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EU Court ruling on how off-label use is to be analysed under competition law

February 2018

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The highest EU court has held that an agreement to disseminate misleading information about the safety of a medicine being used off-label may restrict competition by object.

On 23 January 2018, the Grand Chamber of the Court of Justice ("**ECJ**") delivered its judgment on preliminary reference from the Italian State Council in the *Roche* case, which concerns the off-label use of Avastin for the treatment of ophthalmological pathology in Italy (Case C-179/16). The judgment is noteworthy for its implications for market definition and on the qualification of certain practices as restriction by object in the pharmaceutical sector. Here are the main takeaways:

- medicinal products sold or manufactured unlawfully should not be regarded as part of the same relevant market as lawfully authorized products;
- medicinal products can be used off-label only under strict conditions, and it is for regulatory bodies, not competition authorities, to decide on the lawfulness of the off-label use of a medicinal product (but competition authorities must take this conclusion into account when defining markets);
- medicinal products which are lawfully used off-label can be found to be in the same relevant market as lawfully authorized products, if both products are regarded as therapeutically substitutable;
- an agreement between two firms to disseminate misleading information regarding a medicinal product used off-label, with the view of reducing the competitive pressure from such product, can constitute a by-object restriction within the meaning of Article 101 TFEU (subject to three-prong test set out by the ECJ).

Background

Genentech developed two medicines from related active substances (Avastin and Lucentis). Lucentis was authorized by the European Commission and the European Medicines Agency ("**EMA**") for the treatment of eye diseases, while Avastin was authorized for oncological applications (colorectal cancer). A licence for the exploitation of Lucentis was granted to Novartis, while the right to exploit Avastin was licensed to Roche.

Before Lucentis was placed on the market, Italian doctors started to prescribe Avastin for the treatment of eye diseases, and this off-label use spread widely in Italy. Once Lucentis was placed on the market, the practice continued because of Avastin's perceived lower price (essentially due to substantial re-compounding of single vials into multiple injection doses).

In 2014, the Italian Competition Authority fined Roche and Novartis approximately EUR 90 million each, alleging that they had entered into a market-sharing agreement, colluding to create an artificial differentiation between Avastin and Lucentis to discourage the off-label use of Avastin. Based on its (contested) factual finding that the two products were equivalent for the treatment of eye diseases, the Italian Competition Authority concluded that the agreement had intended to cause a shift in demand in favour of Lucentis by disseminating information aimed at raising concerns regarding the safety of the off-label use of Avastin for ophthalmological purposes.

The two companies appealed the decision before the Regional Administrative Court of Lazio, which dismissed their action, and then lodged an appeal before the Council of State, which stayed the proceedings and referred a series of questions to the ECJ, which covered:

- market definition in the context of authorized and non-authorized medicinal products;
- the possible classification of the conduct in question as an ancillary restriction to the licence agreement; and
- whether such conduct, if proved, could amount to a restriction of competition by object.

Licensed products are not in the same market as illegal off-label products, but it is the regulatory authority that decides this

In its judgment, the ECJ started by stressing that products manufactured and sold illegally could not, as a matter of principle, be viewed as substitutable or interchangeable with lawfully authorized products, in particular because of the risks involved for public health (§52).

The ECJ then confirmed that, although the off-label use of an authorized medicinal product or its repackaging (or, presumably, re-compounding) for such a purpose is not directly prohibited by EU rules, it is subject to strict conditions (§§57-58). The ECJ referred *inter alia* to its *Commission v Poland* judgment, in which it found that one of the conditions for off-label use to be authorized was the lack of an equivalent, authorized product on the market.[1] Yet this aspect is not discussed further in the Court's judgment despite the fact that, once Lucentis was approved, there was an equivalent, authorized product on the market.

Notably, the ECJ also stated that national courts and pharmaceutical authorities are the bodies responsible for the analysis of off-label conditions, not the competition authority. Therefore, in assessing whether off-label and authorized products are part of the same relevant market, a competition authority first has to refer to their conclusions (§61). If they have decided that the necessary conditions were not respected, it can reasonably be inferred from this judgment that the competition authority would have to conclude that the two products do not belong to the same relevant market.

If medicines are legally being used off-label, then market definition is based on therapeutic substitution

In the present case, however, the ECJ said that the uncertainty as to the legality of the off-label use of Avastin was not enough to preclude it from being in the same market as Lucentis (§64). This means that where the conditions for off-label use are met, or where no unlawful off-label use has been established by the competent bodies, there seems to be no bar from considering authorized and off-label drugs to be part of the same market, provided of course they are effectively used for the same therapeutic indication.

In this regard, the Court underlined that, given the attributes of the pharmaceutical sector, the relevant market is "in principle, capable of comprising medicinal products that may be used for the same therapeutic indications, since the prescribing doctors are primarily guided by considerations of therapeutic appropriateness and the efficacy of medicines" (§65), confirming in passing the importance of therapeutic substitution when defining markets in the pharmaceutical sector.

The ECJ's judgment will avoid competition authorities having to make complex assessments as to the lawfulness of the off-label use of a particular drug, which they are not well-equipped to make. The judgment clearly says, however, that competition authorities must take into account the decisions of the regulatory bodies. The corollary must be that the relevant regulatory bodies must clearly be under a duty to react swiftly when alerted by pharmaceutical companies of the possible unlawful off-label use of a drug. This is all the more important as it follows from the ECJ judgment that their decision (or lack thereof) on such issue bears consequences for the definition of the relevant market.

[1] Judgment of 29 March 2012, *Commission v Poland*, C-185/10, EU:C:2012:181, para. 36.

A restriction aimed at limiting the commercial autonomy of third parties is not ancillary

In line with its analysis in the *MasterCard* judgment,[2] the ECJ found that the conduct in question could not qualify as an ancillary restraint to the licensing agreement concluded between Novartis and Roche, escaping the prohibition of Article 101 TFEU. The ECJ underscored that the objective of the conduct, entered into several years after the licence, was to influence the behaviour of third parties such as healthcare professionals, rather than to restrict the commercial autonomy of the licensing parties themselves (§§72-73).

Communicating misleading information about the safety of a pharmaceutical product can be qualified as restriction by object

In the last part of the judgment, the ECJ goes on to answer the following question: does an agreement between two pharmaceutical companies which concerns the dissemination, in a context of scientific uncertainty, of information relating to adverse reactions resulting from the use of one medicinal product for indications not covered by its market authorization ("**MA**"), with a view to reducing the competitive pressure resulting from that use on another medicinal product covered by an MA covering those indications, constitute a restriction of competition "by object" for the purposes of that provision (§77).

As an aside, it is interesting to note that the ECJ significantly reformulated the question originally asked by the Council of State (compare §77 and §36(5)). This may not facilitate the Council of State's resolution of the case.

To answer the question, the ECJ first reaffirmed that the concept of restriction of competition by object should be interpreted restrictively, and that the key criterion is whether the degree of harm displayed by the agreement is sufficient to obviate the need to look at its actual effects (§78).

The ECJ also confirmed that, in the pharmaceutical sector, the assessment must take into account the impact of EU rules on pharmaceutical products (§§79-80). Amongst these rules is pharmacovigilance, which must be respected by MA holders, under the control of the EMA, coordinating with the competent national agencies. In short, pharmacovigilance imposes an obligation to supply the EMA, the Commission, and the Member States with any new information relevant for the issuance of an MA and any other new information which might have an impact on the benefits and risks of the product.[3]

The ECJ then essentially assessed whether, through the conduct in question, the parties merely satisfied their pharmacovigilance obligations.

It first observed that pharmacovigilance obligations normally weigh on the MA holder, and not on the company marketing a competing product, so the involvement of a competitor could indicate that the conduct had a different purpose (§91).

Second, the ECJ ruled that the information Roche and Novartis had communicated to the public and to the various authorities could, if it did not satisfy the regulatory requirements laid down in Regulation 658/2007 (namely, being complete and accurate) (first condition of the test), be regarded as misleading if the purpose of that information (second condition of the test) was:

- to mislead the EMA and the Commission, in order to obtain the inclusion of the adverse reactions to Avastin in the summary of product characteristics, so as to enable the MA holder to launch a communication campaign aimed at healthcare professionals, patients and other persons with a view to exaggerating that perception artificially; and
- to emphasise, in a context of scientific uncertainty, the public perception of the risks associated with the off-label use of Avastin, given, *inter alia*, the fact that the EMA and the Commission did not amend the summary of characteristics of that product in respect of its "adverse reactions" but merely issued "Special warnings and precautions for use" (§92).

Given the characteristics of the pharmaceutical market, the ECJ concluded that conduct found to pursue the objective of spreading such misleading information would lead to a reduction in demand and, consequently, of the competitive pressure exercised by the off-label product. It would therefore display a sufficient degree of harm to competition to constitute a restriction by object (§§93-95).

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2 Judgment of 11 September 2014, *MasterCard and Others v Commission*, C382/12 P, paras 8-90.

3 Article 16(2) of Regulation No. 726/2004.

Three thoughts on the ECJ's ruling that on the by object test

There are three overarching points that one can make about the ECJ's conclusions on by object:

- First, it is clear that the ECJ meant to narrow down its finding on the existence of a restriction by object to an agreement to disseminate misleading information. Hence it does not reverse the key point established by the *Cartes Bancaires* judgment, namely that the concept of restriction by object should be narrowly interpreted and should be reserved for obvious cases or cases where there is experience of their negative effects.

- Second, the ECJ was clearly mindful to construe very narrowly the concept of misleading information, by reference to very specific factual circumstances. In this respect, it is worth noting the numerous references to the factual conclusions by the Italian Competition Authority's decision that was being challenged – something that seems unusual for the ECJ. It is also unusual for the concept of "misleading" to appear in the judgment when it was not part of the referring court's questions. As with any preliminary reference, it will be up to the Council of State to decide whether such factual circumstances are indeed met in this case, and whether the information can be seen as misleading as per the ECJ's definition.

- Third, beyond the specific facts of the dispute, the judgment is significant in that it is the first time that the concept of restriction by object is applied to an agreement which (if the factual premises set out by the ECJ were subsequently to be confirmed by the national courts) aimed to disseminate allegedly misleading information about the safety of a medicinal product. While the judgment somehow echoes the decisional practice of the French Competition Authority, which has sanctioned a number of pharmaceutical companies for denigrating competing generic products,[4] it is worth noting that the ECJ's test for misleading in the present case appears to be more narrowly defined than the test in the French cases.

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[4] French Competition Authority Decision n° 13-D-21 related to practices implemented by Schering Plough on the French market of the high dosage buprenorphine commercialized in town, 18 December 2013; French Competition Authority Decision n° 13-D-11 related to practices implemented by Sanofi-Aventis in the pharmaceutical sector, 14 May 2013.