Provisional text

JUDGMENT OF THE COURT (First Chamber)
21 November 2018 (*)
(Reference for a preliminary ruling — Medicinal products for human use — Directive 2001/83/EC — Article 3(1) — Article 6 — Directive 89/105/EEC — Regulation (EC) No 726/2004 — Articles 3, 25 and 26 — Repackaging of a medicinal product for use as a treatment not covered by its marketing authorisation (off-label use) — Reimbursement by the national healthcare insurance system)

In 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,

THE COURT (First Chamber),

composed of R. Silva de Lapuerta, Vice-President, acting as President of the First Chamber, J.-C. Bonichot, A. Arabadjiev, C.G. Fernlund (Rapporteur) and S. Rodin, Judges,
Advocate General: H. Saugmandsgaard Øe,
Registrar: V. Giacobbo-Peyronnel, Administrator,
having regard to the written procedure and further to the hearing on 26 April 2018,
after considering the observations submitted on behalf of:
Novartis Farma SpA, by G. Origoni della Croce, A. Lirosi, V. Salvatore, P. Fattori and E. Cruellas Sada, avvocati,
Roche Italia SpA, by E. Raffaelli, A. Raffaelli, E. Teti and P. Todaro, avvocati,
Regione Veneto, by E. Zanon, E. Mio, C. Zampieri, L. Manzi and B. Barel, avvocati,
Società Oftalmologica Italiana (SOI) — Associazione Medici Oculisti Italiani (AMOI), by R. La Placa, avvocato,
the Regione Emilia-Romagna, by M.R. Russo Valentini, avvocatessa and R. Bonatti, avvocato,
the Italian Government, by G. Palmieri, acting as Agent, and by M. Russo and P. Gentili, avvocati dello Stato,
Ireland, by L. Williams, E. Creedon and A. Joyce, acting as Agents, and by M. Gray, BL,
the Greek Government, by V. Karra, M. Vergou and K. Georgiadis, acting as Agents,
the Polish Government, by B. Majczyna and M. Malczewska, acting as Agents,
the Finnish Government, by H. Leppo, acting as Agent,
the Swedish Government, by A. Falk, C. Meyer-Seitz, H. Shev, L. Zettergren and L. Swedenborg, acting as Agents,
the European Commission, by G. Conte, A. Sipos and K. Petersen, acting as Agents,
after hearing the Opinion of the Advocate General at the sitting on 25 July 2018,
gives the following

Judgment

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 (OJ 2001 L 311, p. 67), as amended by Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 (OJ 2012 L 299, p. 1) ('Directive 2001/83'), of Articles 3, 25 and 26 of, and the Annex to, Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ 2004 L 136, p. 1), as amended by Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 (OJ 2012 L 316, p. 38) ('Regulation No 726/2004'), and of Article 1(3) of Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ 1989 L 40, p. 8).

The request has been made in the context of proceedings between Novartis Farma SpA, on the one hand, and the Agenzia Italiana del Farmaco (AIFA) (Italian Medicines Agency) ('the AIFA'), Roche Italia SpA and the Consiglio Superiore di Sanità (Federal Board of Health, Italy) ('the CSS'), on the other, concerning the entry of a medicinal product, 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').

Legal context

European Union law

Directive 2001/83

Recitals 2 and 35 of Directive 2001/83 state:

'(2) The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.

...

(35) It is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Community through to supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions. ...'

Article 2(1) of Directive 2001/83 provides:

'This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.'

Under Article 3(1) and (2) of that directive:

'This Directive shall not apply to:

Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula);

Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).'

Article 4(3) of the directive provides:

'The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.'

Article 5(1) of Directive 2001/83 provides:

'A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.'

Under Article 6(1) of that directive:

'No medicinal product may be placed on the market of a Member State unless [an MA] has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use [(OJ 2006 L 378, p. 1)] and Regulation (EC) No 1394/2007 [of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ 2007 L 324, p. 121)].

When a medicinal product has been granted an initial [MA] in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial [MA]. All these [MAs] shall be considered as belonging to the same global marketing authorisation, ...'

Article 23(2) of the directive states:

'The [MA] holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I.

In particular, the [MA] holder shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the [MA], as well as data on the use of the medicinal product where such use is outside the terms of the [MA].'

Article 40(1) and (2) of Directive 2001/83 reads as follows:

'1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorisation. This manufacturing authorisation shall be required nothwithstanding that the medicinal products manufactured are intended for export.

2. The authorisation referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

However, such authorisation shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes.'

Article 101(1) of that directive provides:

'Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Union pharmacovigilance activities.

The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the [MA] as well as from use outside the terms of the [MA], and to adverse reactions associated with occupational exposure.'

Directive 89/105

Article 1(3) of Directive 89/105 provides:

'Nothing in this Directive shall permit the marketing of a proprietary medicinal product in respect of which the authorisation provided for in Article [6] of Directive [2001/83] has not been issued.'

Regulation No 726/2004

The second paragraph of Article 1 of Regulation No 726/2004 reads as follows:

'The provisions of this Regulation shall not affect the powers of Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions. In particular, Member States shall be free to choose from the particulars shown in the [MA] those therapeutic indications and pack sizes which will be covered by their social security bodies.'

Article 3(1) of that regulation states:

'No medicinal product appearing in the Annex may be placed on the market within the Community unless [an MA] has been granted by the Community in accordance with the provisions of this Regulation.'

Article 4 of the regulation lays down that applications for MA are to be submitted to the European Medicines Agency (EMA). The requirements for the submission and examination of those applications are set out in Articles 5 to 15 of the regulation.

Articles 25, 25a et 26 of Regulation No 726/2004 read as follows:

'Article 25

The Agency shall, in collaboration with the Member States, develop standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients in accordance with the provisions referred to in Article 107a of Directive 2001/83/EC.

Article 25a

The Agency shall, in collaboration with the national competent authorities and the Commission, set up and maintain a repository for periodic safety update reports (hereinafter the "repository") and the corresponding assessment reports so that they are fully and permanently accessible to the Commission, the national competent authorities, the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group referred to in Article 27 of Directive 2001/83/EC (hereinafter the "coordination group").

The Agency shall, in collaboration with the national competent authorities and the Commission, and after consultation with the Pharmacovigilance Risk Assessment Committee, draw up the functional specifications for the repository.

The Management Board of the Agency shall, on the basis of an independent audit report that takes into account the recommendations of the Pharmacovigilance Risk Assessment Committee, confirm and announce when the repository has achieved full functionality and meets the functional specifications drawn up pursuant to the second paragraph.

Any substantial change to the repository and the functional specifications shall always take into account the recommendations of the Pharmacovigilance Risk Assessment Committee.

Article 26

1. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorised in the Union. By means of that portal, the Agency shall make public at least the following:

the names of members of the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and the members of the coordination group, together with their professional qualifications and with the declarations referred to in Article 63(2) of this Regulation;

agendas and minutes from each meeting of the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and of the coordination group as regards pharmacovigilance activities;

a summary of the risk management plans for medicinal products authorised in accordance with this Regulation;

the list of medicinal products referred to in Article 23 of this Regulation;

a list of the locations in the Union where pharmacovigilance system master files are kept and contact information for pharmacovigilance enquiries, for all medicinal products authorised in the Union;

information about how to report to national competent authorities suspected adverse reactions to medicinal products ...

Union reference dates and frequency of submission of periodic safety update reports established in accordance with Article 107c of Directive 2001/83/EC;

protocols and public abstracts of results of the post-authorisation safety studies ...

the initiation of the procedure provided for in Articles 107i to 107k of Directive 2001/83/EC ...

conclusions of assessments, recommendations, opinions, approvals and decisions taken by the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation ...

2. Before the launch of this portal, and during subsequent reviews, the Agency shall consult relevant stakeholders, including patient and consumer groups, healthcare professionals and industry representatives.'

Italian law

It is clear from the information provided by the referring court that Article 1 of decreto-legge 21 ottobre 1996, n. 536, recante 'Misure per il contenimento della spesa farmaceutica e la rideterminazione del tetto di spesa per l'anno 1996', convertito dalla legge del 23 dicembre 1996, n. 648 (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) (GURI No 11 of 15 January 1997), as amended by decreto-legge del 20 marzo 2014, n. 36, convertito dalla legge del 16 maggio 2014, n. 79 (Decree-Law No 36 of 20 March 2014, converted into statute by Law No 79 of 16 May 2014) (GURI No 115 of 20 May 2014) ('Decree-Law No 536/96') provides that:

'4. Where there is no valid therapeutic alternative, advanced medicinal products the marketing of which is authorised in other States but not in national territory, medicinal products not yet authorised but that are subject to clinical trials and medicinal products intended to be used for a therapeutic indication other than the authorised indication, which are included on a list drawn up and periodically updated by the Commissione unica del farmaco [(Single Medicines Commission, Italy)], in accordance with the procedures and criteria adopted by that commission, can be prescribed and are fully reimbursable by the National Health Service from 1 January 1997. The costs arising from the present paragraph, estimated at 30 000 000 000 Italian lire (ITL) per annum, shall be covered by the National Health Service up to the spending cap set for pharmaceutical assistance.

4bis Even where there is an alternative therapy amongst the medicinal products authorised following evaluation by the AIFA, medicinal products which can be used for a therapeutic indication other than the authorised indication are included on the list referred to in paragraph 4 ... and are reimbursed by the [SSN], provided that indication is known and is in line with research conducted by the national and international medical-scientific community, on the basis of economic and suitability considerations. In such a case, the AIFA shall activate the appropriate monitoring mechanisms to safeguard patient safety and take the necessary decisions in good time.'

The dispute in the main proceedings and the questions referred for a preliminary ruling

Lucentis and Avastin are biotechnological products subject to the MA centralised procedure laid down in Regulation No 726/2004.

The MA for Avastin, granted in 2005, covers cancer treatments exclusively. A company belonging to the pharmaceutical group Roche holds that MA.

The MA for Lucentis was granted in 2007. It relates to the treatment of eye disease, in particular, age-related macular degeneration. A company belonging to the pharmaceutical group Novartis, to which Novartis Farma belongs, holds that MA.

It is clear from the explanations of the referring court that those medicinal products differ both structurally and pharmacologically as well as in terms of their packaging and unit price. Although based on the same technology, these medicinal products have different active ingredients, 'ranibizumab' for Lucentis and 'bevacizumab' for Avastin. The latter is sold in 4 millilitre (ml) vials. Lucentis is sold as an injectable solution (2.3 milligrammes (mg) for 0.23 ml of solution) for a single-use injection of 0.5 mg monthly directly into the eye ('intravitreal use').

Avastin is often prescribed for treating ophthalmological diseases which are not mentioned in the MA. In order to be used for such treatments, Avastin must be extracted from its original vial and divided into single-use 0.1 ml syringes for intravitreal injection. When used for ophthalmologic purposes the repackaged Avastin costs the SSN EUR 82 per dose and Lucentis EUR 902.

By decision No 24823 of 27 February 2014, the Autorità Garante della Concorrenza e del Mercato (Authority responsible for competition compliance and enforcement of market rules, Italy) fined Roche and Novartis for infringement of competition law. In an action brought against that decision, the Consiglio di Stato (Council of State, Italy) referred questions to the Court of Justice for a preliminary ruling, to which the Court replied in its judgment of 23 January 2018, *F. Hoffmann-La Roche and Others* (C-179/16, EU:C:2018:25).

On 15 April 2014, the CSS issued an opinion on the use of Avastin in ophthalmology, which states, inter alia, that the preparation of that medicinal product for intravitreal use is a 'sterile magistral pharmaceutical preparation'.

In keeping with that opinion of the CSS, by decision No 622 of 24 June 2014 ('Decision No 622/2014'), the AIFA entered the use of Avastin for the treatment of age-related macular degeneration onto the list of reimbursable medicinal products pursuant to Article 1(4)bis of Decree-Law No 536/96.

Article 2 of Decision No 622/2014 reads as follows:

'1. The medicinal product bevacizumab — (Avastin) shall be supplied subject to the following conditions, which aim to protect patients where that medicinal product is used for an indication not included in the registration:

to guarantee sterility, the packaging of the medicinal product bevacizumab in single-use doses for intravitreal use must be carried out exclusively by hospital pharmacies satisfying the requirements laid down, in compliance with rules that ensure the doses are properly prepared;

bevacizumab can only be administered for intravitreal use by highly specialised ophthalmological departments in public hospitals designated by the regions;

the medicinal product may only be administered once the patient has signed a declaration of informed consent, including the scientific reasons accompanied by adequate information about the existence of approved alternative therapies at a higher cost to the SSN;

a monitoring record must be created to which the adverse reactions declaration form is annexed.'

Under Article 3 of Decision No 622/2014:

'The medicinal product, reimbursable by the SSN, must be prescribed by the user departments for each patient by completing the computerised prescription form, according to the indications set out on the website https://www.agenziafarmaco.gov.it/registri/, which form an integral part of the present decision.'

Article 4 of Decision No 622/2014 concerning the '[r]eassessment of conditions' provides:

'The AIFA reserves the right to reach any different assessment and to make any more appropriate decision in order to ensure patient safety under Article 1(4)bis [of Decree-Law No 536/96] as a result of the analysis of data gathered from monitoring or of any other available scientific evidence.'

Decision No 79 of the AIFA of 30 January 2015 is related to Decision No 622/2014 and is confined to amending certain indications regarding the persons that can administer Avastin for ophthalmologic purposes.

Novartis Farma challenged the opinion of the CSS of 15 April 2014 and Decisions of the AIFA No 622/2014 and No 79 of 30 January 2015 in an action brought before the Tribunale amministrativo regionale per il Lazio (Regional Administrative Court, Lazio, Italy).

Following the decision to dismiss that action, Novartis Farma appealed against that decision before the Consiglio di Stato (Council of State). In those proceedings, it submitted that for the SSN to allow reimbursement of the

ophthalmologic use of Avastin laid down in Article 1(4)bis of Decree-Law No 536/96 is incompatible with EU pharmaceutical law.

Novartis Farma thus claims that Article 1(4)bis of Decree-Law No 536/96 generalises the possibility of using a medicinal product off-label, even where an alternative treatment is available, for exclusively financial reasons, without the widespread use of the cheaper medicinal product having been preceded by an analysis of the ineffectiveness of the available medicinal products. According to Novartis Farma, that provision breaches the mandatory character of an MA, as follows from Article 6(1) of Directive 2001/83, and is incompatible with Directive 89/105.

Novartis Farma also submits that Article 1(4)bis of Decree-Law No 536/96, by conferring on the AIFA the power to '[activate] the appropriate monitoring mechanisms to safeguard patient safety and [take] the necessary decisions in good time', is capable of leading to an encroachment by that national authority on the regulatory spheres which Regulation No 726/2004 attributes to the EMA.

Novartis Farma claims that the repackaging of Avastin does not comply with the conditions required by EU pharmaceutical law in order to be covered by the exemption for medicinal products prepared in a pharmacy under Article 3(1) of Directive 2001/83.

The AIFA submits that Directive 2001/83 was not intended to apply to a situation such as that at issue in the main proceedings. The provisions of Article 1(4)bis of Decree-Law No 536/96 do not concern the MA of a medicinal product, but the conditions for its reimbursement. In accordance with Article 5 of Directive 2001/83, the situation at issue in the case in the main proceedings falls outwith the scope of that directive.

According to the AIFA, under Article 2(1) and Article 3(1) of Directive 2001/83, that directive is not applicable to the preparation of Avastin for use in treating eye diseases. In addition, the Court of Justice has already held, in the judgment of 11 April 2013, *Novartis Pharma* (C-535/11, EU:C:2013:226), that repackaging Avastin for intravitreal use does not require authorisation to manufacture under Article 40(2) of Directive 2001/83.

The AIFA also claims that Article 1(4)bis of Decree-Law No 536/96 does not encroach on the powers which Regulation No 726/2004 confers on the EMA.

The referring court expresses doubts arising from the judgment of 16 July 2015, *Abcur* (C-544/13 and C-545/13, EU:C:2015:481) concerning the interpretation of Article 3(1) of Directive 2001/83.

In those circumstances, the Consiglio di Stato (Council of State) decided to stay the proceedings and to refer the following questions to the Court of Justice 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?

(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?

(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]?

(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?'

Admissibility of the request for a preliminary ruling

The Italian Government submits that the questions referred for a preliminary ruling do not fall within the scope of EU law and are not necessary to the outcome of the case in the main proceedings. Since the off-label use of a medicinal product is not governed by EU law, the questions referred to the Court are manifestly inadmissible.

Ireland takes the view that the questions referred for a preliminary ruling are inadmissible in that they are hypothetical. The referring court has not provided sufficient explanations regarding the facts of the case and the relevance of the questions referred to the outcome of the case in the main proceedings.

The Regione Emilia-Romagna (the Region of Emilia-Romagna, Italy) and the Società Oftalmologica Italiana (SOI) — Associazione Medici Oculisti Italiani (AMOI) submit that the first question referred for a preliminary ruling is inadmissible in that it is irrelevant to the outcome of the case in the main proceedings. The Region of Emilia-Romagna assets, on the same ground, that the second question referred is also inadmissible.

In that regard, it must be borne in mind that, in the context of the cooperation between the Court and the national courts established in Article 267 TFEU, it is solely for the national court, before which the dispute has been brought and which must assume responsibility for the subsequent judicial decision, to determine in the light of the

particular circumstances of the case both the need for a preliminary ruling in order to enable it to deliver judgment and the relevance of the questions which it submits to the Court. Consequently, where the questions submitted concern the interpretation of EU law, the Court is, in principle, bound to give a ruling (judgment of 6 September 2016, *Petruhhin*, C-182/15, EU:C:2016:630, paragraph 19 and the case-law cited).

It follows that questions on the interpretation of EU law referred by a national court in the factual and legislative context which that court is responsible for defining and the accuracy of which is not a matter for this Court to determine, enjoy a presumption of relevance. The Court may refuse to rule on a question referred for a preliminary ruling by a national court only where it is quite obvious that the interpretation of EU law that is sought bears no relation to the actual facts of the main action or its purpose, where the problem is hypothetical, or where the Court does not have before it the factual or legal material necessary to give a useful answer to the questions submitted to it (judgment of 26 July 2017, *Persidera*, C-112/16, EU:C:2017:597, paragraph 24 and the case-law cited).

In the present case, the questions, which concern the interpretation of Directive 89/105, Directive 2001/83 and Regulation No 726/2004, have been referred in respect of a dispute regarding the conformity with those provisions of EU law of national measures intended to allow Avastin to be used for indications not covered by its MA. They thus bear a direct relation to the purpose of the main action and are not hypothetical.

It follows that the questions referred for a preliminary ruling are admissible.

Consideration of the questions referred

Preliminary observations

By its questions, the referring court wishes, in essence, to ascertain whether the national measures at issue in the main proceedings, which lay down the conditions under which the national healthcare insurance system, for financial reasons, reimburses Avastin repackaged in order to be administered to patients for the treatment of ophthalmological indications not covered by its MA, frustrate the effectiveness of Directive 89/105 and of Directive 2001/83 and the powers conferred on the European Union under the centralised procedure introduced by Regulation No 726/2004.

It should be noted that, in accordance with Article 168(7) TFEU, EU law does not detract from the power of the Member States to organise their social security systems and to adopt, in particular, measures intended to govern the consumption of pharmaceutical products in order to promote the financial stability of their healthcare insurance schemes (judgment of 22 April 2010, *Association of the British Pharmaceutical Industry*, C-62/09, EU:C:2010:219, paragraph 36).

The organisation and management of health services and the allocation of the resources assigned to them are the responsibility of the Member States. Article 4(3) of Directive 2001/83 and the second paragraph of Article 1 of Regulation No 726/2004 thus state that the provisions of those instruments are not to affect the powers of Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions.

However, although EU law, in particular Directive 89/105, does not detract from the powers of the Member States in this area, the fact remains that, in exercising those powers the Member States must comply with EU law (judgment of 2 April 2009, *A. Menarini Industrie Farmaceutiche Riunite and Others*, C-352/07 to C-356/07, C-365/07 to C-367/07 and C-400/07, EU:C:2009:217, paragraphs 19 and 20).

In addition, the EU rules on pharmaceutical products 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 (judgment of 23 January 2018, *F. Hoffmann-La Roche and Others*, C-179/16, EU:C:2018:25, paragraph 59).

Having regard to those considerations, in order to ascertain whether national measures such as those at issue in the main proceedings are precluded by the conditions laid down in the EU rules, it is appropriate to consider, in the first place, the second question referred on the contours of the scope of Directive 2001/83, then, in turn, the first, fourth and third questions referred for a preliminary ruling.

The second question

By its second question, the referring court asks, in essence, whether Article 3(1) of Directive 2001/83 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 that directive.

In the case in the main proceedings, the application of Directive 2001/83 to Avastin has not been called into question. By contrast, the referring court asks whether the transformations which that medicinal product undergoes when being repackaged for the purposes of its use in treating eye diseases not covered by the terms of its MA, in circumstances in conformity with the national measures the legality of which is challenged, may fall within the scope of Article 3(1) of that directive and therefore take Avastin thus modified outside of the scope of the directive.

For the purposes of answering that question, it must be borne in mind that the scope of Directive 2001/83 is defined according to what falls within it in Article 2(1) thereof, which provides that the directive is to apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process. Article 3(1) and (2) of the directive sets out certain exceptions to its scope in respect of medicinal products prepared in a pharmacy, either in accordance with a medical prescription for an individual patient, or in accordance with the prescriptions of a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question. It follows therefrom that, in order to fall within the scope of Directive 2001/83, the medicinal product in question must, firstly, satisfy the conditions laid down in Article 2(1) of that directive and, secondly, must not fall within one of the exceptions expressly provided for in Article 3 of that directive (judgment of 16 July 2015, *Abcur*, C-544/13 and C-545/13, EU:C:2015:481, paragraphs 38 and 39).

It is therefore the industrial character of the production of a medical product which determines whether that product falls within the scope of Directive 2001/83, bearing in mind that the EU legislature specifically specified

that medicinal products prepared in a pharmacy in accordance with the conditions set out in Article 3 of that directive are expressly excluded from its scope.

The Court must therefore hold that the exclusion from the scope of Directive 2001/83 set out in Article 3 thereof covers only medicinal products 'prepared' in a pharmacy, that is to say those produced in a pharmacy, namely magistral formulas and officinal formulas. Avastin does not fall within either of those categories. It is not produced in dispensing or hospital pharmacies, but industrially in Roche's laboratories, which holds its MA.

It is also clear from the file before the Court that the processes for repackaging Avastin undertaken in accordance with the national measures at issue in the main proceedings do not significantly change the composition, form or other fundamental characteristics of that medicinal product. Those repackaging processes cannot be regarded as the 'preparation' of a new medicinal product derived from Avastin by means of a magistral formula or an officinal formula. They do not therefore fall within the scope of Article 3 of Directive 2001/83.

Furthermore, an interpretation of Article 3 of Directive 2001/83 which would result in Avastin which has undergone repackaging processes in accordance with the national measures at issue in the main proceedings being excluded from the scope of all of the provisions of that directive, would mean breaking the control introduced by that directive over the entire chain of distribution of medicinal products.

In that regard, the Court notes that, in accordance with the essential aims of Directive 2001/83, inter alia, to safeguard public health, recital 35 thereof states that the directive aims 'to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the [European Union] through to supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions'. As the Advocate General stated in point 63 of his Opinion, that objective would be defeated if a repackaging process undertaken after a medicinal product had been placed on the market could have the effect of excluding that product from the scope of Directive 2001/83 within which it had until then fallen.

The application of Article 3 of Directive 2001/83 in a situation such as that at issue in the main proceedings would have the effect of frustrating the effectiveness of several provisions of that directive intended to safeguard the control of medicinal products over the entire chain of their distribution. Thus, the second subparagraph of Article 6(1) thereof provides expressly that 'when a medicinal product has been granted an initial [MA] ..., any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation ... or be included in the initial [MA]. All these [MAs] shall be considered as belonging to the same global marketing authorisation ...'.

Similarly, under the second subparagraph of Article 40(2) of Directive 2001/83, no manufacturing authorisation is required both for total and partial manufacture and for the various processes of dividing up, packaging or presentation of a medicinal product where 'those processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes'.

That exception would therefore be superfluous if Article 3 of Directive 2001/83 were to result in the exclusion from the scope of that directive, and therefore from the obligation to obtain an MA and manufacturing authorisation, of a medicinal product which, after having been placed on the market and produced in accordance with the requirements of the directive, had been repackaged in accordance with the second subparagraph of Article 40(2) of the directive.

As regards the pharmacovigilance system, the Court also notes that, according to the second subparagraph of Article 101(1) of Directive 2001/83, '[that system] shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the [MA] as well as from use outside the terms of the [MA], and to adverse reactions associated with occupational exposure'. The effectiveness of that provision would be frustrated if Article 3 of Directive 2001/83 could be applied to a repackaging process intended to allow Avastin to be used off-label in accordance with the national measures at issue in the main proceedings, thereby excluding that use from the scope of that directive, including from the provisions of the directive on pharmacovigilance.

The answer to the second question referred is therefore that Article 3(1) of Directive 2001/83 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 that directive.

The first question

By its first question, the referring court asks, in essence, whether Article 6 of Directive 2001/83 must be interpreted as precluding national measures such as those at issue in the main proceedings which determine the conditions under which Avastin may be repackaged in order to be used for the treatment of ophthalmological indications not covered by its MA and, if so, whether Article 5 of that directive must be interpreted as allowing such measures to be justified as a derogation.

As has been stated in paragraph 51 above, the EU rules on pharmaceutical products 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.

Those conditions include the requirement of holding an MA and manufacturing authorisation, both authorisations being stated in Articles 6 and 40 of Directive 2001/83 respectively. In order to provide the referring court with a helpful answer to allow it to resolve the dispute before it, the Court considers that it is also necessary to give an interpretation of Article 40 of that directive even if that article is not specifically mentioned in the request for a preliminary ruling before it (judgment of 11 April 2013, *Berger*, C-636/11, EU:C:2013:227, paragraph 31).

As regards placing a medicinal product on the market, the first subparagraph of Article 6(1) of Directive 2001/83 provides that no medicinal product may be placed on the market of a Member State unless an MA has been issued by the competent authorities of that Member State in accordance with that directive or unless an authorisation has been issued in accordance with the centralised procedure provided for in Regulation No 726/2004 for medicinal products referred to in the annex to that regulation (judgments of 23 January 2018, *F. Hoffmann-La Roche and*

Others, C-179/16, EU:C:2018:25, paragraph 53, and of 29 March 2012, *Commission* v *Poland*, C-185/10, EU:C:2012:181, paragraph 26).

The principle of a mandatory MA also applies, according to the second subparagraph of that article, when a medicinal product has been granted an initial [MA] in accordance with the first subparagraph, in so far as, in that case, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions are also to be granted an authorisation in accordance with the first subparagraph or be included in the initial [MA].

In accordance with that principle, the Court thus held that where a medicinal product was the subject of two separate central marketing authorisations, one for packs of five items and the other for packs of 10 items, EU pharmaceutical rules precluded that product from being marketed in a package consisting of two packs of five items which had been joined together and relabelled, unless an MA was issued in that regard, on the ground that the detailed and specific requirements regarding the packaging of medicinal products subject to a central MA were intended to prevent consumers from being misled and thereby to protect public health (judgment of 19 September 2002, *Aventis*, C-433/00, EU:C:2002:510, paragraph 25).

In a case similar to that at issue in the main proceedings, the Court held that the repackaging of Avastin for off-label use in the treatment of eye diseases did not require a new MA, provided that that process does not result in any modification of the medicinal product and that it is carried out solely on the basis of individual prescriptions making provision for that process (judgment of 11 April 2013, *Novartis Pharma*, C-535/11, EU:C:2013:226, paragraph 42).

The reasoning behind that decision is that, contrary to the facts of the case which gave rise to the judgment of 19 September 2002, *Aventis* (C-433/00, EU:C:2002:510), the process of repackaging Avastin takes place prior to that medicinal product being placed on the market, after a doctor has prescribed its use in such conditions for a patient through an individual prescription.

The Court thus stated that the drawing off of liquid medicinal products from the original vials, and the transfer into ready-to-use syringes of the portions so drawn off, without any modifications of those products, is in reality analogous to actions which, in the absence of another undertaking's activities, could otherwise be, or have been, carried out, under their responsibility, by doctors prescribing the treatment or by pharmacies themselves in their dispensaries, or else in hospitals (judgment of 11 April 2013, *Novartis Pharma*, C-535/11, EU:C:2013:226, paragraphs 42 and 43).

Subject to factual findings to be made by the referring court, the repackaging of Avastin under the conditions laid down in the national measures at issue in the main proceedings, does not therefore require an MA to be obtained in so far as that process is prescribed by a doctor by means of an individual prescription and undertaken by pharmacists for that medicinal product to be administered in hospitals.

As regards the manufacturing of a medicinal product, while, under Article 40(1) of Directive 2001/83, the manufacture of medicinal products is subject in general to the requirement of holding an authorisation, the second subparagraph of Article 40(2) of the directive provides that the manufacturing authorisation is not required for processes such as the preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply of medicinal products, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes. It follows that, where those manufacturing processes are not carried out for such purposes, pharmacists are not exempt from the requirement to hold manufacturing authorisation (judgments of 28 June 2012, *Caronna*, C-7/11, EU:C:2012:396, paragraph 35, and of 11 April 2013, *Novartis Pharma*, C-535/11, EU:C:2013:226, paragraphs 51 and 52).

As the Advocate General stated in point 79 of his Opinion, despite the fact that it may be found before the referring court that the pharmacies authorised to divide up and repackage Avastin under the national measures at issue in the main proceedings do not hold the authorisation required under Article 40(1) of Directive 2001/83, those pharmacies could nevertheless fall within the exception under the second subparagraph of Article 40(2) of that directive. Subject to findings of fact to be made by the referring court, it must be held that if it is found that, in accordance with the national measures at issue in the main proceedings, Avastin is, on the basis of an individual prescription, repackaged to be used off-label for the treatment of eye diseases, by a pharmacy lawfully authorised to that effect, for that medicinal product to be administered in hospitals, such a process falls within the exception of the directive and does not require manufacturing authorisation.

It follows that, since the process of repackaging Avastin covered by the decisions of the AIFA at issue in the main proceedings does not require an MA under Article 6 of Directive 2001/83 or manufacturing authorisation, within the meaning of Article 40 of that directive, it is not necessary to answer the first question in so far as it concerns the interpretation of Article 5 of the directive.

In the light of all of the foregoing considerations, the answer to the first question referred is that Article 6 of Directive 2001/83 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 MA.

The fourth question

By its fourth question, the referring court asks, in essence, whether Article 1(3) of Directive 89/105, according to which nothing in that directive is to permit the marketing of a medicinal product in respect of which the MA provided for in Article 6 of Directive 2001/83 has not been issued, must be interpreted as precluding national measures such as those at issue in the main proceedings.

Given the answer to the first question, there is no need to answer the fourth question.

The third question

By its third question, the referring court asks, in essence, whether Articles 3, 25 and 26 of Regulation No 726/2004 must be interpreted as precluding a national measure such as that taken pursuant to Article 1(4)bis

of Decree-Law No 536/96 which authorises the AIFA to monitor medicinal products such as Avastin the off-label use of which is reimbursed by the SSN and, where relevant, introduce measures necessary to safeguard patient safety, on the ground that that measure encroaches on the exclusive powers of the EMA in respect of medicinal products subject to the centralised procedure.

It is true that Regulation No 726/2004, in particular Articles 5 to 9, confers on the EMA exclusive responsibility for evaluating applications for an MA under the centralised procedure. However, it is clear from the answer to the first question, that repackaging Avastin under the conditions set by the national measures at issue in the main proceedings does not require an MA to be obtained. Accordingly, those measures cannot undermine the exclusive powers conferred on the EMA in evaluating applications for MA under the centralised procedure any more than Article 1(4)bis of Decree-Law No 536/96.

As regards the pharmacovigilance system for medicinal products placed on the EU market, the Court notes that, in accordance with Article 23(2) and Article 101(1) of Directive 2001/83, that system also covers any use of a medicinal product outside the terms of its MA. As regards medicinal products covered by the centralised procedure, Chapter 3 of Title II of Regulation No 726/2004, in particular Articles 25 and 26 thereof, introduces pharmacovigilance mechanisms bringing together the national competent authorities and the EMA, the latter of which ensures their coordination.

Those articles do not therefore preclude a national measure, such as that taken pursuant to Article 1(4)bis of Decree-Law No 536/96, which authorises the AIFA to activate the appropriate monitoring mechanisms to safeguard patient safety and to take the necessary decisions in good time, provided that their implementation furthers or reinforces the pharmacovigilance system introduced by Regulation No 726/2004.

In the light of all of the foregoing considerations, the answer to the third question referred is that Articles 3, 25 and 26 of Regulation No 726/2004 must be interpreted as not precluding a national measure such as that taken pursuant to Article 1(4)bis of Decree-Law No 536/96 which authorises the AIFA to monitor medicinal products such as Avastin the off-label use of which is reimbursed by the SSN and, where relevant, to introduce measures necessary to safeguard patient safety.

Costs

Since these proceedings are, for the parties to the main proceedings, a step in the action pending before the national court, the decision on costs is a matter for that court. Costs incurred in submitting observations to the Court, other than the costs of those parties, are not recoverable.

On those grounds, the Court (First Chamber) hereby rules:

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 that directive, as amended by Directive 2012/26.

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.

Articles 3, 25 and 26 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended by Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012, 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, recante 'Misure per il contenimento della spesa farmaceutica e la rideterminazione del tetto di spesa per l'anno 1996', convertito dalla legge del 23 dicembre 1996, n. 648 (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, convertito dalla legge del 16 maggio 2014, n. 79 (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) (Italian Medicines Agency (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.

[Signatures]

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* Language of the case: Italian.