AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Update about Avastin Case (Case C-29_17): CJEU decision 21 November 2018

Avv. Francesca Mastroianni

51° Emacolex meeting, 15-17 May 2019, Warsaw

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>

Case C-29_17

- Request for a preliminary ruling under Article 267 TFEU from the Consiglio di Stato (Council of State, Italy), made by decision of 22 September 2016, received at the Court on 19 January 2017, in the proceedings Novartis Farma SpA v Agenzia Italiana del Farmaco (AIFA), Roche Italia SpA, Consiglio Superiore di Sanità (intervening parties: Ministero della Salute, Regione Veneto, Società Oftalmologica Italiana (SOI) — Associazione Medici Oculisti Italiani (AMOI), Regione Emilia-Romagna).

Object of the proceeding

- This request for a preliminary ruling concerns the interpretation of Articles 3(1), 5 and 6 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
- The request has been made in the context of proceedings between Novartis Farma SpA, on the one hand, and AIFA, Roche Italia SpA and the Consiglio Superiore di Sanità (Federal Board of Health, Italy) ('the CSS'), on the other, concerning the entry of Avastin, used off-label for the treatment of eye diseases, onto the list of medicinal products reimbursed by the Servizio Sanitario Nazionale (National Health Service, Italy) ('the SSN').

Questions referred for a preliminary ruling

(1) *Do the provisions of Directive 2001/83 and in particular Articles 5 and 6 thereof, with reference in particular to recital 2 of the directive, preclude the application of a national law ... which, in order to pursue the objective of containing expenditure, encourages, by inclusion in the list of medicinal products reimbursable by the [SSN], the use of a drug beyond the therapeutic indication authorised for patients in general, regardless of any consideration of the therapeutic needs of the individual patient and notwithstanding the existence and market availability of medicinal products authorised for the specific therapeutic indication?*

Questions referred for a preliminary ruling

(2) *Can Article 3(1) of Directive 2001/83...be applicable when the preparation of the pharmaceutical product is done in a pharmacy on the strength of a medical prescription for an individual patient, but is nonetheless done in batches, in equal quantities and repeatedly, without taking account of the specific needs of the individual patient, and when the product is dispensed to the hospital and not to the patient (given that the pharmaceutical product is listed in class H-OSP) [medicinal products exclusively for hospital use] and is used in a facility other than that in which the product was prepared?*

Questions referred for a preliminary ruling

(3) *Do the provisions of Regulation No 726/2004, and in particular Articles 3, 25 and 26 thereof together with the Annex, which confer on the … Agency … exclusive responsibility for evaluating the quality, safety and efficacy of medicinal products for which the therapeutic indication is the treatment of oncological pathologies, both in the context of the procedure for granting [the MA] (compulsory centralised procedure) and for the purposes of the monitoring and coordination of pharmacovigilance activities after the product has been placed on the market, preclude the application of a national law that reserves to the [AIFA] the power to judge the safety of medicines as regards their use 'off-label', the authorisation of which falls within the exclusive competence of the European Commission on the basis of the technical and scientific evaluations carried out by the [EMA]?*

Questions referred for a preliminary ruling

(4) *Do the provisions of Directive 89/105, and in particular Article 1(3) thereof, preclude the application of a national law that permits the Member State, in its decisions on the reimbursability of health expenses borne by the patient, to provide for the reimbursability of a medicinal product used beyond the ambit of the therapeutic indications stated in the [MA] issued by the European Commission, or by a specialised European agency, following a centralised evaluation procedure, when the conditions set out in Articles 3 and 5 of Directive [2001/83] are not satisfied?*

Decision of the Court

Article 3(1) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended by Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012, must be interpreted as meaning that Avastin, after being repackaged according to the conditions laid down by the national measures at issue in the main proceedings, falls within the scope of Directive 2001/83, as amended by Directive 2012/26.

Decision of the Court

Article 6 of Directive 2001/83, as amended by Directive 2012/26, must be interpreted as not precluding national measures such as those at issue in the main proceedings which lay down the conditions under which Avastin may be repackaged in order to be used for the treatment of ophthalmological indications not covered by its market authorisation.

Decision of the Court

Articles 3, 25 and 26 of Regulation (EC) No 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, must be interpreted as not precluding a national measure such as that taken pursuant to Article 1(4)bis of decreto-legge 21 ottobre 1996, n. 536, (Decree-Law No 536 of 21 October 1996 on 'Measures for containing pharmaceutical expenditure and for adjusting the maximum level of expenditure for 1996', converted into statute by Law No 648 of 23 December 1996), as amended by decreto-legge del 20 marzo 2014, n. 36, (Decree-Law No 36 of 20 March 2014, converted into statute by Law No 79 of 16 May 2014) which authorises the Agenzia Italiana del Farmaco (AIFA) to monitor medicinal products such as Avastin the off-label use of which is reimbursed by the Servizio Sanitario Nazionale (National Health Service, Italy) and, where relevant, to introduce measures necessary to safeguard patient safety.

AIFA position

- The Court recognized the full legitimacy of the national provisions regulating the off-label use of medicinal products, well aware that this use has not, to date, been subject to any regulatory intervention by the European Union aimed at harmonizing regulatory provisions of the MS and that the Directive 2001/83 itself explicitly provides for the right of States to intervene in the matter with their own national measures.
- The Court recognized the off-label prescription of medicines as a fundamental tool for the protection of public health, especially in cases, such as the one at stake, in which the lack of initiative from the company that owns a registered in filing an appropriate application for extension of the authorized indications is likely to produce serious repercussions on collective health, especially when considering the high costs of the authorized treatments.

AIFA position

- The work of AIFA appears to be fully consistent with the principles set out in the rulings of the C.J.E.U. of November 21st 2018.
- Regardless of the qualification of the preparation for intravitreal use (IVT) obtained from the re-packaging of the industrial medicine (as a magistral preparation or as an industrial drug used for off-label indications), the regulatory framework that this Agency set out with all its determinations (622/2014, 79/2015 and 799/2017) guarantees the permanence of a punctual obligation to obtain written informed consent from every single patient eligible for treatment, as well as the obligation, for the specialist, to prescribe the drug to each patient individually, by filling in a specific computerized prescription form.

AIFA position

- In particular, much attention was paid by AIFA to safety aspects, both in the preparation and in the administration of the preparation for ophthalmic use, as testified moreover, however, by the numerous decisions of the administrative Courts, all stating the existence of a strong obligation to ensure that the fractionation, repackaging and subsequent intravitreal injection take place in compliance with the highest standards of safety and in compliance with the drug dispensing regime (H-OSP) of the drug.

AIFA position

- It is clear that, despite the exclusion of the Avastin qualification for intravitreal use as a magistral galenic formula carried out by the EU Court of Justice, the activities of manipulation and preparation of the drug, both in its authorized and in its off-label use must in any case take place in accordance with the "*Rules for the good preparation of medicines in pharmacies*", 12th edition (NBP), where it is expressly provided that "*all mixtures, dilutions, splits, etc. are also technically comparable to masterly preparations., performed for the individual patient on medical indication".*

AIFA position

- This is also confirmed by the determinations of insertion/ maintenance of Bevacizumab in the lists pursuant to law n. 648/96, where it is expressly prescribed that the splitting and packaging of Bevacizumab for intravitreal use can be carried out only by pharmacies operating in compliance with the rules of good preparation as required by the *Italian Pharmacopoeia* XII edition, in order to guarantee sterility and safety of the preparation.

AIFA position

- The efforts made by AIFA in the adjustment of the regulatory regime of the drug to the changed regulatory framework resulting from the choices of the national legislator and to the subsequent jurisdictional measures, have always been directed to maintaining the character of individuality of the prescriptions and uses of bevacizumab IVT, basing each intervention on the primary scope of maintaining the highest level of protection of public health.

Thank you for your attention!

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