which had knock-on effects for its period of data exclusivity. Mr Justice Jay found that argument to be "*ingenious*" but ultimately unsuccessful.

The judgment has important implications for pharmaceutical regulation and the status of Commission authorisation decisions, both now and potentially post-Brexit. The High Court made key rulings about the role of national licensing authorities and their duties under the common regulatory framework, including the requirement that they should give effect to the package of rights emanating from the grant of a marketing authorisation by the Commission.

Factual Background

Teva is a pharmaceutical company which manufactures and supplies innovative and generic medicines. The Secretary of State for Health, as the UK licensing authority, acts through the MHRA. The interested party, Biogen Idec Ltd ("**Biogen**"), holds the marketing authorisation for Tecfidera, which was granted by the European Commission (the "**Commission**") on 30 January 2014 (the "**Commission Decision**") pursuant to the Centralised Procedure (see 'Pharmaceutical Regulation' below).

Tecfidera's active substance is dimethyl fumarate ("**DMF**"). This is also an active substance within a different medicinal product, Fumaderm, which was granted an MA in Germany in 1994. Fumaderm, which is used to treat psoriasis, additionally contains three monoethyl fumarate esters ("**MEF**"). Due to the lapse of time and loss of documents, the precise basis on which Fumaderm was authorised in Germany was not clear. It was clear that the Commission concluded in 2014, when authorising Tecfidera, that DMF and MEF are different active substances.

On 22 December 2016, Teva applied to the MHRA under the Decentralised Procedure (see 'Pharmaceutical Regulation' below) for an MA for its generic medicinal product with DMF as the sole active substance. Teva nominated Tecfidera as the "reference medicinal product". The MHRA refused to validate Teva's application on the grounds that Teva was not entitled to apply for an MA when the data exclusivity period for Tecfidera had not expired (and was not due to expire until 4 February 2024).

Pharmaceutical Regulation in the EU

The regulation of medicinal products in the EU has been fully harmonised, including by Directive 2001/83/EC on the Community Code relating to Medicinal Product for Human Use (the "**Directive**") and Regulation 726/2004 laying down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary use and establishing a European Medicines Agency ("the **Regulation**") (collectively the "**Common Regulatory Framework**").

Under the Common Regulatory Framework, medicinal products cannot be marketed in Member States without an MA. The Common Regulatory Framework provides four different procedures for applications for and the granting of MAs. The three most relevant to this case are:

1. The National Procedure: an MA is granted by the competent authority of an individual MS permitting marketing within that MS. Articles 8 and 10 of the Directive are applicable. Article 8 requires that an application

be accompanied by a dossier (which would include the results of clinical trials). By way of derogation from Article 8, Article 10(1) provides an abridged procedure whereby applications need not be accompanied by a dossier if the applicant can demonstrate that the product is a generic of an already-authorised reference product. Teva's application was made under Article 10(1), but under the variant Decentralised Procedure (below).

2. The Centralised Procedure: an MA granted by the Commission gives the right to market a medicinal product across the EU as a whole. It is required for medicinal products listed in the Annex to the Regulation (Article 3(1) of the Regulation). Further, an application may be made to the Commission for unlisted products where the applicant can demonstrate significant therapeutic, scientific or technical innovation (Article 3(2)(b) of the Regulation). Biogen's application for Tecfidera was made under Article 3(2)(b).

3. The Decentralised Procedure: the reference MS takes the lead in assessing the application, and any concerned MS nominated by the applicant participates in agreeing the assessment and then grants its own MA.

Article 6(1) of the Directive introduces the concept, central to this case, of the Global Marketing Authorisation ("**GMA**"). It provides that when a medicinal product is granted an MA, "*any additional strengths, pharmaceutical forms, administrative routes, presentation as well as any variation and extensions shall also be granted an authorisation […] or shall be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purposes of Article 10.1*".

Jay J explained at [**91**] that "*the rights which flow from the initial MA to the advantage of the MA holder […] are not limited to the right to market the medicinal product […]. This is because the initial MA is always the starting-point for the GMA, which is in turn the wellspring for a further bundle of rights which protect the innovative development of the active substance*". These rights include 10 years of data exclusivity, during which competitors cannot make a generic application under Article 10(1) using the medicinal product as a reference product (collectively the "**Package of Rights**").

Teva's First Ground

Teva's case is that MEF has no clinically relevant therapeutic effect in Fumaderm and therefore the sole active substance in Fumaderm is DMF. It follows that Tecfidera and Fumaderm contain the same active substance, and so Tecfidera falls within the GMA of Fumaderm. Consequently, Teva argued,

Tecfidera's data exclusivity period does not run from 2014 to 2024, but instead the relevant period relates to Fumaderm and has expired.

Teva's argument faces the barrier that the Commission concluded in 2014 that Tecfidera and Fumaderm do not belong to the same GMA. This conclusion appears in a recital to the Commission Decision. Teva's first ground is that this recital was not binding on the MHRA. Teva's submissions contained three elements:

1. The recital is not binding because the GMA (and hence data exclusivity) of the reference medicinal product cannot be determined within the Common Regulatory Framework at the time the MA is issued (for the reference medicinal product). It can only be decided at the time the generic application falls to be considered under Article 10(1). Teva's argument relied centrally on the phrase "*in particular for the purposes of Article 10.1*" in Article 6(1) (quoted above).

2. It follows, or is in any event the case, that the recital is not the operative part of the Commission's decision. It carries no legal effects at all and, in particular, no legal effects in relation to Teva. The issue of whether Tecfidera is within the GMA of Fumaderm must be addressed by the MHRA.

3. There are policy reasons why the recital does not bind the MHRA. Teva was not able to challenge the Commission decision on Tecfidera. If that decision then bound the MHRA there would be a lack of effective judicial scrutiny over the authorisation system.

In relation to (1), Jay J declined to make a reference to Luxembourg, finding that he was able to conclude on the basis of the material and arguments before him that decisions as to GMA may properly be made under Article 6(1), at the time of the authorisation of the reference product, and need not (contrary to Teva's submission) be made only at the later stage of a generic application under Article 10(1). Thus the Commission, at the time of Tecfidera's centralised authorisation, was permitted to make a decision in relation to Tecfidera's GMA.

The Directive stresses in its recitals that disparities between national provisions hinder trade in medicinal products. Differences in evaluation are to be avoided by the adoption of the same standards and protocols for awarding an MA by all the Member States (see [**9**]). Therefore, not only is there nothing in the Common Regulatory Framework to prevent the Commission having taken a decision on Tecfidera's GMA in 2014, but there were many "*sound policy reasons for doing so*" (see [**110**]).

Jay J did not find it instructive to focus on whether the Commission's conclusion

was located within a recital or not, as this "*elevates form over substance*" ([**117**]). Rather the "*crucial question*" was whether the Commission's decision produced legal effects in relation to Tecfidera's GMA, and this was answered in the affirmative given the Commission's power to determine the issue of GMA in a legally binding manner pursuant to Article 6. Jay J thus reasoned that "*[e]ither that decision* [the Commission's] *was correct, as I have found, or it must be treated as correct in this Court.*"

It follows that when it falls to a national competent authority to determine a generic application under Article 10(1) it must reach a conclusion which "respects the rights which inhere in that product", namely the Package of Rights described above, including any decision as to data exclusivity and GMA, should one be made ([**119**]).

Teva's Second Ground

Teva accepted that it also needed to succeed on its second ground, which was that the MHRA applied the wrong test in concluding that DMF and MEF are different active substances. Teva contended that the MHRA asked whether MEF was an active substance at some high level of abstraction, asking whether DMF and MEF are pharmaceutically active and have different therapeutic moieties. Teva submitted that the MHRA should instead have asked whether MEF makes a clinically relevant contribution to the therapeutic effect of Fumaderm ([**123**]).

The judge addressed Ground 2, even though Teva lost its application having lost on Ground 1. At [**145**], the judge set out how the issue of whether MEF is a different active substance from DMF "*falls to be addressed as a matter of principle*".

He did so following an analysis of the definition of "*active substance*" in Article 1(3a) of the Directive, namely "*any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a diagnosis*".

Jay J's principled approach to MEF and DMF (see [**145**]) can be formalised more generally as follows. There is a three stage-analysis to determine whether a purported or target active substance (the "**Target Substance**") is a different active substance from another substance accepted to be active (the "**Accepted Substance**") in a medicinal product, as follows:

1. Determine whether Target Substance exerts a therapeutic pharmacological action in the medicinal product in question.

2. If the answer to (1) is yes, determine whether the pharmacological action exerted by the Target Substance shares the same therapeutic moiety as that exerted by the Accepted Substance. (If two molecules share the same therapeutic moiety, that means that the functional part of the molecules under comparison are the same, or cannot be regarded as materially dissimilar (at [59]).)

3. If the answer to (2) is yes, determine whether the Target Substance and Established Substance differ in their safety and efficacy profile.

Comments

This judgement has important implications, even setting aside its commercial importance to Teva and Biogen, and the MHRA's concern as to the legal integrity of its decision-making in this case (both recognised at [**6**]). The High Court found that the MHRA was compelled, in considering Teva's application for an MA, to give effect to Biogen's rights emanating from the Commission's grant of the MA. The broad principle is that where the Commission makes a decision on GMA, recorded in its authorisation decision, this will generate specific data exclusivity rights, which subsequent national competent authorities are compelled to respect when faced with generic applications. Jay J was not invited to, and did not, reach any view as to whether Teva would have been bound to accept Tecfidera's GMA even if GMA had not been included in the Commission Decision [**105**].

It is interesting that Jay J did not approach this from the traditional approach of considering whether the Commission Decision (or a recital contained therein) was binding on the MHRA, or indeed the national court, as an emanation of the state. Instead, he looked at the regulatory framework and the package of concomitant rights emanating from the MA, which the national court was required to uphold. He also declined to make a preliminary reference but in this new judicial climate, preferred to decide the matter for himself. His ruling could have implications for post-Brexit pharmaceutical regulation. Regardless of the formal status of the Decision itself, that the High Court held that, in light of the Common Regulatory Framework and its role and obligations, the MHRA should take account of the Commission's findings and could not apply its own unilateral scientific evaluation. This is important for legal certainty and the effectiveness of the rights given to MA holders (and generic manufacturers) so they know their legal position from the outset when an MA is given. Those rights cannot be disturbed by subsequent generic applications or disagreement by a national competent authority with the scientific assessment.

Jay J commented at [**152**], "*[m]y initial reaction to Teva's case when I was reading into these papers was that it appeared to be an ingenious attempt to exploit a loophole in the scheme of the Directive, and a classic instance of having one's cake and eating it. […] [A]t the end of this exercise I confess that*

I find myself having travelled more or less full circle." The 'loophole' in question is as follows. Jay J considered that the difficulty arose because of the way the important concept of GMA was added into the Directive, by amendment, in 2004. It was inserted in an unhelpful place and not given a definition. Jay J noted that "*in the absence of a proper working definition or a more explicit setting out of the decision-making process, courts are left to their own devices in giving substantive and procedural content to this concept*". This judgment of the High Court has now collated and considered previous dicta on, as well as contributed to, the substantive and procedural content of the GMA concept.

When considering Teva's first ground, Jay J stated that he could see the force of the argument that "*the possibility of a genuine casus omissus or legislative gap has been generated*" ([**105**]). The situation which led to this case was not contemplated by the EU statutory scheme, namely the Commission having reached a conclusion on GMA in a recital to an authorisation decision of what is later used as a reference product. However, the judge declined to make a reference to Luxembourg, preferring to decide the issue for himself. He stated that "*in the circumstances, I am both able and content to plot a safer and less controversial pathway [than that which made the legislative gap appear] through these provisions*" ([**106**]). This lack of appetite to make a reference could be a symptom of Brexit-related uncertainty. The approach of finding one's own "pathway through the provisions", even to fill what could otherwise be seen as a legislative gap, could be a precursor for post-Brexit litigation.

Anneli Howard and Anneliese Blackwood were instructed by the Government Legal Department for the Defendant.

The judgment is available here.

The comments made in this case note are wholly personal and do not reflect the views of any other members of Monckton Chambers, its tenants or clients.

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