Reports of Cases

OPINION OF ADVOCATE GENERAL
SAUGMANDSGAARD ØE
delivered on 25 July 2018 [1]

Case C-29/17

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

(Request for a preliminary ruling from the Consiglio di Stato (Council of State, Italy)

(Reference for a preliminary ruling — Medicinal products — Directive 2001/83/EC — Scope — Exclusion — Article 3(1) — Power to derogate — Article 5(1) — Marketing authorisation — Article 6(1) — Manufacturing authorisation — Article 40(1) and (2) — Regulation (EC) No 726/2004 — Marketing authorisation issued on completion of the centralised procedure — Article 3(1) — Reimbursement by the national healthcare insurance system of a medicinal product used for a treatment not covered by its marketing authorisation (off-label use))

I. Introduction

1. By its request for a preliminary ruling, the Consiglio di Stato (Council of State, Italy) asks the Court of Justice to interpret Articles 3(1), 5(1) and 6(1) of Directive 2001/83/EC, [2] Articles 3, 25 and 26 of Regulation (EC) No 726/2004 [3] in conjunction with the Annex thereto and Article 1(3) of Directive 89/105/EEC. [4]

1 Original language: French.

2 Directive 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).

3 Regulation 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).

4 Council Directive of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ 1989 L 40, p. 8).

2. The request has been made in proceedings between Novartis Farma SpA and the Agenzia Italiana del Farmaco (Italian Medicines Agency, 'the AIFA') concerning whether the decisions by which that agency included a medicinal product in the list of medicinal products reimbursed by the Servizio Sanitario Nazionale (National Health Service, Italy, SSN) were lawful in so far as that product is used for therapeutic indications not included in its marketing authorisation ('MA').

3. That medicinal product, Avastin, has been authorised to treat certain types of cancer. It is also used to treat a common disease of the retina, age-related macular degeneration ('AMD'), even though the MA for Avastin does not mention that therapeutic indication. That use, known as 'off-label' use, involves Avastin being taken out of its original vial and repackaged in a strength and presentation and with a route of administration not covered by its MA.

4. Continuing the line of cases that includes Novartis Pharma [5] and F. Hoffmann-La Roche and Others [6], this case brings issues arising from that off-label use of Avastin to the attention of the Court of Justice for a third time. The referring court's questions concern essentially whether reimbursement by the SSN of that medicinal product when it is used off label is compatible with the requirements under the EU pharmaceutical rules on the placing on the market of medicinal products. The referring court also enquires of the Court of Justice how the pharmacovigilance powers for medicinal projects subject to the centralised authorisation procedure under Regulation No 726/2004 are distributed between the national authorities and the European Union.

II. Legal context

A. EU law

1. Directive 2001/83

5. Article 2(1) of Directive 2001/83 states that the 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'.

6. Article 3 of the directive reads as follows:

'This Directive shall not apply to:

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

…'

7. Article 5(1) of that directive provides that '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'.

5 Judgment of 11 April 2013 (C-535/11, EU:C:2013:226).

6 Judgment of 23 January 2018 (C-179/16, EU:C:2018:25).

8. Article 6(1) of that directive states:

'No medicinal product may be placed on the market of a Member State unless a[n 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 [No 726/2004] …

When a medicinal product has been granted an initial [MA] in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, routes of administration, 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 …'

9. Article 8(3) of Directive 2001/83 indicates the information and documents that must accompany applications for MAs. In particular, Article 8(3)(j) refers to the summary of the product characteristics. According to Article 11 of that directive, that document must indicate, amongst other information, the strength and the pharmaceutical form, the qualitative and quantitative composition of all the constituents, the therapeutic indications, the posology and the method of administration of the medicinal product.

10. Article 40 of the directive is worded 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 …

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.'

2. Directive 89/105

11. Article 1(3) of Directive 89/105 provides that 'nothing in this Directive shall permit the marketing of a proprietary medicinal product in respect of which the authorisation provided for in Article [6(1)] of Directive [2001/83] has not been issued'.

3. Regulation No 726/2004

12. Regulation No 726/2004 establishes a centralised procedure for authorising medicinal products at EU level.

13. Under Article 3(1) of that regulation, 'no medicinal product appearing in the Annex may be placed on the market within the [European Union unless [an MA] has been granted by the [European Union] in accordance with the provisions of [that] Regulation.' Point 1 of that annex includes medicinal products developed by means of certain biotechnological processes.

14. According to Article 13(1) of that regulation, an MA granted on completion of the centralised procedure is valid throughout the European Union and confers the same rights and obligations in each of the Member States as an MA granted by that Member State in accordance with Article 6 of Directive 2001/83.

15. Article 16(2) of Regulation No 726/2004 provides that the holder of an MA issued after the centralised procedure must immediately provide the European Medicines Agency (EMA), the European Commission and the Member States with any new information that might entail the amendment of the particulars or documents referred to, in particular, in Article 8(3) of Directive 2001/83. The information to be provided '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]'.

16. Furthermore, Articles 21 to 29 of that regulation provide for a system of pharmacovigilance for the medicinal products authorised at EU level.

17. In accordance with Article 24(1) of the regulation, that system includes the EMA, in collaboration with the Member States and the Commission, setting up and maintaining a database to collate information regarding in particular 'suspected adverse reactions in human beings arising from use of the medicinal product within the terms of the [MA] as well as from uses outside the terms of the [MA]'.

18. Under Article 25 of that regulation, '[the EMA] 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 …'.

19. Under Article 26 of Regulation No 726/2004, the EMA, in collaboration with the Member States and the Commission, must set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorised in the EU.

B. Italian law

20. Article 1(4) of decreto-legge n. 536, 21 ottobre 1996, convertito senza modificazioni dalla legge n. 648, 23 dicembre 1996 (Decree-Law No 536 of 21 October 1996, converted unamended into Law No 648 of 23 December 1996 ('Law No 648/96') provides that:

'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) ('List 648'), in accordance with the procedures and criteria adopted by that commission, can be prescribed and are fully reimbursable by the [SSN] from 1 January 1997 ...'

21. Article 3(2) of decreto-legge n. 36, 20 marzo 2014, convertito con modificazioni dalla legge n. 79, 16 maggio 2014 (Decree-Law No 36 of 20 March 2014, converted as amended into Law No 79 of 16 May 2014, 'Law No 79/2014'), inserted Article 1(4)bis, worded as follows, into Article 1 of Law No 648:

'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 [List 648] 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 activates the appropriate monitoring mechanisms to safeguard patient safety and make the necessary adaptations in good time.'

III. The main proceedings, the questions referred and the procedure before the Court of Justice

22. A company belonging to the Novartis group holds an MA for a biotechnological product known as Lucentis, the main ingredient of which is ranibizumab. That MA was granted following the centralised procedure under Regulation No 726/2004. It covers the treatment of AMD. Lucentis is presented in the form of a vial containing 0.23 ml of medicinal solution. Each vial can be used for a single 0.05 ml intravitreal injection. The SSN reimburses the cost of Lucentis.

23. A company belonging to the Roche group holds an MA for a different biotechnological product, Avastin, the active ingredient of which is bevacizumab. That medicinal product differs from Lucentis in a number of structural and pharmacological ways. Avastin has been authorised, also under the centralised procedure, for indications for the treatment of cancer. It is presented in the form of a vial containing 4 ml of medicinal substance to be diluted for infusion.

24. A number of doctors also prescribe Avastin to treat AMD, even though its MA does not cover that therapeutic indication. It is clear from the order for reference that under Italian law off-label use of a medicinal product is permitted where the doctor, exercising the therapeutic freedom of medical practitioners, considers it appropriate for the patient's health. The Avastin must in that case be repackaged by taking the medicinal substance out of the original vial and dividing it into several single-use syringes each containing 0.1 ml, for intravitreal injection.

25. On the basis of Article 1(4)bis of Law No 648/96 and in accordance with an opinion of 15 April 2014 of the Consiglio Superiore de Sanità (Federal Board of Health, Italy), the AIFA adopted Decision 622 of 24 June 2014 ('Decision No 622/2014'), including the medicinal product 'bevacizumab–Avastin' on List 648 (which lists the medicinal products reimbursable by the SSN[7]) for the treatment of AMD.[8]

26. The referring court states that the decision by the Italian legislature to authorise inclusion on that list was probably dictated by purely financial reasons. According to information provided by the Federal Board of Health in the opinion referred to above, a vial of Lucentis costs the SSN EUR 902, compared with EUR 82 for the dose of Avastin required for an intravitreal injection. In that opinion, the Federal Board of Health found that the preparation of bevacizumab for intravitreal use is a 'sterile magistral pharmaceutical preparation'.

27. Article 2(1) of Decision 622/2014 provides:

'The medicinal product bevacizumab-Avastin is 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:

(a) 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;

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

7 See point 21 of this Opinion.

8 Whilst the referring court did not restate these factual details in the present case, I think it is helpful to note that, as the Court of Justice set out in its judgment of 23 January 2018, *F. Hoffmann-La Roche and Others* (C-179/16, EU:C:2018:25, paragraphs 27 to 29), Avastin was first used off label before any medicinal products authorised to treat AMD were placed on the market. In 2007 the AIFA included Avastin on List 648 for the treatment of AMD under Article 1(4) of Law No 648/96, in so far as at that time no alternative therapy was authorised for that therapeutic indication. Once Lucentis and other medicinal products authorised for that indication were included on that list in 2008, the AIFA stopped allowing reimbursement of Avastin to treat AMD. The insertion of Article 1(4)bis into Law No 648/96 has meant that the AIFA can again include Avastin on List 648 for the treatment of AMD even though there are medicinal products on the market the MA of which covers that therapeutic indication.

(c) 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;

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

28. According to Article 3 of that decision, 'the medicinal product, reimbursable by the SSN, must be prescribed by the user departments for each patient by completing the computerised prescription form …'.

29. Article 4 of that decision provides that 'the AIFA reserves the right to reach any different assessment and to make any more appropriate decision in order to ensure patient safety… as a result of the analysis of data gathered from monitoring or of any other available scientific evidence'.

30. Decision No 622/2014 was amended by Decision No 79 of 30 January 2015 ('Decision No 79/2015' and, together with Decision No 622/2014, 'the AIFA decisions') in respect of identifying the persons that can administer the medicinal product in question. Those persons now include not only highly specialised ophthalmological departments within public hospitals designated by the regions, but all highly specialised hospitals designated by the regions. [9]

31. The referring court also states that pharmacies prepare Avastin for the purpose of use in eyes on the basis of individual prescriptions. However, those prescriptions are not customised according to the different individual needs of each person, and the preparation in question is therefore produced in equal quantities for each patient, in batches and repeatedly. [10]

32. Before the Tribunale amministrativo regionale per il Lazio (Regional Administrative Court, Lazio, Italy) Novartis Farma contested whether the AIFA decisions were lawful. According to Novartis Farma, those decisions are such as to advantage its competitor, Roche Italia, by appreciably reducing the market share of Lucentis for the treatment of AMD.

33. That action was dismissed in a judgment of 13 January 2016. Novartis Farma appealed that judgment before the Consiglio di Stato (Council of State).

34. In its appeal, Novartis Farma claims that the AIFA decisions are unlawful as a result of the knock-on effect of Article 3(2) of Law No 79/2014, inserting Article 1(4)bis of Law No 648/96 that forms the legal basis of those decisions, in so far as Article 3(2) disregards EU law because it authorises medicinal products used for therapeutic indications not covered by their MAs to be included on List 648 even where there are medicinal products authorised for those indications.

35. According to Novartis Farma, that article infringes Article 6(1) of Directive 2001/83, under which any variation, in particular to the therapeutic indications, strength, route of administration or presentation of a medicinal product, must obtain a new MA or an amendment of the existing MA. The only derogations from that article are, it claims, those under Article 3(1) or Article 5(1) of Directive 2001/83, which do not apply in the present case. Infringement of Article 6(1) of that directive, it argues, also gives rise to infringement of Article 1(3) of Directive 89/105.

9 As emerges from the case file submitted to the Court, Decision No 79/2015 was in turn amended by Decision No 799 of 28 April 2017 ('Decision No 799/2017') in respect of designating the persons that can repackage Avastin in single-use doses. That process can now be carried out not only by hospital pharmacies, but by all pharmacies — including dispensing pharmacies — that satisfy the requirements laid down. The AIFA adopted that decision as a result of a judgment of 9 January 2017, included in the case file in these proceedings, by which the Consiglio di Stato (Council of State) annulled Article 2(1)(a) of Decision No 622/2014 in so far as it reserved that right to hospital pharmacies alone. Roche Italia SpA has apparently filed a third party application against that judgment.

10 This is apparent from the wording of the second question referred.

36. Novartis Farma furthermore claims that Article 3(2) of Law No 79/2014, in so far as it gives the AIFA monitoring powers where medicinal products are used off label, encroaches upon the powers that Regulation No 726/2004 confers on the EMA in relation to authorising the marketing of medicinal products and pharmacovigilance.

37. In its defence, the AIFA argues, amongst other matters, that Avastin is not prepared industrially for use in eyes. The resulting medicinal product therefore does not fall within the scope of Directive 2001/83 and is, the AIFA claims, a 'magistral formula' within the meaning of Article 3(1) of that directive. Moreover, the Italian Republic is entitled to avail itself of the power under Article 5(1) of that directive to derogate from its provisions. In any event, the AIFA submits, first, that the main proceedings do not concern the placing on the market of a medicinal product, only its use off label. Secondly, under the second subparagraph of Article 40(2) of that directive the process in question can be carried out without a manufacturing authorisation. It also asserts that the monitoring powers given to the AIFA do not in any way interfere with the EMA's powers.

38. 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 the second recital 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 [EMA] 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 national regulatory authority (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 [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 [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?'

39. Novartis Farma, Roche Italia, the Società Oftalmologica Italiana (SOI) — the Associazione Medici Oculisti Italiani (AMOI) (SOI-AMOI), the Regione Emilia-Romagna (Region of Emilia-Romagna, Italy), the Regione Veneto (Region of Veneto, Italy), Ireland, the Italian, Greek, Polish, Finnish and Swedish Governments and the Commission filed written observations.

40. Novartis Farma, Roche Italia, SOI-AMOI, the regions of Emilia-Romagna and Veneto, the Italian and Polish governments and the Commission attended the hearing on 26 April 2018.

IV. Analysis

A. The first and second questions referred

1. Preliminary observations

41. By its first question, the Consiglio di Stato (Council of State) asks, in essence, whether EU pharmaceutical rules preclude a provision of national legislation, such as Article 1(4)bis of Law No 648/96, that allows medicinal products used for off-label therapeutic indications to be reimbursed, exclusively in order to contain expenditure by the national healthcare insurance system, even where there are medicinal products the MA of which does cover those indications. According to that court, that reimbursability encourages off-label uses, regardless of the therapeutic needs of each patient.

42. The first limb of that question concerns whether such a provision complies with Article 6(1) of Directive 2001/83. According to that article, medicinal products cannot be placed on the market in the Member States unless an MA has previously been obtained for them. When an initial MA has been granted for a medicinal product, any addition or variation relating in particular to the strength, route of administration, presentation or therapeutic indications must be covered by a new MA or be added to the initial MA. [11]

43. In the event that a provision such as Article 1(4)bis of Law No 648/96 is incompatible with the requirements under Article 6(1) of Directive 2001/83, the referring court enquires, by the second limb of its first question, whether Article 5(1) of that directive permits a Member State to derogate from those requirements in a situation such as that in the main proceedings.

44. The referring court believes that if Article 1(4)bis of Law No 648/96 infringes Directive 2001/83, the decisions by which the AIFA, applying that article, included Avastin on the list of reimbursable medicinal products for treating AMD and specified the conditions under which that product can be repackaged and administered to patients, would as a result be unlawful.

45. It should be noted in that regard that, under Article 168(7) TFEU, 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 reaffirm those national powers, stating 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.

11 Although Article 6(1) of Directive 2001/83 does not so state expressly, any variation relating to the therapeutic indications must be regarded as a 'variation' within the meaning of that article, as borne out by point 2(a) of Annex II of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of [MAs] for medicinal products for human use and veterinary medicinal products (OJ 2008 L 334, p. 7).

46. As the case-law shows, the Member States also still have powers not only to regulate the reimbursement of medicinal products in order to promote the financial stability of their healthcare insurance schemes,[12] but to regulate the conditions under which doctors can prescribe those products.[13] It is therefore the Member States alone that are responsible, where necessary, for governing how doctors exercise their therapeutic freedom.[14]

47. Nevertheless, the Court of Justice has repeatedly held that the Member States must exercise their powers in compliance with EU law.[15] This means, as I see it, that EU law does not preclude Member States' healthcare insurance systems from reimbursing a medicinal product used off label, provided nevertheless that the product in question is, amongst other requirements, placed on the market and manufactured in compliance with EU pharmaceutical rules. A Member State, unless it is to deprive those rules of effectiveness, cannot, through its medicines reimbursement policy, condone the placing on the market or manufacture of medicinal products where those products do not have the authorisations required under those rules.

48. Thus, Article 1(4)bis of Law No 648/96, to the extent that it confers power on the AIFA to establish that the SSN can reimburse medicinal products used off label even where there are authorised alternative medicinal products, does not thereby contravene EU law, whether or not such reimbursement is perceived as encouraging doctors to prescribe those products.[16] The reimbursement must, nevertheless, be confined to medicinal products manufactured and marketed in compliance with EU pharmaceutical rules.

49. In the light of the foregoing, in order to provide the referring court with an answer of use to it,[17] it is necessary to provide that court with factors enabling it to ascertain whether the decisions the lawfulness of which is at stake in the main proceedings, by which the AIFA exercised its power under Article 1(4)bis of Law No 648/96, relate to medicinal products of that kind. I note, in that respect, that the AIFA decisions relate to the medicinal products resulting from the repackaging of vials of Avastin, by pharmacies that comply with the conditions laid down by those decisions, into several syringes containing only the dose necessary for an intravitreal injection, that are then delivered to hospitals where their contents are subsequently administered to patients.

12 See, to that effect, judgments 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, paragraph 19); of 22 April 2010, *Association of the British Pharmaceutical Industry* (C-62/09, EU:C:2010:219, paragraph 36), and of 29 March 2012, *Commission* v *Poland* (C-185/10, EU:C:2012:181, paragraph 47).

13 See, in that regard, judgment of 23 January 2018, *F. Hoffmann-La Roche and Others* (C-179/16, EU:C:2018:25, paragraph 59). See, also, judgment of 11 June 2015, *Laboratoires CTRS* v *Commission* (T-452/14, not published, EU:T:2015:373, paragraph 79).

14 In paragraph 56 of the judgment of 23 January 2018, *F. Hoffmann-La Roche and Others* (C-179/16, EU:C:2018:25), the Court of Justice held that a doctor can prescribe a medicinal product off label in the situations covered by the power to derogate from the scope of Directive 2001/83 under Article 5(1) of that directive. That fact cannot in my view be understood as limiting a doctor's therapeutic freedom to prescribe an off-label medicinal product to those exceptional situations alone. To my mind, it means only that, even where a medicinal product is placed on the market or manufactured in breach of the requirements under Directive 2001/83, a Member State can, under certain specific circumstances, exclude that product from application of that directive, so that doctors can exercise their therapeutic freedom in the interests of their patients (see point 90 et seq of this Opinion).

15 See, inter alia, judgments 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, paragraph 20), and of 29 March 2012, *Commission* v *Poland* (C-185/10, EU:C:2012:181, paragraph 47).

16 The Region of Emilia-Romagna, the Region of Veneto, SOI-AMOI and the Italian and Polish governments dispute the thesis, apparent from the wording of the first question referred, that Article 1(4)bis of Law No 648/96 encourages doctors to prescribe medicinal products off label. According to those parties, that article merely gives effect to doctors' therapeutic freedom. I note on that point that in any event, in its judgment of 22 April 2010, Association of the British Pharmaceutical Industry (C-62/09, EU:C:2010:219, paragraphs 32 to 37), the Court of Justice held that, in compliance with EU pharmaceutical rules, the national authorities responsible for public health are free to regulate the consumption of medicinal products to promote the financial stability of their healthcare insurance systems, where necessary by means of a scheme of financial incentives to prescribing, provided that scheme is based on objective criteria and does not discriminate in any way between national medicinal products and those from other Member States.

17 In the procedure laid down by Article 267 TFEU, it is for the Court of Justice to provide the national court with an answer which will be of use to it and enable it to determine the case before it, if necessary reformulating the questions referred to it (see, in particular, judgment of 22 February 2018, *SAKSA* (C-185/17, EU:C:2018:108, paragraph 28 and the case-law cited)).

50. Ascertaining whether those decisions relate to such medicinal products involves, initially, examining whether those products fall within the scope of Directive 2001/83 (section 2 below). That issue also forms the subject matter of the referring court's second question. Assuming that Directive 2001/83 does indeed apply to those medicinal products, it will be appropriate, secondly, to identify the content of the requirements it lays down as regards the placing on the market and manufacture of medicinal products in a situation such as that at issue in the main proceedings (section 3 below). In the event that those requirements were not satisfied in the present case, it would be necessary, thirdly, to examine whether the Member State in question is nevertheless entitled to derogate from them under Article 5(1) of that directive (see section 4 below).

51. The Novartis Farma judgment [18] has already more than adequately outlined the reasoning needed to answer those questions. The factual context of that case can nevertheless be distinguished from the dispute in the main proceedings in so far as that case concerned the repackaging of Avastin by a company which then delivered the resulting individual doses to the pharmacies that had ordered them. In particular, since that repackaging was not carried out by a pharmacy, Article 3(1) of Directive 2001/83 was inapplicable from the outset, and the Court of Justice accordingly did not address that aspect. That article in fact only relates to medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient, commonly known as the 'magistral formula'. The situation at issue in the present case, on the other hand, concerns the repackaging of Avastin by pharmacies to be supplied to hospitals.

2. Whether Avastin as prepared for the treatment of AMD falls within the scope of Directive 2001/83

52. By its second question, the referring court enquires whether Article 3(1) of Directive 2001/83 excludes from the scope of that directive a medicinal product such as that resulting from the processes, carried out under the AIFA decisions, to divide up and repackage Avastin for use in ophthalmology.

53. The referring court asks, in particular, whether the definition of 'magistral formula' within the meaning of that article includes a medicinal product of that nature where the processes in question, although they take place in pharmacies on the strength of individual medical prescriptions, are carried out in batches on the basis of an identical dosage for each patient. It also asks the Court of Justice what is the effect, in that context, of the fact that the medicinal product is administered in a facility other than that where those processes took place.

54. In addition, although the second question referred does not allude specifically to that issue, the Region of Veneto, SOI-AMOI and the Greek Government argue that the dividing up and repackaging of Avastin for the treatment of AMD are not carried out industrially. Accordingly, the resulting product, as well as being covered in any event by the exclusion from the scope of Directive 2001/83 under Article 3(1) of that directive, falls outside that scope as defined by the products to which it does apply, in Article 2(1). [19]

55. I would emphasise at the outset that, if the referring court's second question were answered in the affirmative, the product in question would then not be caught either by the requirements relating to placing on the market and manufacture, or by any of the other requirements under that directive — including those relating to pharmacovigilance. The provisions of Title II of Directive 2001/83, which include Articles 2 and 3, do indeed delimit the scope of that directive as a whole.

18 Judgment of 11 April 2013 (C-535/11, EU:C:2013:226).

19 The Court of Justice held in its judgment of 16 July 2015, *Abcur* (C-544/13 and C-545/13, EU:C:2015:481, paragraph 39), and reiterated in its judgment of 26 October 2016, *Hecht-Pharma* (C-276/15, EU:C:2016:801, paragraph 29), that in order to fall within the scope of that directive, a medicinal product, firstly, must 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.

56. To my mind, how that question should be answered depends primarily on whether or not the product obtained as a result of removing Avastin from its original file and transferring it into several single-use syringes for use in ophthalmology should be regarded, for the purposes of applying that directive, as a different medicinal product from the medicinal product Avastin, developed by the Roche group and covered by an MA for therapeutic indications for cancer. [20]

57. I note, in that respect, that preparing Avastin to treat AMD involves modifications relating to the strength, packaging and route of administration of that medicinal product. On the other hand, neither the order for reference nor the case file submitted to the Court indicates that preparing it in that way affects the medicinal substance itself. On the contrary, the AIFA decisions merely allow Avastin to be repackaged in single doses, under conditions intended to ensure sterility. [21]

58. In those circumstances, it is already plain from the lessons to be learned from the *Novartis Farma* judgment [22] that the medicinal product repackaged in that way cannot be regarded as a different product from the product Avastin for the purposes of applying Directive 2001/83. [23]

59. In that judgment the Court of Justice examined whether a company's activities that consisted of dividing up and repackaging vials of Avastin into syringes containing only the dose prescribed by a doctor for an intravitreal injection, and delivering those syringes to the pharmacies that had ordered them, required that company to obtain an MA. According to the Court, provided those processes do not modify the medicinal product and are carried out only on the basis of individual medical prescriptions, those activities cannot be equated with a new placing on the market of a medicinal product included in point 1 of the Annex to Regulation No 726/2004, and no MA is therefore required. The Court of Justice left it to the national court to ascertain whether those conditions were satisfied, [24] in the light of the fact that, in its order for reference, that court had proceeded on the basis that the dividing up and repackaging of Avastin did not modify its composition. [25]

60. The premiss underlying that approach, it seems to me, was that, provided the medicinal substance itself is not thereby altered, the changes to the strength, packaging and route of administration of Avastin so that it can be used off label do not give rise to the creation of a different medicinal product for the purposes of applying EU pharmaceutical rules. [26]

61. To my mind, where the repackaging in several individual doses of a medicinal product that falls within the scope of Directive 2001/83 does not involve the medicinal substance being modified, the product repackaged in that way continues to be covered by that directive. Accordingly, that product is still, amongst other matters, subject to the pharmacovigilance system established in that directive. [27]

20 It is common ground that the medicinal product Avastin is one of the biotechnological products covered by point 1 of the Annex to Regulation No 726/2004. That product was placed on the market after an MA had been obtained in accordance with Article 3(1) of that regulation. Nor is it disputed that Avastin falls within the scope of Directive 2001/83 as a medicinal product prepared industrially, intended to be placed on the market in the Member States and not covered by any of the exclusions under Article 3 of that directive.

21 See point 27 of this Opinion.

22 Judgment of 11 April 2013 (C-535/11, EU:C:2013:226, paragraphs 40 to 42).

23 The AIFA decisions likewise seem to reflect that view in so far as they included the product 'bevacizumab-Avastin' on List 648.

24 The referring court, that is to say, the Landgericht Hamburg (Regional Court, Hamburg, Germany), found that the processes in question did modify the product because they did not satisfy the terms of the MA for Avastin (judgment of 14 January 2014 (416 HKO 78/11), paragraph 117). The Oberlandesgericht Hamburg (Higher Regional Court, Hamburg, Germany) set the judgment aside on that point (judgment of 18 December 2015 (3 U 43/14), paragraph 210). The appeal court took the view that the proviso that the medicinal product must not be modified, set out in the judgment of 11 April 2013, *Novartis Pharma* (C-535/11, EU:C:2013:226, paragraphs 40 to 42), requires only that the composition of the medicinal product remains unchanged.

25 Judgment of 11 April 2013, *Novartis Pharma* (C-535/11, EU:C:2013:226, paragraphs 28 and 41).

26 In the same vein, in its judgment of 23 January 2018, *F. Hoffmann-La Roche and Others* (C-179/16, EU:C:2018:25, paragraphs 55 and 58), the Court of Justice perceived the situation at issue as one of the repackaging of Avastin for intravitreal injection. It did not describe the product resulting from that repackaging as a new medicinal product different from the one that already had an MA.

27 Under Articles 16(2) and 24(1) of Regulation No 726/2004 and Articles 23(2), second subparagraph, and 101(1) of Directive 2001/83, the pharmacovigilance obligations on the holders of MAs, the EMA and the national health authorities also include off-label uses of the medicinal products falling within the scope of those texts.

62. Indeed, as the wording of Articles 2 and 3 of Directive 2001/83 testifies, whether or not that directive applies depends not on each process a medicinal product undergoes, but on each medicinal product considered as such. As Ireland submits in essence, wherever a medicinal product falls within the scope of that directive, all the processes it undergoes — including its initial manufacture, placing on the market and, where applicable, subsequent processes to divide up and repackage the product — are governed by that directive.

63. With that in mind, recital 35 of Directive 2001/83 indicates that the directive seeks to exercise control over the entire chain of distribution of medicinal products, from their manufacture through to supply to the public (whilst the pharmacovigilance obligations apply after they are supplied to the public). That objective would be defeated if an action by a pharmacy intended to adapt the strength and packaging of the medicinal product so that it can be administered to patients — whether in the context of an off-label use or of a treatment covered by that product's MA [28] — had the effect of breaking that chain of control.

64. The same applies, I submit, even where the processes to divide up and repackage the product in question, taken in isolation, are not industrial and are carried out by pharmacies on the basis of individual prescriptions.

65. On the other hand, those factors are capable of affecting the content of the requirements that Directive 2001/83 imposes on those processes and on the supply of the medicinal product repackaged in that way to hospitals. They are therefore relevant to determining whether the pharmacies must have, on the one hand, a manufacturing authorisation under Article 40(1) of that directive in order to repackage a vial of Avastin into several single-use dose syringes and, on the other hand, an MA under Article 6(1) of that directive in order to supply those syringes to hospitals. [29]

66. In that respect, I note, at this stage, that under the second subparagraph of Article 40(2) of Directive 2001/83, no manufacturing authorisation is required for preparation, dividing up or changes in the 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 specific exemption would be meaningless if the fact that a pharmacy divides up and repackages a medicinal product on production of individual prescriptions had the effect of removing that product from the scope of Directive 2001/83 and, consequently, of automatically excluding those processes from the rule that a manufacturing authorisation is in principle required.

67. For the sake of completeness, I would add that, conversely, if the pharmacies performed processes on an existing medicinal product covered by an MA which did modify the medicinal substance of that product, [30] the resulting product would have to be regarded as a new medicinal product for the purposes of applying EU pharmaceutical rules. It would then be necessary to examine whether or not that product fell within the scope of Directive 2001/83 and, in particular, whether it was exempt from application of the directive under Article 3(1).

28 On that point, the Region of Emilia-Romagna observed at the hearing that many of the medicinal products administered only in hospital, including Avastin when it is used in cancer treatment, must be prepared in a pharmacy in order to adapt the strength to each patient.

29 See point 70 et seq of this Opinion.

30 That would be the case, inter alia, in a situation where a pharmacy unpackaged a medicinal product falling within the scope of Directive 2001/83 in order to extract the active substances from it and to create a medicinal product with a different composition on the basis of those ingredients.

68. In the *Abcur* judgment,[31] the Court of Justice held that for that article to apply, it is necessary only that the conditions expressly provided for in it are met. The Court also clarified that the condition that the pharmacy must have prepared the medicinal product in question 'in accordance with a medical prescription for an individual patient' means that the prescription must be drawn up before the product is prepared. It must therefore be prepared specifically for a previously identified patient.

69. Incidentally, the Court did not require the prescriptions to be customised for each patient according to different therapeutic needs. The fact that an identical dosage is prepared for all patients, according to a standardised medical protocol, therefore does not preclude application of Article 3(1) of Directive 2001/83.[32] Nor is it relevant whether or not the medicinal product in question is administered in a facility other than the pharmacy that prepared it, since that article does not contain any such requirement.

3. Requirements relating to placing on the market and manufacture

(a) The requirement for an MA

70. It is apparent from the order for reference that the pharmacies that repackage vials of Avastin in individual syringes and supply them to hospitals do not hold an MA for that purpose. Neither the treatment of AMD, nor the strength, route of administration and presentation required for that therapeutic indication are covered either by the MA for Avastin held by the Roche group or by any new MAs those pharmacies may have obtained.

71. As I described above, the Court of Justice has already established, in *Novartis Farma*,[33] that a company could divide up and repackage vials of Avastin and supply pharmacies with the resulting single-use syringes without previously obtaining an MA, provided the dividing up and repackaging, first of all, do not lead to any modification of the medicinal product and secondly, are carried out on the basis of individual prescriptions.

72. The first of the conditions set out in that judgment and already examined above, appears to be satisfied in the present case.[34] The second condition, for its part, is satisfied provided the medicinal product in question is prepared exclusively on production of individual medical prescriptions, whilst there is no additional requirement that each of those prescriptions must indicate a customised dose. Indeed, the Court did not find that the fact that the company in question in that case batch produced standardised doses of Avastin for use in eyes prevented that condition from being satisfied.

73. The Court based its approach instead on the fact that the dividing up and repackaging of the medicinal product on the strength of medical prescriptions occur after it has been placed on the market and are analogous to actions that, in the absence of the activities of the company in question, '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'.[35] In other words,

31 Judgment of 16 July 2015 (C-544/13 and C-545/13, EU:C:2015:481, paragraphs 55 and 71).

32 As stated in paragraph 42 of the judgment of 16 July 2015, *Abcur* (C-544/13 and C-545/13, EU:C:2015:481), it was argued before the national court that one of the medicinal products in question was a standardised product. The Court of Justice did not find that this fact, of itself, prevents Article 3(1) of Directive 2001/83 from applying.

33 Judgment of 11 April 2013 (C-535/11, EU:C:2013:226, paragraphs 41 to 43).

34 See points 57 to 60 of this Opinion.

35 Judgment of 11 April 2013, *Novartis Pharma* (C-535/11, EU:C:2013:226, paragraph 43).

those processes are not the result of placing products on the market targeted at a group of unidentified persons, but rather of supplying individual patients previously identified by the doctor prescribing the treatment. In the present case, under the AIFA decisions, the Avastin must be divided up and repackaged by none other than hospital pharmacies.[36]

74. Accordingly, the activity of the pharmacies authorised to do so by the AIFA decisions, consisting of dividing up and repackaging vials of Avastin on the basis of individual medical prescriptions, without thereby altering the medicinal substance, and then supplying the individual doses resulting from those processes to hospitals which will administer them to patients, does not require an MA to be obtained.

75. Nevertheless, as the Court of Justice observed in *Novartis Farma*,[37] Avastin as prepared in order to treat AMD remains governed by the provisions of Directive 2001/83, in particular as regards its manufacture. Accordingly, it is necessary to examine whether the dividing up and repackaging of Avastin require a manufacturing authorisation under Article 40(1) of that directive. Although the referring court did not mention that article in the wording of its questions, that examination does appear necessary in order to provide that court with an answer of use to it. Moreover, Roche Italia, the regions of Emilia-Romagna and Veneto, SOI-AMOI, the Polish Government and the Commission submitted written observations to the Court on that matter.

(b) The requirement for a manufacturing authorisation

76. Under Article 40(1) of Directive 2001/83 the Member States must ensure that the manufacture of medicinal products falling within the scope of that directive is subject to an authorisation being issued in accordance with national law. Under the first subparagraph of Article 40(2) of that directive, that authorisation is required for both total and partial manufacture, and for the processes of dividing up, packaging or presentation of medicinal products (which may take place, as in the present case, after the product in question has been placed on the market).

77. Articles 41 to 53 of Directive 2001/83 specify the conditions that those national authorisation regimes must satisfy. In particular, the manufacturer in question must make an application and supply a range of information in support of it.[38] The competent authority of the Member State in question only issues the manufacturing authorisation once it has satisfied itself that the information supplied is accurate.[39] A manufacturing authorisation therefore involves, more than merely complying with the requirements laid down by the national rules for the manufacture of medicinal products, being issued with a specific individual formal decision entitling its holder to manufacture medicinal products.

78. In the present case, the AIFA decisions stipulate that only 'hospital pharmacies satisfying the requirements laid down, in compliance with rules that ensure that the doses are properly prepared' can divide up and repackage Avastin for use in eyes.[40] Neither those decisions, nor any other evidence in the case file submitted to the Court indicates, in contrast, that those pharmacies have to hold a manufacturing authorisation. At the hearing, the Italian Government gave evidence that, according to the information available to it, those processes are not covered by manufacturing authorisations within the meaning of Article 40(1) of Directive 2001/83.

36 Under Decision No 799/2017, those processes can now also take place in dispensing pharmacies meeting the requirements laid down (see footnote 9 of this Opinion).

37 Judgment of 11 April 2013 (C-535/11, EU:C:2013:226, paragraph 44).

38 See the second paragraph of Article 41 of Directive 2001/83.

39 See the first paragraph of Article 42 of Directive 2001/83.

40 See points 27 and 30 of this Opinion. Since the entry into force of Decision 799/2017, dispensing pharmacies may also carry out such practices.

79. Assuming that the referring court confirms that the pharmacies authorised to divide up and repackage Avastin under the AIFA decisions do not hold manufacturing authorisations, those processes can nevertheless, in my view, fall within the exemption under the second subparagraph of Article 40(2) of that directive. [41]

80. To fall within that exemption, the processes in question must, first, be carried out 'by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes'. That requirement must in my view be considered satisfied in so far as the processes in question are performed in accordance with the parameters laid down in the AIFA decisions.

81. It is also necessary to ascertain, secondly, whether the Avastin is divided up and repackaged 'solely for retail supply'.

82. Directive 2001/83 does not define 'retail supply'. The ordinary meaning of that expression is the supply of goods to the public in single units or small quantities. In the *Caronna* judgment, [42] the Court of Justice construed that concept as opposed to that of 'wholesale distribution'. Article 1(17) of Directive 2001/83 defines 'wholesale distribution' and distinguishes it from, precisely, supplying medicinal products to the public. [43]

83. As can be seen from Novartis Farma, [44] complying with that requirement does not require the medicinal products that have been divided up and repackaged to be supplied directly to the patients for whom they are intended. [45] In that case, the individual syringes obtained from a vial of Avastin were in fact supplied to the pharmacies that had placed orders for them. The Court held that that circumstance did not prevent the requirement in question from being satisfied, entailing as it did only that the relevant processes should be included within a system for retail supply by pharmacies. In that respect, the Court attached particular importance to whether or not those processes were carried out on the basis of individual medical prescriptions. [46]

84. In the present case, it is apparent from the order for reference that the Avastin is divided up and repackaged on production of medical prescriptions. The individual doses prepared in that way are supplied to hospitals where they are subsequently administered to the patients concerned. Incidentally, Avastin is in the class of medicinal products which can only be administered in hospital, and therefore could not be supplied directly to patients. Accordingly, the dividing up and repackaging of Avastin does not, in my view, require a manufacturing authorisation.

85. However, Roche Italia told the Court that dispensing pharmacies repackage Avastin on a large scale, without previously receiving named prescriptions as Italian law and EU law require. Moreover, according to Roche Italia, those pharmacies supply the product repackaged in that way to ophthalmologists to be administered in their private surgeries, whereas the national rules require that it be administered only in a hospital environment.

41 See judgments of 11 April 2013, *Novartis Pharma* (C-535/11, EU:C:2013:226, paragraph 52) and of 23 January 2018, *F. Hoffmann-La Roche and Others* (C-179/16, EU:C:2018:25, paragraph 58).

42 Judgment of 28 June 2012 (C-7/11, EU:C:2012:396, paragraphs 35 and 36).

43 Article 1(17) of Directive 2001/83 defines the 'wholesale distribution of medicinal products' as 'all activities consisting of procuring, holding, supplying or exporting medicinal products, *apart from supplying medicinal products to the public*. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorised or entitled to supply medicinal products to the public in the Member State concerned' (my italics).

44 Judgments of 11 April 2013 (C-535/11, EU:C:2013:226, paragraph 53).

45 Furthermore, when the legislature intended that a provision of Directive 2001/83 should only apply if the medicinal product in question is supplied directly to patients, as it did in relation to the exemption for officinal formulae under Article 3(2) of that directive, it expressly referred to that proviso (see, to that effect, judgment of 16 July 2015, *Abcur* (C-544/13 and C-545/13, EU:C:2015:481, paragraphs 69 and 70)).

46 That does not mean, however, that the benefit of the exemption under the second subparagraph of Article 40(2) of Directive 2001/83 is always reserved for processes carried out on the basis of medical prescriptions. That article can in fact also apply to processes relating to medicinal products supplied without a prescription.

86. To my mind, even assuming it to be true, the fact that certain pharmacies purportedly prepare and deliver that product in breach of the requirements under Italian and EU law is irrelevant for the purposes of replying to the questions posed by the referring court. Those practices would, in reality, fall outside the parameters laid down by the AIFA decisions and Article 1(4)bis of Law No 648/96 which is the legal basis of those decisions. They therefore cannot, to my mind, affect the validity of those measures. As SOI-AMOI, the Italian Government and the Commission emphasised at the hearing, it falls to the Italian authorities to penalise any such unlawful practices. [47]

87. In the light of the foregoing, the processes to divide up and repackage Avastin, to the extent that they are carried out on the basis of individual prescriptions by pharmacies authorised for that purpose by AIFA decisions, do not require a manufacturing authorisation under Article 40(1) of Directive 2001/83. Supplying the products obtained in that way to hospitals to be administered to patients does not, for its part, need to be covered by an MA under Article 6(1) of that directive, in conjunction with Article 3(1) of Regulation No 726/2004.

88. In so far as activities such as those referred to in the AIFA decisions comply with the requirements under the provisions of Directive 2001/83 on the placing on the market and manufacture of medicinal products, those decisions do not depend, in order to be lawful, on whether or not the Italian Republic is entitled under Article 5(1) of that directive to derogate from its provisions — which is the subject matter of the second limb of the first question referred.

89. For the sake of completeness, I will, however, address that question, since the answer would be necessary in order to resolve the dispute in the main proceedings if the Court were to find that such activities are in breach of those requirements.

4. The applicability of Article 5(1) of Directive 2001/83

90. The second limb of the first question referred concerns whether the power that Article 5(1) of Directive 2001/83 confers on the Member States to exempt certain medicinal products from application of the provisions of that directive, under their national legislation, applies in a situation such as that in the main proceedings. [48]

91. Exercise of that power involves two conditions being complied with. First, the Member State in question must be seeking to fulfil 'special needs'; secondly, the medicinal products must be 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'.

92. In the judgment in *Commission* v *Poland*, [49] the Court of Justice examined the extent to which Article 5(1) of Directive 2001/83 allowed a medicinal product to be marketed in a Member State without being covered by an MA under Article 6(1) of that directive.

47 At the hearing, Roche Italia also drew attention to a judgment of 7 March 2018 in which the Tribunale amministrativo regionale per la Lombardia (Regional Administrative Court, Lombardy, Italy) confirmed that administrative penalties imposed on a dispensing pharmacy for unlawfully preparing Avastin for use in eyes were lawful.

48 As Advocate General Jääskinen observed in his Opinion in *Commission* v *Poland* (C-185/10, EU:C:2011:622, point 27), Article 5(1) of Directive 2001/83 allows the Member States a degree of flexibility so that they can 'cope efficiently with individual circumstances or certain emergency situations, where time is of the essence'.

49 Judgment of 29 March 2012 (C-185/10, EU:C:2012:181).

93. After establishing that Article 5(1) of Directive 2001/83 must be interpreted strictly because it is a derogating provision, the Court held, first, that the concept of 'special needs', to which that article refers, applies only to individual situations justified by medical considerations and presupposes that the medicinal product is necessary to meet the needs of the patient. Secondly, the requirement that the medicinal product must be supplied in response to a 'bona fide unsolicited order' means that the medicinal product must have been prescribed by the doctor as a result of an actual examination of his patients and on the basis of purely therapeutic considerations. [50]

94. The Court inferred from the foregoing that the article in question can only apply to situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent — that is to say, no medicinal product having the same active substances, the same dosage and the same form — on the national market or which is unavailable on that market. [51]

95. Moreover, the Court held that financial considerations cannot, in themselves, lead to recognition of the existence of such special needs. It expressly ruled out the possibility that a Member State could rely on Article 5(1) of Directive 2001/83, which must be applied only exceptionally, for the sole purpose of ensuring the financial stability of the social security system or of allowing patients who have only limited financial means to have access to the treatment which they need. [52]

96. In the *Novartis Farma* judgment, [53] the Court of Justice applied those principles when it set out the circumstances in which Article 5(1) of Directive 2001/83 permits the processes to divide up and repackage Avastin for use in ophthalmology to be exempt from the requirement to obtain a manufacturing authorisation under Article 40(1) of that directive.

97. The Court inferred from those principles that, since the active ingredients of Avastin and Lucentis are different, 'a doctor, when faced with a particular condition and relying solely on therapeutic considerations specific to his patients, including considerations pertaining to how the medicine is administered, may take the view that a treatment not covered by the marketing authorisation, in accordance with the pharmaceutical form and the dosage which he considers appropriate and using Avastin which has a Community marketing authorisation, is preferable to treatment with Lucentis'. [54]

98. In the light of that case-law, a Member State can in my view only rely on the derogation in Article 5(1) of Directive 2001/83 to exclude Avastin as prepared for the treatment of AMD from the requirements of that directive — whether those relating to the placing on the market or to the manufacture of medicinal products — where a patient cannot be treated using a medicinal product authorised for that therapeutic indication. [55] That would be the case where the medicinal products the MAs of which cover the treatment of AMD, such as Lucentis, are either ineffective or contraindicated for a particular patient, or unavailable on the market in a Member State.

50 Judgment of 29 March 2012, *Commission* v *Poland* (C-185/10, EU:C:2012:181, paragraphs 31, 34 and 35).

51 Judgment of 29 March 2012, *Commission* v *Poland* (C-185/10, EU:C:2012:181, paragraphs 36 and 37). See, also, judgments of 16 July 2015, *Abcur* (C-544/13 and C-545/13, EU:C:2015:481, paragraphs 56 and 57) and of 23 January 2018, *F. Hoffmann-La Roche and Others* (C-179/16, EU:C:2018:25, paragraph 57).

52 Judgment of 29 March 2012, *Commission* v *Poland* (C-185/10, EU:C:2012:181, paragraphs 38 and 46 to 48).

53 Judgment of 11 April 2013 (C-535/11, EU:C:2013:226, paragraph 46).

54 Judgment of 11 April 2013, *Novartis Pharma* (C-535/11, EU:C:2013:226, paragraph 48).

55 The Conseil d'État (Council of State, France) took that approach in its judgment No 392459 of 24 February 2017 (FR:CECHR:2017:392459.20170224, paragraphs 12 to 17), to which Roche Italia refers in its Observations.

99. In contrast, contrary to what the Region of Emilia-Romagna and the Italian Government have argued in essence, that situation is not present where a doctor chooses the medicinal product used off label for reasons relating solely to containing the costs to the healthcare insurance system. Even where that medicinal product is just as efficacious and safe as the medicinal products the MAs of which cover the treatment of AMD, such a scenario does not justify using the derogation in Article 5(1) of Directive 2001/83.

100. The fact that the AIFA included Avastin on List 648 for the treatment of AMD, under Article 1(4)bis of Law No 648/96, having previously satisfied itself that the product is therapeutically efficacious and safe, is not in my view sufficient to satisfy the requirements set out in Article 5(1) of Directive 2001/83.

101. It would fall to the national court, where applicable, to examine whether, under domestic law, Avastin can only be used off label in situations in which, for purely therapeutic reasons, the doctor finds that a particular patient cannot be treated using a medicinal product authorised to treat AMD and available on the national market.[56]

B. The third question referred

102. By its third question, the referring court asks whether the power that Article 1(4)bis of Law No 648/96 confers on the AIFA to '[activate] the appropriate monitoring mechanisms to safeguard patient safety and make the necessary adaptations in good time' when a medicinal product used off label is included on List 648 encroaches on the EMA's exclusive power to assess the efficacy, safety and quality of medicinal products with a view to issuing an MA for the medicinal products subject to the central authorisation procedure under Article 3 of Regulation No 726/2004. It also asks whether that power of the AIFA conflicts with the EMA's pharmacovigilance powers, as set out in particular in Articles 25 and 26 of that regulation.

103. There is scarcely any doubt, in my view, that those questions must be answered in the negative.

104. The exclusive power that Regulation No 726/2004 confers on the EMA in fact relates only to the evaluations carried out so that the Commission can issue the MA for a medicinal product.[57] The AIFA's monitoring powers do not concern those evaluations in any way.

105. Nor do those powers of the AIFA hinder the EMA in exercising its pharmacovigilance powers, after the MA has been issued. As can be seen in particular from Articles 25 and 26 of that regulation, the EMA operates the pharmacovigilance system in cooperation with the national authorities. Article 1(4)bis of Law No 648/96 does not in any way interfere with the EMA's powers in so far as it confers on the AIFA monitoring powers, complementary to those the EMA exercises, in relation to the off-label use of medicinal products.

56 As apparent from the order for reference, the AIFA decisions do not seem to confine the reimbursement of Avastin to those situations (see, in particular Article 2(1)(c) of Decision No 622/2014), and Article 1(4)bis of Law No 648/96 was probably adopted in response to compelling financial reasons (see points 26 and 27 of this Opinion). That notwithstanding, Novartis Farma, Roche Italia, SOI-AMOI and the Italian Government have indicated that, according to Italian legislation, doctors can only prescribe an off-label medicinal product where the patient cannot be treated by means of a medicinal product used in accordance with its MA. The latter rely, in particular, on Article 3 of decreto-legge n. 23, 17 febbraio 1998, convertito con modificazioni dalla legge n. 94, 8 aprile 1998 (Decree-Law No 23 of 17 February 1998, converted as amended into Law No 94 of 8 April 1998 ('the Di Bella Law'). The referring court, for its part, stated that doctors can prescribe a medicinal product off label where they consider it appropriate for their patients' health, but did not indicate whether that situation implies that there must be no authorised alternative therapy suitable for treating the patient concerned (see point 24 of this Opinion). In the event that the referring court confirmed that the legislation on off-label prescribing does impose such a requirement, it would be for that court to determine whether it is apparent, from reading that legislation in conjunction with the AIFA decisions, that under Italian law Avastin can only be used, and with all the more reason can only be reimbursed, in order to meet the therapeutic needs of particular patients.

57 See, in particular, Articles 5 to 9 of Regulation No 726/2004.

C. The fourth question referred

106. By its fourth question, the referring court asks the Court of Justice, essentially, whether the AIFA decisions are compatible with Article 1(3) of Directive 89/105, according to which nothing in that directive permits the placing on the market of a medicinal product that has not obtained the MA provided for in Article 6(1) of Directive 2001/83.

107. It is not necessary to answer that question in so far as it can be concluded from the foregoing considerations that the pharmacies authorised for that purpose by the AIFA decisions can supply Avastin as divided up and repackaged on the basis of individual prescriptions to hospitals without holding an MA.

108. In any event, it seems to me that Article 1(3) of Directive 89/105 is intended only to clarify that the directive applies without prejudice to the EU rules on the placing on the market of medicinal products. To my mind that article cannot, as such, be interpreted as precluding national legislation according to which the healthcare insurance system reimburses a medicinal product, even if the requirements under that legislation are not complied with.

V. Conclusion

109. In the light of the foregoing, I propose that the Court should answer the questions referred by the Consiglio di Stato (Council of State, Italy), as follows:

(1) Article 3(1) of Directive 2001/83 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, does not apply to a medicinal product for which a marketing authorisation (MA) has been granted and that, after it was placed on the market, underwent processes to divide up and repackage that medicinal product carried out by pharmacies but that did not modify the medicinal substance comprising it.

(2) Article 6(1) of Directive 2001/83, in conjunction with Article 3(1) of Regulation 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, does not preclude application of national legislation that, with the sole aim of easing the burden on the budget of the healthcare insurance system, allows that system to reimburse a medicinal product used for a therapeutic indication not covered by its MA, even though medicinal products the MA of which does include that therapeutic indication are available on the market, provided that medicinal product was placed on the market and manufactured in accordance with the provisions of that regulation and that directive.

In that respect, activities by which pharmacies lawfully authorised to do so divide up and repackage a medicinal product into several individual doses on the strength of individual prescriptions and without thereby modifying the medicinal substance, and supply those individual doses to the hospitals where they will be administered to the patients concerned, do not require that an MA be obtained under Article 6(1) of Directive 2001/83, in conjunction with Article 3(1) of Regulation No 726/2004.

According to the second subparagraph of Article 40(2) of Directive 2001/83, nor do those activities require that a manufacturing authorisation be obtained under Article 40(1) of that directive.

(3) Article 5(1) of Directive 2001/83 permits a Member State to exclude a medicinal product from application of the provisions of that directive only in situations where the doctor believes, as a result of an actual examination of his patients and on the basis of purely therapeutic considerations, that treatment using that medicinal product is necessary in order to respond to the therapeutic needs of those patients that cannot be satisfied by any medicinal product having the authorisations required under that directive and available on the national market. Article 5(1) of Directive 2001/83 therefore precludes a Member State from relying on the power under that article for exclusively financial reasons.

(4) No provision of Regulation No 726/2004 precludes national legislation that confers power on a national authority to adopt decisions relating to the safety of medicinal products in connection with use of those products for indications not covered by their MA.