SHIRE V EMA: HAS THE CJEU ADOPTED ANOTHER 'EVERGREEN' ORPHAN?

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Dear Editor,

On 29 July, the Court of Justice of the European Union (CJEU)[1] upheld the General Court's ruling[2] that new medicinal products containing the same 'active substance' as existing orphan medicines are entitled to their own separate ten year market exclusivity, if they satisfy the criteria under the Orphan Regulation.[3] The judgments explain substantive provisions of the legislation and the European Medicines Agency's (EMA) role in applying them.

In this case, the EMA refused to validate Shire's 2015 application for orphan designation of 'Idursulfase-IT'.[4] This is an intrathecal version of idursulfase designed for patients suffering from a severe form of Hunter Syndrome with accompanying 'cognitive disorders'.[5] The EMA argued that the application was too late because a 'general' orphan designation for idursulfase (2001)[6] for Hunter Syndrome, and a market authorisation (MA) for Elaprase® (2007 intravenous formulation), had *already* been granted to Shire.[7] To decide otherwise would infringe Elaprase® MA under Article 5(1) of the Orphan Regulation.[8]

In dismissing the appeal, the CJEU affirmed the position that when validating orphan designation applications, the remit of the EMA, in verifying whether the *same* medicinal product is *already* the subject of MA,[9] is 'purely administrative' in scope (*per* Article 5(1) and Article 5(4)).[10] Under Article

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1 Case C-359/18 P *EMA v Shire Pharmaceuticals Ireland* [2019] ECLI:EU:C:2019:639 [hereinafter *Shire* 2019].
2 Case T-80/16 *Shire Pharmaceuticals Ireland Ltd v European Medicines Agency* [2018] ECLI:EU:T:2018:165 [hereinafter *Shire* 2018].
3 European Parliament and Council Directive (EC) 141/2000 of 16 December 1999 on orphan medicinal products [2000] OJ L18/1, as amended by Regulation (EC) 596/2009 [2009] OJ L188/14 [hereinafter 'Orphan Regulation'].
4 *Shire* 2018 (n 2) [9], referred to as the 'contested decision'.
5 ibid [3].
6 ibid [42], where the 2001 European Commission decision (EU/3/01/078) where the designation refers in general/broad terms to *'iduronate-2-sulfatase'* for treatment of Hunter Syndrome.
7 *Shire* 2019 (n 1) [10].
8 ibid [9].
9 ibid [28].
10 *Shire* 2018 (n 2) [52].

5(2) of the Orphan Regulation, the EMA is supplied with 'two categories' of information from the sponsor to assist them in their determination:[11]

1) **Article 5(2)(a)-(c):** name of sponsor, active ingredient, and proposed therapeutic indication.[12]
2) **Article 5(2)(d)**: justification that criteria in Article 3(1) are satisfied.[13] In this case, Article 3(1)(b) is of relevance, as it requires the sponsor to establish that the medicinal product in question is for an orphan condition for which there is no satisfactory authorised treatment *or*, if such treatment exists, that the medicinal product will be of 'significant benefit' compared to authorised treatment.[14] In the latter situation, the sponsor must also establish that the second medicinal product is not 'identical' to the first.[15]

The EMA argued that, in assessing whether a medicinal product was 'identical', it was confined to the 'exhaustively defined….simple and unequivocal criteria'[16] of 'active substance' and 'indication', i.e. category one above.[17] The Court considered that limiting the *identity* of a medicinal product to these criteria would be insufficient grounds to refuse an orphan designation.[18] The General Court's position that 'medicinal product' and 'active substance' are distinct concepts (the latter being a component of the former), and are afforded individual legal definitions under the Medicinal Product's Directive 2001/83,[19] was reiterated.[20] As a result, 'all other relevant factors' must be accounted for when the EMA is making an assessment on a 'medicinal product', and not merely the above two criteria.[21] This view was in light of the 'combined reading' of Article 5(2) and 3(1) which requires a sponsor to provide evidence of lack of sameness and a 'significant benefit'.[22]

A key issue before the Courts is who determines whether a medicinal product provides a 'significant benefit'. The Court held that, given the 'technical and scientific nature' of this criterion,[23] it is the Committee for Orphan Medicinal Products (COMP) who is allocated this exclusive competence

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11 *Shire* 2019 (n 1) [29].
12 ibid.
13 Orphan Regulation (n 3) Article 5(2)(d).
14 *Shire* 2019 (n 1) [30].
15 ibid [31].
16 ibid [19].
17 ibid [32].
18 ibid [36].
19 European Parliament and Council Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use [2001] OJ L 311/67 [hereinafter 'Medicinal Product's Directive'].
20 *Shire* 2019 (n 1) [37].
21 ibid.
22 ibid [31]
23 ibid [34].

under Article 4 and 5(5)-(7) of the Orphan Regulation.[24] The consequence of this for a case such as *Shire*, is that when 'significant benefit' is claimed, the characterisation of what constitutes the 'identity' of a medicinal product is extended to the purview of COMP and not to the EMA.[25] As a result, provided the conditions under Article 5(1) and (2) above are satisfied, the EMA is obliged to validate an application and furnish it to the COMP.[26]

In dismissing the last ground of appeal as unfounded, the Court agreed with the lower court that the definition of 'medicinal product' under Article 1(3b) of Medicinal Product's Directive encompasses excipients as well as active substance.[27] The *factual* findings that Elaprase® and Idursulfase-IT are different 'medicinal products' based on their 'composition, method of administration and therapeutic effect' was not subject to the *review* by the CJEU.[28]

It is unfortunate, in this author's view, that concerns regarding potential *misuse* in granting an additional ten year market exclusivity[29] were not appealed before the CJEU. The concern raised before the General Court was that companies may be incentivised to strategically delay releasing their improved products before the original product's exclusivity expires in an effort to '*evergreen*'[30] their monopoly.[31] This would be contrary to the Regulation's purpose of incentivising innovation in rare diseases.[32] The General Court was not persuaded, and strictly applied the provisions of the Regulation to dismiss this argument.[33] The General Court relied on the controversial *Teva* ruling,[34] where generic entry was refused because Novartis was granted an independent exclusivity period for a *similar* medicinal product covering the *same* indication as its previous reference medicine.[35] Article 8(3)(a) allows for derogation when similar orphan medicines are permitted MA where consent from the MA holder is obtained.[36] In both *Shire* and *Teva* the Courts opted for robust interpretations of the

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[24] ibid [33].
[25] ibid [35].
[26] ibid [39], upholding *Shire* 2018 (n 2) [52].
[27] ibid [45].
[28] ibid [40].
[29] *Shire* 2018 (n 2) [80] *et seq*.
[30] Case T-140/12 *Teva Pharma and Teva Pharmaceuticals Europe v European Medicines Agency* [2015] ECLI:EU:T:2015:41 [60], applicants used the term *evergreen* to describe the perpetual elongation of market exclusivity.
[31] *Shire* 2018 (n 2) [47].
[32] Orphan Regulation (n 3), Recital 1 and 2. See further, Laëtitia Bénard, Jacqueline Bore and Eveline Van Keymeulen, 'Has the Orphan Regulation Met its Aims?' (2018) 2(4) *European Pharmaceutical Law Review* 179.
[33] *Shire* 2018 (n 2) [81].
[34] *Teva* 2015 judgement (n 30) upheld by Case C-138/15 P *Teva Pharma BV and Teva Pharmaceuticals Europe BV v European Medicines Agency* [2016] ECLI:EU:C:2016:136. See further Mayank Dixit, 'Pernicious Effect of Similar Medicinal Product's Orphan Exclusivity: CJEU Dismisses Teva's Appeal (C-138/15 P)' (European Law Blog, 11 April 2016) <https://europeanlawblog.eu/2016/04/11/pernicious-effect-of-similar-medicinal-products-orphan-exclusivity-cjeu-dismisses-tevas-appeal-c-13815-p/> accessed 4 December 2019.
[35] ibid.
[36] Orphan Regulation (n 2) Article 8(3)(a).

legislation which may result in situations where companies are rewarded for shrewdly overcoming legal hurdles as opposed to innovative endeavours.

In 2016, the Council of Europe[37] noted the following potential concerns regarding the current orphan regime:

> *the increasing trend of MA of new medicinal products for small indications, including, in some cases, the authorisation of a single product for 'segmented' patient groups within a disease area, and the authorisation of one substance for several rare diseases, and in this respect notes with concern that companies may seek very high prices while the added value of some of these products is not always clear.*[38]

While *Shire* is a welcome decision in terms of incentivising further research by pharmaceutical companies into enhancing their own medicinal products,[39] it may also have the unintended consequence of fostering an environment where pharmaceutical companies stratify their patient populations in an effort to extend their market exclusivity period in an '*evergreen*' manner.[40] While the COMP is tasked with zealously preventing such 'artificial' categorisation attempts,[41] it is conceivable that, in light of the narrative in *Shire,* some of these attempts may not be preventable.

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[37] European Council, 'Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States', (Press Release, 17 June 2016) <https://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/> accessed 4 December 2019.
[38] ibid [17].
[39] See, Jens Grabenstein, 'The same but better (Part 2) - Shire v European Medicines Agency (C-359/18 P)' (Carpmaels & Ransford, 6 August 2019) <https://www.carpmaels.com/shire-v-emea-part2/> accessed 4 December 2019.
[40] *Teva* 2015 (n 30).
[41] Daniel J. O'Connor *et al,* 'Defining orphan conditions in the context of the European orphan regulation: challenges and evolution' (2019) 18(7) Nature Reviews Drug Discovery 479, <https://www.nature.com/articles/nrd.2018.128> accessed 4 December 2019.