AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Case C-179/16 (F. Hoffmann - La Roche Ltd): CJEU decision 2018 January 23th

Avv. Francesca Mastroianni

49th EMACOLEX Meeting
Sofia, 29-30 May 2018

Public Declaration of transparency/interests*

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Francesca Mastroianni, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. < I am not receiving any compensation>

Matter of the Court Case (1)

- By decision no. 24823 of 27 February 2014, the Italian Competition Authority ('the AGCM') ruled that the companies F. Hoffmann-La Roche Ltd ('Roche') and Novartis AG, through subsidiaries Novartis Farma SpA ('Novartis Italia') and Roche SpA ('Roche Italia') as well, had put in place, in breach of Article 101 TFEU, a horizontal agreement restricting competition and designed to achieve an artificial 'differentiation' of the medicinal products Avastin and Lucentis by manipulating the perception of the risks involved in the use of Avastin in the field of ophthalmology.

- The companies thus penalized, contested the AGCM decision before the Regional Administrative Court which, by judgment no. 12168 of 2 December 2014, dismissed the actions.

Matter of the Court Case (2)

- Those companies have therefore brought an appeal before the Consiglio di Stato (Council of State) against the AGCM decision to sanction them for having put in place, in breach of Article 101 TFEU, a horizontal agreement restricting competition and designed to achieve an artificial ‘differentiation’ of the medicinal products Avastin and Lucentis by manipulating the perception of the risks involved in the use of Avastin in the field of ophthalmology.

AVASTIN- LUCENTIS: a comparison

- Avastin and Lucentis are both biotech medicines based on the same operating mechanism.
  - Lucentis' active ingredient - ranibizumab - is an engineered fragment of Avastin's active ingredient, bevacizumab with some differences in the amino acid sequences of the FAB.
  - Both medicines were developed by Genentech when the company was already part of the Roche Group. Genentech has then assigned the distribution of Lucentis to Novartis and sells to it the active principle (ranibizumab).
- Avastin was approved by a centralised procedure in 2005 for the treatment of specific forms of metastatic cancers by means of endovenous infusion, while Lucentis was approved by a centralised procedure in 2007 for the treating of age related macular degeneration (AMD) by means of intravitreal injection.

Law no. 648/1996 (1)

- Regulates the access to off-label medicines when no valid therapeutic alternatives are available;
- Includes a dynamic list of off-label medicines;
- Medicines included in the list are 100% reimbursed by the National Health System in respect of the following conditions:
  - Innovative medicines already marketed in third countries;
  - Medicines not yet authorised, undergoing Phase II clinical trials (showing valid efficacy and tolerability data);
  - Medicines to be used for a therapeutic indication, different from the authorised one.

Law no. 648/1996 (2)

- A new legislation (Law decree 20 March 2014, no. 36) modified Law no. 648/1996 by introducing a new paragraph that states that AIFA may authorize an off-label use of a drug even when a valid authorised alternative exists, provided that:

➢ the off-label indication is recognized as valid within the national and the international scientific community and it is consistent with researches conducted according to appropriateness and economic sustainability principles;

➢ in all such cases, the drug is added to the list of authorized off-label uses and the costs are borne by the National Health System.

Off-label use

- The off-label use of medicinal products authorized on the market is admitted by Italian law at certain conditions for the purpose of granting the reimbursement of medicinal products for a largest number of patients.
- The impact of a CJEU judgment on the market would not be relevant in term of availability of medicines.
- The Council of State, in date 11th March 2016, asked the Court of Justice for a preliminary concerning Avastin – Lucentis off label use.

Questions referred to the Court

(1) *On a proper construction of Article 101 TFEU, can the parties to a licensing agreement be regarded as competitors if the licensee company operates on the relevant market concerned solely by virtue of that agreement? Do possible restrictions of competition between the licensor and the licensee in such a situation, although not expressly provided for in the licensing agreement, fall outside the scope of Article 101(1) TFEU or fall within the scope of the exception set out in Article 101(3) TFEU and, if so, within what limits?*

(2) *Does Article 101 TFEU allow the national competition authority to define the relevant market independently of the content of [MAs] for medicinal products granted by the competent pharmaceutical regulatory authorities ([AIFA and the EMA]) or, on the contrary, with respect to authorised medicinal products, must the relevant market for the purposes of Article 101 TFEU instead be held to be primarily shaped and established by the appropriate regulatory authority in a way that is binding even on the national competition authority?*

Questions referred to the Court

(3) *In the light of the provisions of Directive [2001/83], in particular Article 5 thereof, which relates to MAs for medicinal products, does Article 101 TFEU allow a medicinal product used off label and a medicinal product that has received an MA in respect of the same therapeutic indications [and is used in accordance with that MA] to be regarded as interchangeable and, thus, to be included in the same relevant market?*

(4) *Pursuant to Article 101 TFEU, for the purposes of defining the relevant market, is it important to establish, in addition to the substantive interchangeability of pharmaceutical products on the demand side, whether or not those products have been offered on the market in accordance with the regulatory framework for the marketing of medicinal products?*

(5) *In any event, can a concerted practice intended to emphasise that a medicinal product is less safe or less efficacious be regarded as a restriction of competition by object when the idea that that product is less efficacious or less safe, although not supported by reliable scientific evidence, cannot, in the light of the level of scientific knowledge available at the time of the events in question, be indisputably excluded either?'*

The Court rules

"1. Article 101 TFEU must be interpreted as meaning that, for the purposes of the application of that article, a national competition authority may include in the relevant market, in addition to the medicinal products authorised for the treatment of the diseases concerned, another medicinal product whose marketing authorisation does not cover that treatment but which is used for that purpose and is thus actually substitutable with the former. In order to determine whether such a relationship of substitutability exists, the competition authority must, in so far as conformity of the product at issue with the applicable provisions governing the manufacture or the marketing of that product has been examined by the competent authorities or courts, take account of the outcome of that examination by assessing any effects it may have on the structure of supply and demand."

The Court rules (2)

“ 2. Article 101(1) TFEU must be interpreted as meaning that an arrangement put in place between the parties to a licensing agreement regarding the exploitation of a medicinal product which, in order to reduce competitive pressure on the use of that product for the treatment of given diseases, is designed to restrict the conduct of third parties promoting the use of another medicinal product for the treatment of those diseases, does not fall outside the application of that provision on the ground that the arrangement is ancillary to that agreement.”

The Court rules (3)

"3. Article 101(1) TFEU must be interpreted as meaning that an arrangement put in place between two undertakings marketing two competing products, which concerns the dissemination, in a context of scientific uncertainty, to the European Medicines Agency, healthcare professionals and the general public of misleading information relating to adverse reactions resulting from the use of one of those medicinal products for the treatment of diseases not covered by the marketing authorisation of that product, with a view to reducing the competitive pressure resulting from such use on the use of the other product, constitutes a restriction of competition 'by object' for the purposes of that provision.

4. Article 101 TFEU must be interpreted as meaning that such an arrangement cannot be exempt under Article 101(3) TFEU."

Remarks

- The Court generally confirmed the interpretation of competition law as applied by the Italian authorities.
  The national court has to verify some of the factual assumptions made during the procedure, as their correctness may have an impact on the outcome of the national case.
- On the question of market definition and whether Avastin and Lucentis compete on the same market, the Court recognised that a competition authority may include the off-label use (of Avastin) in the definition of the relevant market.
- In this context, the Court confirms previous case law that the EU rules on pharmaceutical products do not prohibit neither the off-label prescription of a medicinal product nor its repackaging for such use, but do require that they comply with the conditions laid down in those rules (e.g. Articles 5 and 40 of Directive 2001/83).

Remarks (2)

- Regarding the arrangements between two undertakings (that market two competing products) to disseminate information relating to adverse reactions from the off-label use could amount to a restriction of competition, the Court basically sided with the Italian competition authority.
- The Court also specify that if those companies submit misleading information by "*artificially exaggerate the risk associated with the off-label use*" of Avastin to counteract the competitive pressure on the sales of Lucentis resulting from such off-label use, this may indeed amount to an infringement of competition rules. In this regard, the company cannot just defend itself by referring to its pharmacovigilance obligations.
- The Court especially notes that an agreement between two companies to disseminate information specifically related to the product marketed by only one of them might be seen as evidence that the dissemination of this information had other purposes than pharmacovigilance.

Remarks (3)

- The Court explains that the information submitted by the companies must be considered to be misleading. This would be the case if its purpose is, first, to confuse the EMA and the Commission by requesting through a variation to introduce in the product information exaggerated warnings against the off-label use of Avastin (of note, EMA/Commission did not amend the product summary as requested by the company, but agreed only to a different message) and, secondly, to emphasise, in a context of scientific uncertainty, the public perception of the risks associated with the off-label use of Avastin.
- The Court explicitly mentions that companies could be subject to a financial penalty under the pharma penalty provisions if they attempt to introduce misleading messages through a variation. Already the attempt would be punishable.
- Lastly, the Court recalls that an arrangement cannot be exempt under Article 101(3) TFEU if it includes restrictions that are not indispensable. The dissemination of misleading information in respect of a medicinal product cannot be regarded as 'indispensable'. An arrangement intended to disseminate such misleading information therefore cannot be exempt.

European Commission' interest

• After "case Avastin", Commission started a public enquiry to know how Member States regulate off label prescription of MPs.

•The study concerns the off-label use of medicinal products in the European Union and is currently carried out by a consortium composed of:

- NIVEL (the Netherlands Institute for Health Service Research);
- RIVM (the Dutch National Institute for public health and the environment);
- EPHA (European Public Health Alliance).

Future perspectives in the light of the study on off-label use

• Exploring new rules for reimbursement and new models of authorization; an example of such models, discussed in the EU in a broader context than off- label use is the use of adaptive pathways as “scientific concept for medicine development and data generation in which allows for early and progressive patient access to a medicine”.

- This model is based on three principles:
  -interactive development of medicines;
  -gathering evidence through real life use to supplement clinical trial data;
  -early involvement of patients and HTA bodies in discussion on a medicine’s development.
- Adaptative pathways is primarily meant for treatments in areas of high medical need where data on evidence are not easily being collected by traditional routes. The standards for risk- benefit evaluation are the same for other products and the approach builds on regulatory process already in place within the existing EU legal framework.

Thank you for your attention!

CONTACTS
t +0033 06 5978 4575
email f.mastroianni@aifa.gov.it
www.agenziafarmaco.gov.it