Court of Justice EU, 23 January 2018, Hoffmann-La Roche

COMPETITION LAW – PHARMACEUTICAL LAW

National competition authorities are allowed to consider medicinal products of which the MA lays outside the treatment of the diseases at issue, but can be used for this and therefore can be regarded as substitutable with other medicinal products as products in the same market

- It is for national courts to decide whether such substitutability exists

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

An agreement restricting the conduct of third parties, which consists in encouraging the use of another medicinal product for the treatment of the same condition, does not escape the application of that provision on the ground the arrangement cannot be considered to be ancillary and objectively necessary for the implementation of the licensing agreement

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

An arrangement which consists in dissemination of misleading information relating to adverse reactions with a view to reducing the competitive pressure constitutes a restriction of competition 'by object' under Article 101(1) TFEU

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

An arrangement intended to disseminate such misleading information in respect of a medicinal product cannot be regarded as indispensable under Article 101(1) TFEU

- Such an arrangement cannot be exempt

Therefore, the answer to the second part of the first question is that Article 101 TFEU must be interpreted as meaning that an arrangement such as that described in paragraph 9 above cannot be exempt under Article 101(3) TFEU.

Source: curia.europa.eu

Court of Justice EU, 23 January 2018

(K. Lenaerts, A. Tizzano, R. Silva de Lapuerta, M. Ilešič, J. Malenovský, C.G. Fernlund (Rapporteur), C. Vajda, A. Borg Barthet, J.-C. Bonichot, A. Arabadjiev, F. Biltgen, K. Jürimäe and C. Lycourgos)

JUDGMENT OF THE COURT (Grand Chamber)

23 January 2018 (*)

(Reference for a preliminary ruling — Competition — Article 101 TFEU — Agreements, decisions and concerted practices — Medicinal products — Directive 2001/83/EC — Regulation (EC) No 726/2004 — Allegations of risks associated with the use of a medicinal product for a treatment not covered by its marketing authorisation (off-label) — Definition of relevant market — Ancillary restriction — Restriction of competition by object — Exemption)

In Case C‑179/16,

REQUEST for a preliminary ruling under Article 267 TFEU from the Consiglio di Stato (Council of State, Italy), made by decision of 3 December 2015, received at the Court on 25 March 2016, in the proceedings

F. Hoffmann-La Roche Ltd,
Roche SpA,
Novartis AG,
Novartis Farma SpA
v
Autorità Garante della Concorrenza e del Mercato,
intervening parties:
Associazione Italiana delle Unità Dedicate Autonome Private di Day Surgery e dei Centri di Chirurgia Ambulatoriale (Aiudapds),
Società Oftalmologica Italiana (SOI) — Associazione Medici Oculisti Italiani (AMOI),
Regione Emilia-Romagna,
Altroconsumo,
Regione Lombardia,
Coordinamento delle associazioni per la tutela dell'ambiente e dei diritti degli utenti e consumatori (Codacons),
Agenzia Italiana del Farmaco (AIFA),
THE COURT (Grand Chamber),
composed of K. Lenaerts, President, A. Tizzano, Vice-President, R. Silva de Lapuerta, M. Ilešič, J. Malenovský, C.G. Fernlund (Rapporteur) and C. Vajda, Presidents of Chambers, A. Borg Barthet, J.-C. Bonichot, A. Arabadjiev, F. Biltgen, K. Jürimäe and C. Lycourgos, Judges,
Advocate General: H. Saugmandsgaard Øe,
Registrar: R. Schiano, Administrator,
having regard to the written procedure and further to the hearing on 3 May 2017,
after considering the observations submitted on behalf of:
– F. Hoffmann-La Roche Ltd, by M. Siragusa, P. Merlino and G. Faella, avvocati,
– Roche SpA, by E. Raffaelli, P. Todaro, A. Raffaelli and E. Teti, avvocati,
– Novartis AG and Novartis Farma SpA, by G.B. Origoni della Croce, A. Lirosi, P. Fattori, L. D'Amario and S. Di Stefano, avvocati,
– the Autorità Garante della Concorrenza e del Mercato, by P. Gentili, avvocato dello Stato,
– the Associazione Italiana delle Unità Dedicate Autonome Private di Day Surgery e dei Centri di Chirurgia Ambulatoriale (Aiudapds), by G. Muccio and G. Zaccanti, avvocati,
– Società Oftalmologica Italiana (SOI) — Associazione Medici Oculisti Italiani (AMOI), by R. La Placa and V. Vulpetti, avvocati,
– Altroconsumo, by F. Paoletti, A. Mozzati and L. Schiano di Pepe, avvocati,
– the Coordinamento delle associazioni per la tutela dell'ambiente e dei diritti degli utenti e consumatori (Codacons), by C. Rienzi, G. Giuliano and S. D'Ercole, avvocati,
– the Regione Emilia-Romagna, by M.R. Russo Valentini and R. Bonatti, avvocati,
– the Italian Government, by G. Palmieri, acting as Agent, and S. Fiorentino, avvocato dello Stato,
– Ireland, by E. Creedon, L. Williams and A. Joyce, acting as Agents, and M. Gray, Barrister,
– the French Government, by D. Colas, D. Segoin and J. Bousin, acting as Agents,
– the European Commission, by T. Vecchi, F. Castilla Contreras, G. Conte and C. Vollrath, acting as Agents,
after hearing the **Opinion of the Advocate General** at the sitting on 21 September 2017,
gives the following

Judgment

1. This request for a preliminary ruling concerns the interpretation of Article 101 TFEU.

2. The request has been made in proceedings between F. Hoffmann-La Roche Ltd ('Roche'), Roche SpA ('Roche Italia'), Novartis AG and Novartis Farma SpA ('Novartis Italia'), of the one part, and the Autorità Garante della Concorrenza e del Mercato (the Italian competition authority, Italy; 'the AGCM'), of the other part, regarding the proceedings brought and the financial penalties imposed by the latter because of an agreement contrary to Article 101 TFEU.

Legal context

3. Penalties were imposed by the AGCM on the undertakings at issue in the main proceedings for infringement of EU competition law during the period between 1 June 2011 and 27 February 2014.

Directive 2001/83/EC

4. In view of the infringement period in question, the present case is governed by the provisions 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 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 (OJ 2007 L 324, p. 121) ('Directive 2001/83'), and, as from 21 July 2012, by the provisions of Directive 2001/83, as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (OJ 2010 L 348, p. 74) ('amended Directive 2001/83').

5. 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 healthcare professional and for use by an individual patient under his direct personal responsibility.'

6. Under Article 6(1) of the directive:

'No medicinal product may be placed on the market of a Member State unless a marketing authorisation [('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.

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 [MA]...'

7. Article 40(1) and (2) of the directive provides:

'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 notwithstanding 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.'

8. Article 101(1) of amended Directive 2001/83 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.'

9. Under Article 106a of amended Directive 2001/83:

'1. As soon as the [MA] holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, he shall be required to inform the national competent authorities, the [European Medicines Agency (the EMA)] and the Commission.

The [MA] holder shall ensure that information to the public is presented objectively and is not misleading.

2. Unless urgent public announcements are required for the protection of public health, the Member States, the [EMA] and the Commission shall inform each other not less than 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.

3. For active substances contained in medicinal products authorised in more than one Member State, the [EMA] shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public.

Under the coordination of the [EMA], the Member States shall make all reasonable efforts to agree on a common message in relation to the safety of the medicinal product concerned and the timetables for their distribution. The Pharmacovigilance Risk Assessment Committee shall, at the request of the [EMA], provide advice on those safety announcements.

...'

Regulation (EC) No 726/2004

10. In view of the infringement period in question, the present case is governed by the provisions 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 (OJ 2004 L 136, p. 1), as amended by Regulation (EC) No 219/2009 of the European Parliament and of the Council of 11 March 2009 (OJ 2009 L 87, p. 109) ('Regulation No 726/2004'), and, as from 2 July 2012, by the provisions of Regulation No 726/2004, as amended by Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 (OJ 2010 L 348, p. 1, and Corrigendum OJ 2012 L 201, p. 138) ('amended Regulation No 726/2004').

11. Under Article 16 of Regulation No 726/2004:

'1. After an authorisation has been granted in accordance with this Regulation, the holder of the [MA] for a medicinal product for human use shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h) of Directive 2001/83/EC, take account of technical and scientific progress and make any variations that may be required to enable the medicinal products to be manufactured and checked by means of generally accepted scientific methods. He shall apply for approval of such variations in accordance with this Regulation.

2. The holder of the [MA] shall forthwith supply to the [EMA], to the Commission and to the Member States any new information which might entail the variation of the particulars or documents referred to in Articles 8(3), 10, 10a, 10b and 11 of Directive 2001/83/EC, in Annex I thereto, or in Article 9(4) of this Regulation.

In particular, he shall forthwith inform the [EMA], the Commission and the Member States of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned.

In order that the risk-benefit balance may be continuously assessed, the [EMA] may at any time ask the holder of the [MA] to forward data demonstrating that the risk-benefit balance remains favourable.

3. If the holder of the authorisation for a medicinal product for human use proposes to make any variation of the particulars and documents referred to in paragraph 2, he shall submit the relevant application to the [EMA].

4. The Commission shall, after consulting the [EMA], adopt appropriate provisions for the examination of variations to [MAs] in the form of a regulation. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).'

12. Article 16 of amended Regulation No 726/2004 provides:

'1. After a[n MA] has been granted in accordance with this Regulation, the [MA] holder shall, in respect of the methods of manufacture and control provided for in points (d) and (h) of Article 8(3) of Directive 2001/83/EC, take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. He shall apply for approval of corresponding variations in accordance with this Regulation.

2. The [MA] holder shall forthwith provide the [EMA], the Commission and the Member States with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Article 10, 10a, 10b and 11, or Article 32(5) of Directive 2001/83/EC, in Annex I thereto, or in Article 9(4) of this Regulation.

In particular, the [MA] holder shall forthwith inform the [EMA] and the Commission 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].

3. The [MA] holder shall ensure that the product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26.

3a. In order to be able to continuously assess the risk-benefit balance, the [EMA] may at any time ask the [MA] holder to forward data demonstrating that the risk-benefit balance remains favourable. The [MA] holder shall answer fully and promptly any such request.

The [EMA] may at any time ask the [MA] holder to submit a copy of the pharmacovigilance system master file. The [MA] holder shall submit the copy at the latest seven days after receipt of the request.

4. The Commission shall, after consulting the [EMA], adopt appropriate provisions for the examination of variations to [MAs] in the form of a regulation. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).'

13. Article 17 of Regulation No 726/2004 reads as follows:

'The applicant or the holder of a[n MA] shall be responsible for the accuracy of the documents and of the data submitted.'

14. Article 22 of that regulation provided:

'The [EMA], acting in close cooperation with the national pharmacovigilance systems established in accordance with Article 102 of Directive 2001/83/EC, shall receive all relevant information concerning suspected adverse reactions to medicinal products for human use which have been authorised by the Community in accordance with this Regulation. Where appropriate, the Committee for Medicinal Products for Human Use shall, in accordance with Article 5 of this Regulation, draw up opinions on the measures necessary. These opinions shall be made publicly accessible.

...

The holder of the [MA] and the competent authorities of Member States shall ensure that all relevant information concerning suspected adverse reactions to the medicinal products authorised under this Regulation are brought to the attention of the [EMA] in accordance with the provisions of this Regulation. Patients shall be encouraged to communicate any adverse reaction to healthcare professionals.'

15. Article 24(5) of Regulation No 726/2004 stated:

'The holder of a[n MA] may not communicate information relating to pharmacovigilance concerns to the general public in relation to its authorised medicinal product without giving prior or simultaneous notification to the [EMA].

In any case, the [MA] holder shall ensure that such information is presented objectively and is not misleading.

Member States shall take the necessary measures to ensure that a[n MA] holder who fails to discharge these obligations is subject to effective, proportionate and dissuasive penalties.'

16. Pursuant to Regulation No 1235/2010, Chapter 3 of Title II of Regulation No 726/2004, that chapter being headed *'Pharmacovigilance'* and comprising Articles 21 to 29 of the regulation, was replaced. Article 28(4) of amended Regulation No 726/2004 is worded as follows:

'In the case of an assessment report that recommends any action concerning the [MA], the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report by the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the [MA] concerned, including a timetable for the implementation of the opinion. Where this opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a

detailed explanation of the scientific grounds for the differences together with the recommendation.
Where the opinion states that regulatory action concerning the [MA] is necessary, the Commission shall adopt a decision to vary, suspend or revoke the [MA]. Article 10 of this Regulation shall apply to the adoption of that decision. Where the Commission adopts such a decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of Directive 2001/83/EC.'
17. Article 84 of the regulation provides:
'1. Without prejudice to the Protocol on the Privileges and Immunities of the European Communities, each Member State shall determine the penalties to be applied for infringement of the provisions of this Regulation or the regulations adopted pursuant to it and shall take all measures necessary for their implementation. The penalties shall be effective, proportionate and dissuasive.
...
2.Member States shall inform the Commission immediately of any litigation instituted for infringement of this Regulation.
3. At the [EMA]'s request, the Commission may impose financial penalties on the holders of [MAs] granted under this Regulation if they fail to observe certain obligations laid down in connection with the authorisations. The maximum amounts as well as the conditions and methods for collection of these penalties shall be laid down by the Commission. Those measures, designed to amend non-essential elements of this Regulation by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).
The Commission shall publish the names of the [MA] holders involved and the amounts of and reasons for the financial penalties imposed.'

Regulation (EC) No 658/2007

18. In view of the infringement period in question, the present case is governed by the provisions of Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with MAs granted under Regulation No 726/2004 (OJ 2007 L 155, p. 10), and, as from 2 July 2012, by the provisions of that regulation as amended by Commission Regulation (EU) No 488/2012 of 8 June 2012 (OJ 2012 L 150, p. 68) ('amended Regulation No 658/2007').
19. Article 1(1) of Regulation No 658/2007 provided:
'This Regulation lays down rules concerning the application of financial penalties to the holders of [MAs], granted under Regulation (EC) No 726/2004, in respect of infringements of the following obligations, in cases where the infringement concerned may have significant public health implications in the Community, or where it has a Community dimension by taking place or having its effects in more than one Member State, or where interests of the Community are involved:
1. the completeness and the accuracy of the particulars and documents contained in an application for [MA] under Regulation (EC) No 726/2004, or of any other documents and data submitted to the [EMA] established by that Regulation, hereinafter "the Agency", in response to obligations laid down in that Regulation'.
20. Article 1(1) of amended Regulation No 658/2007 is worded as follows:
'the obligation to submit complete and accurate particulars and documents in an application for [MA] under Regulation (EC) No 726/2004 submitted to the [EMA], or in response to obligations laid down in that Regulation and Regulation (EC) No 1901/2006 to the extent that the infringement concerns a material particular'.
21. Article 16(1) of Regulation No 658/2007 states:
'Where, following the procedure provided for in Subsection 1, the Commission finds that the [MA] holder has committed, intentionally or negligently, an infringement as referred to in Article 1, it may adopt a decision imposing a fine not exceeding 5% of the holder's Community turnover in the preceding business year.'

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

22. The AGCM, by decision of 27 February 2014 ('the AGCM's decision'), imposed two fines: one on Roche and its subsidiary Roche Italia, amounting to approximately EUR 90.6 million, and the other on Novartis and its subsidiary Novartis Italia, amounting to approximately EUR 92 million, on the ground that those undertakings had concluded an agreement contrary to Article 101 TFEU, designed to achieve an artificial differentiation between the medicinal products Avastin and Lucentis by manipulating the perception of the risks of using Avastin in the field of ophthalmology.
23. The two medicinal products at issue were developed by Genentech, a company established in the United States, which is active only in that country. Genentech entrusted the commercial exploitation of Avastin outside the United States to Roche, its parent company. Since the latter is not active in the field of ophthalmology, Genentech also entrusted the Novartis group with the commercial exploitation of Lucentis outside the United States, by way of a licensing agreement concluded in June 2003.
24. The MA for those medicinal products in the European Union is subject to the centralised procedure laid down in Regulation No 726/2004 on account of their biotechnological characteristics.
25. On 12 January 2005 the Commission granted an MA to Avastin for the treatment of certain tumorous diseases. On 26 September 2005 the Agenzia Italiana del farmaco (AIFA) (the Italian Medicines Agency) included Avastin in the list of medicinal products fully reimbursed by the national health system.
26. On 22 January 2007 the Commission also granted an MA to Lucentis for the treatment of eye diseases. On 31 May 2007, AIFA included Lucentis in the list of non-reimbursable medicinal products.

27. Prior to the placing on the market of Lucentis, some doctors had started prescribing Avastin to their patients with eye diseases. The prescription of Avastin in respect of indications not corresponding to those mentioned in the MA for that product ('off-label') for the treatment of such diseases began to spread worldwide. Given its lower unit price, the use of Avastin for those diseases continued after the placing on the market of Lucentis.
28. In accordance with Italian law, which allowed the off-label use of a medicinal product to be reimbursed in the absence of an authorised valid therapeutic alternative for the treatment of the disease in question, AIFA included, in May 2007, the use of Avastin in connection with the treatment of exudative macular diseases in the list of reimbursable medicinal products.
29. Following the inclusion, on 4 December 2008, of Lucentis and other medicinal products authorised for the treatment of the eye diseases in question in the list of reimbursable medicinal products in Italy, AIFA progressively excluded the reimbursement of off-label Avastin for those diseases.
30. By decision of 30 August 2012 the Commission, having obtained the favourable opinion of the EMA, amended the summary of Avastin's characteristics, in order to mention certain side effects associated with the use of that medicinal product for the treatment of eye diseases not covered by its MA.
31. Following the amendment of the summary of Avastin's characteristics, AIFA, on 18 October 2012, removed Avastin used for therapeutic indications not covered by its MA from the list of reimbursable medicinal products.
32. According to the AGCM's decision, the Roche group and the Novartis group entered into a market-sharing agreement that constitutes a restriction of competition by object. Paragraph 177 of that decision, inter alia, states that Avastin and Lucentis are equivalent in all respects for the treatment of eye diseases. According to that decision, the arrangement was intended to produce and disseminate opinions which could give rise to public concern regarding the safety of Avastin when used in ophthalmology and to downplay the value of scientific opinions to the contrary. That arrangement also related to the proceedings for amendment of the summary of Avastin's characteristics that were pending before the EMA and to the sending of a subsequent formal communication sent to healthcare professionals, both initiated by Roche.
33. According to the AGCM's decision, in particular paragraph 88 thereof, Avastin became the main competitor of Lucentis because of its widespread off-label use in Italy in the field of ophthalmology. The AGCM found, in paragraphs 82 to 88 of that decision, that the arrangement had given rise to a drop in Avastin sales and had caused a shift in demand toward Lucentis. Under paragraph 229 of the AGCM's decision, this had resulted in a cost increase for the national health service, assessed at approximately EUR 45 million in 2012 alone.
34. After the Tribunale amministrativo regionale per il Lazio (Regional Administrative Court, Lazio, Italy) dismissed the actions that they brought against that decision, Roche, Novartis and their Italian subsidiaries lodged an appeal before the Consiglio di Stato (Council of State, Italy).
35. The applicants in the main proceedings claim that, without the licensing agreement between Genentech and Novartis, it would not have been possible for the latter to enter the relevant market within a short space of time. In those circumstances, they argue that Roche and Novartis cannot be regarded as competitors, even potential ones. The applicants in the main proceedings consider that the parties to the licensing agreement could reasonably have provided in that agreement that Roche would not compete with Novartis, the licensee, on the relevant market. Such a restriction would, in their view, fall entirely outside the prohibition laid down in Article 101(1) TFEU.
36. The Consiglio di Stato (Council of State) decided to stay the proceedings and to refer the following questions to the Court for a preliminary ruling:
'(1) On a proper construction of Article 101 TFEU, can the parties to a licensing agreement be regarded as competitors if the licensee company operates on the relevant market concerned solely by virtue of that agreement? Do possible restrictions of competition between the licensor and the licensee in such a situation, although not expressly provided for in the licensing agreement, fall outside the scope of Article 101(1) TFEU or fall within the scope of the exception set out in Article 101(3) TFEU and, if so, within what limits?
(2) Does Article 101 TFEU allow the national competition authority to define the relevant market independently of the content of [MAs] for medicinal products granted by the competent pharmaceutical regulatory authorities ([AIFA and the EMA]) or, on the contrary, with respect to authorised medicinal products, must the relevant market for the purposes of Article 101 TFEU instead be held to be primarily shaped and established by the appropriate regulatory authority in a way that is binding even on the national competition authority?
(3) In the light of the provisions of Directive [2001/83], in particular Article 5 thereof, which relates to MAs for medicinal products, does Article 101 TFEU allow a medicinal product used off label and a medicinal product that has received an MA in respect of the same therapeutic indications [and is used in accordance with that MA] to be regarded as interchangeable and, thus, to be included in the same relevant market?
(4) Pursuant to Article 101 TFEU, for the purposes of defining the relevant market, is it important to establish, in addition to the substantive interchangeability of pharmaceutical products on the demand side, whether or not those products have been offered on the market in accordance with the regulatory framework for the marketing of medicinal products?

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

The request to reopen the oral procedure

37. By letter dated 14 November 2017 Roche Italia requested that the oral procedure be reopened.

38. In support of its request, Roche Italia argues that the activity of launching a new medicinal product developed on the basis of Avastin was characterised as repackaging in points 68 and 82 of the Advocate General's Opinion, although that activity is a more complex task. It is also of the opinion that the judgment of 7 February 2013, Slovenská sporiteľňa (C‑68/12, EU:C:2013:71), to which reference is made in points 89 and 166 of the Opinion, is irrelevant to the outcome of the present case.

39. It is a matter of settled case-law that the Court may, of its own motion, on a proposal from the Advocate General, or at the request of the parties, order the reopening of the oral procedure under Article 83 of its Rules of Procedure, if it considers that it lacks sufficient information or that the case must be decided on the basis of an argument which has not been debated between the parties (judgment of 15 September 2011, Accor, C‑310/09, EU:C:2011:581, paragraph 19 and the case-law cited). By contrast, neither the Statute of the Court of Justice of the European Union nor its Rules of Procedure make provision for the parties to submit observations in response to the Advocate General's Opinion (**judgment of 16 December 2010, Stichting Natuur en Milieu and Others, C‑266/09, EU:C:2010:779**, paragraph 28 and the case-law cited).

40. The observations of Roche Italia are intended as a response to certain points of the Advocate General's Opinion. However, it follows from the case-law cited in the preceding paragraph that there is no provision in the texts governing procedure before the Court for the lodging of such observations.

41. In addition, after hearing the Advocate General, the Court finds that it has sufficient information to answer the questions submitted by the referring court and that all the arguments necessary for the determination of the matter at issue have been debated between the parties.

42. Consequently, the request to reopen the oral procedure must be rejected.

Admissibility of the request for a preliminary ruling

43. The AGCM, the Associazione Italiana delle Unità Dedicate Autonome Private di Day Surgery e dei Centri di Chirurgia Ambulatoriale (Aiudapds) and the Regione Emilia-Romagna (the Region of Emilia-Romagna, Italy) argue that the request for a preliminary ruling is inadmissible on the ground that it does not contain an adequate description of the facts of the case and of the parties' arguments.

44. In that regard, it must be borne in mind that, in the context of the cooperation between the Court and the national courts provided for in Article 267 TFEU, it is solely for the national court before which a 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).

45. 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 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).

46. In the present case, however, the request for a preliminary ruling contains a description of the elements of fact and law behind the dispute that is sufficient to enable the Court to give a useful answer to the questions referred. Those questions, which relate to the interpretation of Article 101 TFEU, form part of a dispute concerning the validity of a decision through which the AGCM applied that provision. They thus bear a direct relation to the purpose of the main action and are not hypothetical. The AGCM and Aiudapds as well as the Region of Emilia-Romagna and all the parties that participated in the proceedings were able, moreover, to present their observations on the questions submitted by the referring court.

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

Consideration of the questions referred

The second to fourth questions

48. By its second to fourth questions, which it is appropriate to examine together, the referring court asks, in essence, whether Article 101 TFEU must be interpreted as meaning that, for the purposes of the application of that article, a national competition authority may include in the relevant market, in addition to the medicinal products authorised for the treatment of the diseases concerned, another medicinal product whose MA does not cover such treatment but which is used for that purpose. If so, the referring court also asks whether the competition authority must take account of whether or not such off-label use complies with the EU rules governing pharmaceutical matters.

49. In order to answer those questions, it should be borne in mind that the sole purpose of the definition of the relevant market, in the context of the application of

Article 101(1) TFEU, is to determine whether the agreement in question is capable of affecting trade between Member States and has the object or effect of preventing, restricting or distorting competition within the internal market (judgment of 11 July 2013, Gosselin Group v Commission, C‑429/11 P, not published, EU:C:2013:463, paragraph 75 and the case-law cited).

50. The relevant product market comprises all those products and/or services which are regarded as interchangeable or substitutable by the consumer, by reason of their characteristics, their prices and their intended use (see judgment of 28 February 2013, Ordem dos Técnicos Oficiais de Contas, C‑1/12, EU:C:2013:127, point 77).

51. The concept of the relevant market implies that there can be effective competition between the products or services which form part of it and this presupposes that there is a sufficient degree of interchangeability between all the products or services forming part of the same market in so far as a specific use of such products or services is concerned (judgment of 13 February 1979, Hoffmann-La Roche v Commission, 85/76, EU:C:1979:36, paragraph 28). Interchangeability or substitutability is not assessed solely in relation to the objective characteristics of the products and services at issue. The competitive conditions and the structure of supply and demand on the market must also be taken into consideration (see, in respect of Article 102 TFEU, judgment of 9 November 1983, Nederlandsche Banden-Industrie-Michelin v Commission, 322/81, EU:C:1983:313, point 37).

52. In that respect, it should be noted that the fact that pharmaceutical products are manufactured or sold illegally prevents them, in principle, from being regarded as substitutable or interchangeable products, both on the supply side, because of the legal, economic and technical risks, as well as the risks of reputational damage, to which they expose the manufacturers and distributors of those products, and on the demand side, in particular due to the risk to public health that they cause among healthcare professionals and patients.

53. Under Article 6 of Directive 2001/83, 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 an authorisation has been granted in accordance with Regulation No 726/2004.

54. In the present case, however, it is not disputed that during the alleged infringement period Avastin was covered by an MA validly issued by the Commission pursuant to that regulation for the treatment of tumorous diseases.

55. The dispute in the main proceedings concerns the use of Avastin for the treatment of eye diseases which were not covered by that MA. The referring court thus asks, in essence, whether the AGCM could include that off-label use of Avastin in the relevant market, even in the event that it failed to comply with the requirements laid down by the EU rules on pharmaceutical products. Indeed, Roche argues on that point that a significant proportion, the majority even, of the Avastin intended for off-label use in Italy was serially repackaged without manufacturing authorisation and was sold to healthcare providers in advance, before the submission of individual prescriptions.

56. In that respect, it should be noted that Directive 2001/83 does not prohibit the use of medicinal products for therapeutic indications not covered by their MA. Article 5(1) of Directive 2001/83 in fact provides that a Member State may, in order to fulfil special needs, exclude from the provisions of that directive medicinal products supplied in response to a bona fide unsolicited order, prepared in accordance with the specifications of an authorised healthcare professional for use by an individual patient under his direct personal responsibility.

57. On that point, the Court has held that it is apparent from all the conditions set out in that provision, read in the light of the fundamental objectives of that directive, and in particular the objective of seeking to safeguard public health, that the exception provided for in that provision can only concern 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 on the national market or which is unavailable on that market (judgments of 29 March 2012, Commission v Poland, C‑185/10, EU:C:2012:181, paragraph 36, and of 16 July 2015, Abcur, C‑544/13 and C‑545/13, EU:C:2015:481, paragraph 56).

58. In addition, the EU rules on pharmaceutical matters govern the conditions under which a medicinal product such as Avastin may be repackaged so as to allow its intravitreal injection. Thus, according to Article 40 of Directive 2001/83, the manufacture of a medicinal product is subject to authorisation, except for repackaging carried out for retail supply by healthcare professionals (judgment of 28 June 2012, Caronna, C‑7/11, EU:C:2012:396, paragraph 35). The repackaging of Avastin with a view to its use in ophthalmology therefore requires an authorisation, as a rule, unless it is carried out solely for the purposes of retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States (**judgment of 11 April 2013, Novartis Pharma, C‑535/11, EU:C:2013:226**, paragraph 52).

59. It follows that 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.

60. Furthermore, as the Advocate General pointed out in point 88 of his Opinion, it is not for the national competition authorities to verify compliance with EU law of the conditions under which a medicinal product such as Avastin is prescribed by doctors, on the demand side, and repackaged, on the supply side, with a view to its off-label use. Such verification can be carried out comprehensively only by the authorities with jurisdiction to ensure compliance with the rules

governing pharmaceutical matters, or by the national courts.

61. Therefore, in order to assess the extent to which a pharmaceutical product whose MA does not cover the treatment of certain diseases is substitutable or interchangeable with another pharmaceutical product that is authorised for the treatment of those diseases, and whether those products therefore fall within the same relevant market as defined in paragraphs 50 and 51 above, the national competition authority must, in so far as conformity of the product at issue with the applicable provisions governing the production or the marketing of the product has been examined by the competent authorities or courts, take account of the outcome of that examination by assessing any effects it may have on the structure of supply and demand.

62. With regard to the dispute in the main proceedings, there is nothing in the case file to suggest that, at the time the AGCM applied Article 101 TFEU, any unlawfulness of the conditions under which Avastin was repackaged and prescribed with a view to its off-label use, as alleged by Roche, had been established by either the authorities jurisdiction to ensure compliance with the rules governing pharmaceutical matters or by the national courts.

63. On the contrary, without prejudice to the verifications which are a matter for the referring court to determine, as the case may be, it is apparent, in particular from paragraphs 70 and 208 of the AGCM's decision, that, at the time the decision was adopted, the EMA and the Commission did not grant Roche's request to include in the list of *'adverse reactions'* set out in the summary of Avastin's characteristics certain side effects resulting from the intravitreal use of that product, and that they took the view that those effects warranted only a mention in the *'Special warnings and precautions for use'*.

64. In those circumstances, the state of uncertainty surrounding the lawfulness of the repackaging and the prescription of Avastin for the treatment of eye diseases did not preclude the AGCM, for the purposes of the application of Article 101(1) TFEU, from finding that that product belonged to the same market as another medicinal product whose MA covers specifically those therapeutic indications.

65. It should also be stressed in this regard that, given the specific features of competition in the pharmaceutical sector, the relevant market for the purposes of the application of Article 101(1) TFEU is, in principle, capable of comprising medicinal products that may be used for the same therapeutic indications, since the prescribing doctors are primarily guided by considerations of therapeutic appropriateness and the efficacy of medicines.

66. However, it is not disputed between the parties to the main proceedings that during the infringement period referred to in the AGCM's decision Avastin was frequently prescribed for the treatment of eye diseases, despite the fact that its MA did not cover those indications. Consequently, this circumstance reveals the existence of a specific relationship of substitutability between that medicinal product and the products authorised for those eye diseases, which include Lucentis. It is all the more true that it was possible to assess accurately the demand for that product for the treatment of eye diseases not covered by its MA since Avastin was subject to prescription.

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

The first part of the first question

68. By the first part of its first question the referring court asks whether, in essence, Article 101(1) TFEU must be interpreted as meaning that any restrictions of competition agreed between the parties to a licensing agreement fall outside the scope of application of the first paragraph of that article even though the licensing agreement does not envisage any such restrictions on the ground that they are ancillary to that agreement.

69. In that regard, it is apparent from the case-law of the Court that if a given operation or activity is not covered by the prohibition laid down in Article 101(1) TFEU, owing to its neutrality or positive effects in terms of competition, a restriction of the commercial autonomy of one or more of the participants in that operation or activity is not covered by that prohibition either if that restriction is objectively necessary to the implementation of that operation or that activity and is proportionate to the objectives of one or the other (see judgment of 11 September 2014, MasterCard and Others v Commission, C‑382/12 P, EU:C:2014:2201, paragraph 89 and the case-law cited).

70. Where it is not possible to dissociate such a restriction from the main operation or activity without jeopardising its existence and aims, it is necessary to examine the compatibility of that restriction with Article 101 TFEU in conjunction with the compatibility of the main operation or activity to which it is ancillary, even though, taken in isolation, such a restriction may appear on the face of it to be covered by the prohibition rule in Article 101(1) TFEU (judgment of 11 September 2014, MasterCard and Others v Commission, C‑382/12 P, EU:C:2014:2201, paragraph 90).

71. Where it is a matter of determining whether a restriction can escape the prohibition laid down in Article 101(1) TFEU because it is ancillary to a main

operation that is not anticompetitive in nature, it is necessary to inquire whether that operation would be impossible to carry out in the absence of the restriction in question. The fact that that operation is simply more difficult to implement or even less profitable without the restriction concerned cannot be deemed to give that restriction the objective necessity required in order for it to be classified as ancillary. Such an interpretation would effectively extend that concept to restrictions which are not strictly indispensable to the implementation of the main operation. Such an outcome would undermine the effectiveness of the prohibition laid down in Article 101(1) TFEU (judgment of 11 September 2014, MasterCard and Others v Commission, C‑382/12 P, EU:C:2014:2201, paragraph 91).

72. In the present case, it should be noted that the conduct described in the AGCM's decision, which concerns the dissemination of allegedly misleading information relating to adverse reactions to Avastin where that product is administered for the treatment of eye diseases, was not designed to restrict the commercial autonomy of the parties to the licensing agreement regarding Lucentis but rather the conduct of third parties, in particular healthcare professionals, with a view to preventing the use of Avastin for that type of treatment from interfering with the use of Lucentis for that same purpose.

73. Furthermore, while, admittedly, the file submitted to the Court contains no information that is capable of casting doubt on the favourable, or at least neutral, nature, in terms of competition, of the licence agreement concluded between Genentech and Novartis, it cannot be held that conduct such as that described in the preceding paragraph was objectively necessary for the implementation of the agreement. Indeed, that conduct was agreed upon several years after the agreement was concluded, and not in the agreement itself or upon its conclusion, with a view to eliminating the substitutability between the use of Avastin and that of Lucentis for the purpose of treating eye diseases, arising in particular from the prescribing practices of doctors.

74. The fact that the conduct penalised in the AGCM's decision was designed to reduce the use of Avastin and to increase the use of Lucentis so as to render more profitable the exploitation by Novartis of the technology rights over Lucentis granted to it by Genentech cannot mean, in the light of the case law referred to in paragraph 71 above, that that conduct is to be regarded as objectively necessary for the implementation of the licensing agreement at issue.

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

The fifth question

76. It is clear from the explanations provided by the referring court and the observations submitted to the Court that the finding of infringement of Article 101 TFEU by the undertakings at issue in the main proceedings concerns only the dissemination of information relating to adverse reactions resulting from the off-label use of Avastin.

77. Although the fifth question also refers to information concerning the efficacy of a medicinal product, it must be considered that, by this question, the referring court is asking, in essence, whether Article 101(1) TFEU must be interpreted as meaning that an arrangement put in place between two undertakings marketing two competing products, which concerns the dissemination, in a context of scientific uncertainty on the matter, of information relating to adverse reactions resulting from the use of one of those medicinal products for indications not covered by its MA, with a view to reducing the competitive pressure resulting from that use on another medicinal product covered by an MA covering those indications, constitutes a restriction of competition *'by object'* for the purposes of that provision.

78. In that regard, it is important to recall that the concept of restriction of competition *'by object'* must be interpreted strictly and can be applied only to certain types of coordination between undertakings which reveal a degree of harm to competition that is sufficient for it to be held that there is no need to examine their effects. Indeed, certain forms of coordination between undertakings can be regarded, by their very nature, as being harmful to the proper functioning of normal competition (see, inter alia, judgments of 20 November 2008, Beef Industry Development Society and Barry Brothers, C‑209/07, EU:C:2008:643, paragraph 17, and of 27 April 2017, FSL and Others v Commission, C‑469/15 P, EU:C:2017:308, paragraph 103).

79. In order to determine whether an arrangement can be considered to be a restriction of competition by object, regard must be had to the content of its provisions, its objectives and the economic and legal context of which it forms a part (see, to that effect, judgments of 8 November 1983, IAZ International Belgium and Others v Commission, 96/82 to 102/82, 104/82, 105/82, 108/82 and 110/82, EU:C:1983:310, paragraph 25, and of 11 September 2014, CB v Commission, C‑67/13 P, EU:C:2014:2204, paragraph 53).

80. When determining that context, it is necessary to take into account the nature of the goods or services affected, as well as the real conditions of the functioning and the structure of the market or markets in question (judgment of 23 November 2006, Asnef-Equifax and Administración del Estado, C‑238/05, EU:C:2006:734, paragraph 49 and the case-law cited). Where the question arises as to whether there is a cartel agreement in the pharmaceuticals sector, account must

be taken of the impact of EU rules on pharmaceutical products (see, by analogy, **judgment of 16 September 2008, Lélos kai Sia and Others, C‑468/06 to C‑478/06, EU:C:2008:504**, paragraph 58).

81. Those rules require that a medicinal product such as Avastin must be subject to a pharmacovigilance system under the control of the EMA in coordination with the competent national agencies for pharmaceutical matters. Under the second paragraph of Article 101(1) of amended 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'*.

82. With regard to medicinal products authorised through the centralised procedure, Article 16(2) of Regulation No 726/2004 imposes on the holder of the MA an obligation to forthwith supply to the EMA, to the Commission and to the Member States any new information which might entail the variation of the information required for issuance of the MA, including the information set out in the summary of the product characteristics.

83. Those obligations were strengthened as from 2 July 2012, the date on which the amendment to Article 16(2) of Regulation No 726/2004 introduced by Regulation No 1235/2010 became applicable. Article 16(2) of amended Regulation No 726/2004 thus provides that the MA holder *'shall forthwith inform the [EMA] and the Commission ... with any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned'*, with that information comprising *'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].'*

84. In addition, pursuant to Article 17 of Regulation No 726/2004, the holder of the MA is responsible for the accuracy of the documents and the data provided.

85. Moreover, the conditions for dissemination of information on medicinal products to healthcare professionals and the general public are governed, in particular, by Article 106a of amended Directive 2001/83, which applies to the holder of an MA granted in accordance with the centralised procedure under Article 22 of amended Regulation No 726/2004. Under Article 106a of amended Directive 2001/83, the MA holder must ensure that *'that information to the public is presented objectively and is not misleading'*. Article 24(5) of Regulation No 726/2004, also applicable to the facts at issue in the main proceedings and repealed with effect from 2 July 2012 by Regulation No 1235/2010, was worded in comparable terms to Article 106a of amended Directive 2001/83.

86. In order to ensure the efficacy of the implementation of the rules governing pharmaceutical matters, they are combined with penalties. With regard to the centralised procedure, Article 84 of Regulation No 726/2004 provides that the Member States are to determine the applicable penalties, which must be *'effective, proportionate and dissuasive'*. That article also provides that the Commission may impose penalties if the MA holder fails to observe the conditions laid down in the MA.

87. The procedure and financial penalties were subsequently specified in Regulation No 658/2007, which stipulates in Article 16(1) thereof that the Commission may impose penalties in the form of fines amounting to up to 5% of the MA holder's annual turnover within the European Union. The list of infringements set out in Article 1(1) of the regulation, in respect of which the Commission may impose penalties in cases where the infringement concerned may have significant public health implications in the European Union, where it has an EU dimension because it takes place or has its effects in more than one Member State, or where EU interests are involved, includes infringement of the obligation to provide complete and accurate particulars and documents in an application for an MA under Regulation No 726/2004 or any other documents and data to be submitted to the EMA in response to the obligations laid down in the regulation.

88. Moreover, in accordance with Article 28(4) of amended Regulation No 726/2004, the EMA and the Commission have exclusive jurisdiction to examine applications for variation of an MA in connection with amendments made to the summary of product characteristics owing to new pharmacovigilance information and, as the case may be, to adopt a decision to vary, suspend or revoke the MA concerned.

89. With regard to the facts at issue in the main proceedings, which are a matter for the referring court alone, as is apparent from paragraphs 177, 189, 193 to 202 and 209 of the AGCM's decision, the AGCM found that by adopting a common strategy to counteract the competitive pressure exerted on the sale of Lucentis by the use of Avastin for the treatment of eye diseases not covered by its MA, the undertakings concerned infringed Article 101 TFEU. According to that decision, the purpose of the arrangement put in place between Roche and Novartis was to create an artificial differentiation between those two medicinal products by manipulating the perception of the risks associated with the use of Avastin for the treatment of those diseases through the production and dissemination of opinions which, based on an *'alarmist'* interpretation of available data, could give rise to public concern regarding the safety of certain uses of Avastin and influence the therapeutic choices of doctors, and by downplaying any scientific knowledge to the contrary.

90. Under paragraph 177 of the AGCM's decision, this arrangement was also intended to disclose to the EMA information that could exaggerate the perception of the risks associated with that use in order to obtain the

amendment of the summary of Avastin's characteristics and to be granted leave to send healthcare professionals a letter drawing their attention to such adverse reactions. According to paragraphs 208, 209 and 215 of the AGCM's decision, this artificial exaggeration of the risks associated with the off-label use of Avastin is substantiated, inter alia, by the fact mentioned in paragraph 63 above that the EMA and the Commission did not grant Roche's request to include in the list of *'adverse reactions*' set out in the summary of Avastin's characteristics certain side effects resulting from the intravitreal use of Avastin, and that they took the view that those effects warranted only a mention in the *'Special warnings and precautions for use'*.

91. In that regard, it should be noted, in the first place, before even examining the relevance for the purpose of establishing a restriction of competition by object under Article 101(1) TFEU of the misleading nature of the information supplied to the EMA and the general public, that the requirements for pharmacovigilance that might call for steps to be taken such as the dissemination to healthcare professionals and the general public of information relating to the risks associated with the off-label use of a medicinal product, as well as the initiation of a procedure before the EMA with a view to including such information in the summary of characteristics of the product, rest, as is apparent from the provisions referred to in paragraph 82 and 87 above, solely with the holder of the MA for that medicinal product and not with another undertaking marketing a competing medicinal product covered by a separate MA. Accordingly, the fact that two undertakings marketing competing pharmaceutical products collude with each other with a view to disseminating information specifically relating to the product marketed by only one of them might constitute evidence that the dissemination of information pursues objectives unrelated to pharmacovigilance.

92. In the second place, with regard to the misleading nature of the information at issue, it must be held that the information whose notification to the EMA and the general public, according to the AGCM's decision, was the subject of a cartel agreement between Roche and Novartis, are, failing compliance with the requirements of completeness and accuracy laid down in Article 1(1) of Regulation No 658/2007, to be regarded as misleading if the purpose of that information, which is a matter for the referring court to determine, was (i) to confuse the EMA and the Commission and have the adverse reactions mentioned in the summary of product characteristics so as to enable the MA holder to launch a communication campaign aimed at healthcare professionals, patients and other persons concerned with a view to exaggerating that perception artificially, and (ii) to emphasise, in a context of scientific uncertainty, the public perception of the risks associated with the off-label use of Avastin, given, inter alia, the fact that the EMA and the Commission did not amend the summary of characteristics of that product in respect of its *'adverse reactions'* but merely issued *'Special warnings and precautions for use'*.

93. However, in such a case, given the characteristics of the medicinal products market, it is likely that the dissemination of such information will encourage doctors to refrain from prescribing that product, thus resulting in the expected reduction in demand for that type of use. The provision of misleading information to the EMA, healthcare professionals and the general public, as is apparent from paragraphs 84 to 87 above, also constitutes an infringement of the EU rules governing pharmaceutical matters giving rise to penalties.

94. In those circumstances, an arrangement that pursues the objectives described in paragraph 92 above must be regarded as being sufficiently harmful to competition to render an examination of its effects superfluous.

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

The second part of the first question

96. By the second part of its first question, the referring court also asks whether Article 101 TFEU must be interpreted as meaning that an arrangement such as that described in the previous paragraph can be exempt under Article 101(3) TFEU.

97. The applicability of the exemption provided for in Article 101(3) TFEU is subject to the four cumulative requirements laid down in that provision. Those requirements are, first, that the arrangement concerned must contribute to improving the production or distribution of the goods or services in question, or to promoting technical or economic progress; secondly, that consumers must be allowed a fair share of the resulting benefit; thirdly, that it must not impose on the participating undertakings restrictions that are not indispensable; and, fourthly, that it must not afford them the possibility of eliminating competition in respect of a substantial part of the products or services in question.

98. In the present case, however, suffice it to note that the dissemination of misleading information in respect of a medicinal product cannot be regarded as *'indispensable'* within the meaning of the third requirement for the purpose of being exempt under Article 101(3) TFEU.

99. By referring several times to a licensing agreement and to the existence of a relationship of competition between the parties to that agreement, the referring court seems to have intended, by its first question, to refer to the requirements laid down in Commission

Regulation (EC) No 772/2004 of 27 April 2004 on the application of Article 81(3) of the Treaty to categories of technology transfer agreements (OJ 2004 L 123, p. 11).

100. However, it is important to note that, in the light of the considerations set out in paragraphs 97 and 98 above and pursuant to Article 101(3) TFEU, an arrangement such as that at issue in the main proceedings cannot, in any event, be exempt under Article 2 of the regulation.

101. Therefore, the answer to the second part of the first question is that Article 101 TFEU must be interpreted as meaning that an arrangement such as that described in paragraph 9 above cannot be exempt under Article 101(3) TFEU.

Costs

102. 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 (Grand Chamber) hereby rules:

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

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

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

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

[Signatures]

OPINION OF ADVOCATE GENERAL SAUGMANDSGAARD ØE

delivered on 21 September 2017 (1)

Case C‑179/16

F. Hoffmann-La Roche Ltd and Others

v

Autorità Garante della Concorrenza e del Mercato (AGCM)

(Request for a preliminary ruling

from the Consiglio di Stato (Council of State, Italy))

(Reference for a preliminary ruling — Competition — Article 101 TFEU — Medicines for the treatment of ocular vascular pathologies — Definition of the relevant product market — Interchangeability of medicinal products — Regulation (EC) No 726/2004 — Marketing authorisation — Prescribing and marketing of medicines for 'off-label' use — Legality — Licensing agreement — Undertakings not in competition — Concept of 'ancillary restriction' — Concept of 'restriction of competition by object' — Allegations of the lesser safety of one medicinal product compared to another — Whether or not misleading — Protection of public health — Pharmacovigilance obligations — Counterfactual hypothesis)

I. Introduction

1. The Consiglio di Stato (Council of State, Italy) has referred to the Court of Justice several questions for a preliminary ruling concerning the interpretation of Article 101 TFEU in the context of a dispute the unusual characteristics of which may be summarised as follows.

2. A certain undertaking has developed two medicines, one for the treatment of cancer, the other for the treatment of ophthalmological conditions. The medicines are based on different active substances that are nevertheless obtained from the same antibody and have the same therapeutic mechanism. The undertaking decided to market the cancer treatment itself and entrusted the marketing of the ophthalmological medicine to another undertaking by means of a licensing agreement.

3. The marketing authorisation ('MA') for the cancer treatment was granted approximately two years earlier than the MA for the ophthalmological medicine. During the interval between the grant of each of the two MAs, a number of medical practitioners gave their patients the cancer treatment, in weaker doses, to treat ocular pathologies. This usage for therapeutic indications and in accordance with methods not

covered by the Summary of Product Characteristics ('SPC') or, therefore, by the MA for the medicine — so-called 'off-label use' — continued even after the grant of the MA for the ophthalmological medicine because of the substantially lower treatment costs.

4. The Autorità Garante della Concorrenza e del Mercato (AGCM) (the Italian competition authority) found that the two undertakings in question had conspired to communicate to the pharmaceutical regulatory authorities, to medical professionals and to the general public statements to the effect that the cancer treatment when used off label was less safe than the ophthalmological medicine. According to the AGCM, the undertakings had no scientific evidence to support these statements and had made them with the aim of discouraging the off-label use of the cancer treatment and consequently increasing sales of the ophthalmological medicine. The AGCM considered that this collusive conduct was a restriction of competition by object, within the meaning of Article 101(1) TFEU, and fined the undertakings accordingly.

5. Having failed in their action at first instance to challenge that decision, the undertakings brought an appeal before the referring court. It is in that context that the referring court questions the Court of Justice about the interplay between the regulatory framework for the placing of medicinal products on the market and EU competition law. In particular, the Court is called upon to clarify to what extent and on what basis the legal uncertainty regarding the lawfulness of prescribing and marketing a medicine with a view to its off-label use and the scientific uncertainty surrounding the risks associated with such use come into play in the application of Article 101 TFEU.

II. Legal context

6. Regulation (EC) No 772/2004, (2) which was applicable at the time of the material facts in the main proceedings, provided for the block exemption of certain technology transfer agreements.

7. Pursuant to Article 1(1)(j)(ii) of that regulation, *'competing undertakings on the relevant product market'* are *'undertakings which, in the absence of the technology transfer agreement, are both active on the relevant product and geographic market(s) on which the contract products are sold without infringing each other's intellectual property rights (actual competitors on the product market) or would, on realistic grounds, undertake the necessary additional investments or other necessary switching costs so that they could timely enter, without infringing each other's intellectual property rights, the(se) relevant product and geographic market(s) in response to a small and permanent increase in relative prices (potential competitors on the product market); the relevant product market comprises products which are regarded by the buyers as interchangeable with or substitutable for the contract products, by reason of the products' characteristics, their prices and their intended use*'.

8. Regulation (EC) No 726/2004 (3) established a centralised procedure for the authorisation of medicinal products at EU level.

9. In accordance with 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 this regulation'*. Point 1 of the annex, which concerns *'medicinal products to be authorised by the [European Union]'*, includes medicines developed by means of certain biotechnological processes.

10. According to Article 13(1) of the 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 Directive 2001/83/EC. (4)

11. In so far as concerns the content of an application for an MA, Article 6(1) of Regulation No 726/2004 refers to the particulars listed, inter alia, in Article 8(3) of Directive 2001/83. Point (j) of Article 8(3) in particular mentions the SPC. In accordance with Article 11 of the directive, the SPC must specify the dosage and the pharmaceutical form of the medicinal product, the qualitative and quantitative composition of all of its constituents, the therapeutic indications, the posology and method of administration, the contra-indications, special warnings and special precautions for use, the adverse reactions and the special precautions for storage and the duration thereof.

12. Article 16(2) of Regulation No 726/2004, in the version which has applied since 2 July 2012, (5) provides that the holder of an MA must immediately provide the European Medicines Agency (EMA), the European Commission and the Member States with any new information which might entail the amendment of the particulars or documents referred to, inter alia, in Article 8(3) of Directive 2001/83. The information to be provided must *'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]'*.

13. Regulation No 726/2004 also instituted a system of pharmacovigilance for the medicinal products authorised under it. As is clear from Article 24(1) of the regulation, in the version which has applied since 2 July 2012, that system serves to collate information *'on 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]'*.

14. In particular, Article 21(1) of Regulation No 726/2004, in the version which has applied since 2 July 2012, provides that *'the obligations of [MA] holders laid down in Article 104 of Directive 2001/83/EC shall apply to ... holders [of MAs] for medicinal products for human use authorised in accordance with this regulation'*.

15. Article 104 of Directive 2001/83, as it results from an amendment which the Member States were to transpose by 21 July 2012, (6) is worded as follows:

'1. The [MA] holder shall operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to the relevant Member State's pharmacovigilance system provided for under Article 101(1).
2. The [MA] holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary. ...
...'

16. In accordance with Article 49(5) of Regulation No 726/2004, an MA holder may not communicate information relating to pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the EMA. An MA holder must, in any event, ensure that such information *'is presented objectively and is not misleading'*.

III. The dispute in the main proceedings, the questions referred and the procedure before the Court

17. By decision of 27 February 2014 ('the AGCM's decision'), a copy of which was placed on the file submitted by the referring court to the Court of Justice, the AGCM found that the companies F. Hoffmann-La Roche Ltd ('Roche') and Novartis AG, through their subsidiaries Roche SpA ('Roche Italia') and Novartis Farma SpA ('Novartis Italia'), had put in place, in breach of Article 101 TFEU, a horizontal agreement restricting competition. According to the AGCM's findings, that agreement was designed to achieve an artificial differentiation of the medicinal products Avastin and Lucentis by manipulating the perception of the risks associated with the use of Avastin in the field of ophthalmology. The AGCM imposed on the four companies administrative fines amounting to approximately EUR 180 million in total.

18. Roche, Roche Italia, Novartis and Novartis Italia ('the applicants in the main proceedings') challenged that decision before the Tribunale amministrativo regionale per il Lazio (Regional Administrative Court, Lazio, Italy) which joined their actions and dismissed them by judgment of 2 December 2014.

19. The applicants in the main proceedings brought an appeal before the Consiglio di Stato (Council of State) in order to have the judgment set aside.

20. In that context, the Consiglio di Stato (Council of State) states that the medicinal products Avastin and Lucentis were developed by Genentech Inc., a biotechnology company under the sole control of the Roche group, in the course of a single research programme. That programme was launched following the discovery of a protein produced by the human body (named 'vascular endothelial growth factor' (VEGF)) that is responsible for the formation of abnormal blood vessels which contribute to the growth of certain cancerous tumours.

21. The researchers at Genentech discovered that inhibiting the action of VEGF, by means of an antibody, could be used in the treatment of certain types of cancer. They then succeeded in obtaining an anti-VEGF antibody that could be administered to humans, bevacizumab, which became the active substance in the medicine Avastin.

22. The researchers also examined other diseases connected with the action of VEGF, including a common eye disease known as age-related macular degeneration (AMD). However, the researchers considered bevacizumab to be unsuitable, in terms of safety and efficacy, for the treatment of AMD and other ocular vascular pathologies.

23. Genentech therefore decided to develop an anti-VEGF treatment specifically for the ophthalmological field. The researchers eventually identified an anti-VEGF antibody fragment, named ranibizumab, which became the active substance in the medicine Lucentis. Ranibizumab is eliminated by the body faster than bevacizumab and it has smaller dimensions, which facilitate its penetration of the retina and its capacity to bind itself to the VEGF.

24. Genentech, which is commercially active only in the United States, granted a licence to exploit Avastin to its parent company Roche and, since Roche is not active in the field of ophthalmology, granted a licence to exploit Lucentis to the Novartis group, so that the two companies could register and market the two medicinal products in the rest of the world. The licensing agreement for Lucentis was concluded in June 2003.

25. The medicinal products Avastin and Lucentis were granted MAs by the EMA for the treatment of certain tumorous diseases and certain ophthalmic diseases respectively.

26. On 26 September 2005, the Agenzia Italiana del Farmaco (AIFA) (the Italian Medicines Agency) transposed the MA granted at EU level for Avastin and decided that the cost of the medicine could be reimbursed by the Servizio Sanitario Nazionale (SSN) (the Italian National Health Service).

27. An MA for Lucentis, for the treatment of AMD, was not obtained from AIFA until 31 May 2007. Initially non-reimbursable because of the lack of any agreement between AIFA and Novartis regarding the reimbursement price, Lucentis was approved for reimbursement by the SSN on 4 December 2008.

28. During the period between the market launch of Avastin and that of Lucentis, certain medical practitioners, following early administrations of Avastin for the treatment of cancer, observed that the health of patients suffering from both a cancerous tumour and AMD improved also in so far as the latter disease was concerned.

29. Since Avastin was, during that period, the only anti-VEGF medicine available on the market, some medical practitioners administered it intravitreally (by injection into the eye) to patients suffering from AMD, even though, under the terms of its SPC, Avastin was not authorised for that therapeutic indication or for that method of administration. This off-label use of Avastin spread worldwide. It continued after Lucentis had been placed on the market because of the lower cost of therapies using Avastin.

30. Italian legislation permits, under certain circumstances, the reimbursement of medicines used off label. At the time of the facts material to the AGCM's decision, such reimbursement was subject to the fulfilment of two conditions. First, no viable alternative therapy must have been authorised for the treatment of the pathology in question. Second, the AIFA must have included the off-label use in question in the list of medicinal products covered by the SSN, the so-called 'List 648'. (7)

31. Following the grant of the MA for Avastin and after its off-label use in ophthalmology had become widespread in Italy, in May 2007, the AIFA included that use in List 648 in connection with the treatment of exudative macular diseases (AMD, retinal vein occlusion (RVO), diabetic macular edema (DME), myopic macular degeneration (MMD)) and neovascular glaucoma, there being no valid therapeutic alternative at that time for treating those diseases.

32. Subsequently, following the approval and authorisation for reimbursement in Italy of the medicinal products Lucentis and Macugen for the treatment of AMD (at the end of 2008) and then the approval and authorisation for reimbursement in Italy of the medicinal product Ozurdex, for the treatment of RVO (in July 2011), AIFA decided that there would be no reimbursement for the use of Avastin in the treatment of those diseases. Finally, on 18 October 2012, AIFA removed Avastin from List 648 entirely, referring for that purpose to certain amendments which the EMA had made to the SPC for that medicine on 30 August 2012. As is apparent from the case file submitted to the Court of Justice, those amendments concerned the addition of certain special warnings and precautions for use relating to the intravitreal use of Avastin.

33. The AGCM has emphasised that, the cost of Avastin having long been covered by the SSN in connection with various ophthalmological uses, the medicine became, at least during the period between its inclusion on List 648 and the commencement of the AGCM's procedure, the principal anti-VEGF medicine used in Italy in the treatment of ocular vascular pathologies, in terms of the number of patients treated. Because of that extremely widespread off-label use of Avastin, it became the principal competitor of Lucentis.

34. According to the AGCM, the applicants in the main proceedings had put in place *'a single and complex horizontal agreement implemented through a multitude of concerted practices'*. The purpose of that agreement was to achieve an *'artificial differentiation'* between the medicines Avastin and Lucentis — which are *'equivalent medicinal products in all respects in the field of ophthalmology'* — by manipulating the perception of the risks involved in the use of Avastin in ophthalmology so as to influence demand in favour of Lucentis. The agreement had been implemented by *'the production and dissemination of opinions which could give rise to public concern regarding the safety of the intravitreal use of Avastin'*, while at the same time *'downplaying the value of scientific evidence to the contrary'*.

35. The AGCM found that the companies had exaggerated the risks involved in the intravitreal use of Avastin and had at the same time alleged that Lucentis had a better safety profile than Avastin. The companies had also relied on the fact that only Lucentis had an MA for ophthalmological indications and that no application had yet been made for an MA for Avastin for such indications.

36. The applicants in the main proceedings had thus sought to *'prevent the off-label use of Avastin from eroding the on-label use of Lucentis'*, which was *'the more costly product ... the sale of which generates profits for both companies'*. The agreement also included *'the common interest of the Roche and Novartis groups in the amendment of the [SPC] for Avastin, currently before the EMA, and in the subsequent issue of a formal communication to medical professionals (a 'direct healthcare professional communication' or DHPC) — one that had been initiated by Roche, as [MA] holder for Avastin ... — that would have a direct effect on the concerted plan to create artificial differentiation'*.

37. Still according to the AGCM, the agreement in question was intended to maximise unlawfully the respective revenues of the Roche and Novartis groups which came, for the Novartis group, from the direct sale of Lucentis and from its 33% shareholding in Roche and, for the Roche group, from royalties received on such sales through the intermediary of its subsidiary Genentech.

38. The concerted practices identified by the AGCM, *'although dependent on the existence of vertical licensing relationships, had taken place outside those relationships'*.

39. The AGCM considered that the arrangement constituted an unlawful market-sharing agreement and therefore constituted a restriction of competition by object, within the meaning of Article 101(1) TFEU. It had been *'put into effect, having an impact on the therapeutic decisions taken by medical practitioners and on the resulting purchasing policies for the medicines Avastin and Lucentis'*. The agreement had *'caused an immediate slowdown in the growth of Avastin and a consequent shift in demand toward the more expensive Lucentis, which [had] resulted in a cost increase for the SSN of nearly EUR 45 million in 2012 alone'*.

40. The AGCM consequently considered that *'the infringement complained of ... must be regarded as very serious'*, in particular, because of its unlawful object, because it had *'been implemented'* and had *'had definite effects on the economic equilibrium of the health system as a whole'*, and also because of the fact that the combined market share of the applicants in the main proceedings of the Italian market for medicinal products for the treatment of ocular vascular pathologies was over 90%.

41. The concerted practices identified by the AGCM had begun in June 2011 at the latest, when Roche

initiated the formal procedure before the EMA to obtain the amendment of the SPC for Avastin and the consequent issue of a formal communication. The concerted practices had not ceased at the time when the AGCM adopted its decision.

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

(2) Does Article 101 TFEU allow the national competition authority to define the relevant market independently of the content of marketing authorisations (MAs) for medicinal products granted by the competent pharmaceutical regulatory authorities (the Agenzia Italiana del Farmaco and the European Medicines Agency) or, on the contrary, with respect to authorised medicinal products, must the relevant market for the purposes of Article 101 TFEU instead be held to be primarily shaped and established by the appropriate regulatory authority in a way that is binding even on the national competition authority?

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

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

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

43. Written observations have been submitted to the Court by Roche, Roche Italia, Novartis and Novartis Italia, the Associazione Italiana delle Unità Dedicate Autonome Private di Day Surgery e dei Centri di Chirurgia Ambulatoriale (Aiudapds), the Società Oftalmologica Italiana (SOI) — Associazione Medici Oculisti Italiani (AMOI) ('SOI-AMOI'), Altroconsumo, the Coordinamento delle associazioni per la tutela dell'ambiente e dei diritti degli utenti e consumatori (Condacons), the AGCM, the Regione Emilia-Romagna (the Region of Emilia-Romagna, Italy), the Italian, Irish and French Governments and the Commission.

44. Roche, Roche Italia, Novartis, AIUDAPDS, SOI-AMOI, Altroconsumo, the AGCM, the Region of Emilia-Romagna, the Italian Government and the Commission attended the hearing on 3 May 2017.

IV. Analysis

A. Preliminary observations

45. What lies behind the present case is a situation marked by the development of a wide-scale medical practice of prescribing a certain medicine for off-label use. (8) This practice developed, against the wishes of the holder of the MA for that medicine, at the initiative of those who create the demand for it, that is to say prescribing medical practitioners, who were further encouraged by the authority's decision to allow reimbursement by the SSN of the medicinal product in question.

46. The prescribing of Avastin for the treatment of ocular vascular pathologies was initially intended to fill a therapeutic lacuna, there being no other equally efficacious medicinal products having an MA for such therapeutic indications. The practice nevertheless continued after the placing on the market and the approval for reimbursement of such medicines. That was essentially for economic reasons, given the considerable price difference between therapies based on Avastin and those based on Lucentis. According to the AGCM, the difference in price per millilitre of the two medicinal products meant that an intravitreal injection of Avastin would have cost at least ten times less than an injection of Lucentis.

47. The off-label use of medicinal products is a medical practice which varies in extent depending on the therapeutic field and the Member State concerned. (9) EU law acknowledges this reality and lays down certain provisions, upstream and downstream of off-label use, which restrict the possibilities for placing medicinal products intended for such use on the market (10) and impose on MA holders certain pharmacovigilance obligations in relation to off-label use. (11)

48. On the other hand, EU law does not govern the prescribing of medicinal products for off-label use. (12) That practice falls within the scope of the therapeutic freedom of medical practitioners, subject to any restrictions imposed on that freedom by the Member States in the exercise of their power to define their health policies. (13) Equally, the decision to approve a medicine used off label for reimbursement by the social security systems lies, in principle with the Member States. (14)

49. In this context, the Member States have adopted diverging policies on the regulation of off-label uses of medicines in general and of Avastin in particular. Some

have chosen to authorise the reimbursement of certain medicines prescribed off label or even to stipulate temporary recommendations for their use. (15) Significant judicial proceedings have arisen regarding the legality, with regard to EU law, of such domestic regulations. (16) Moreover, the Consiglio di Stato (Council of State) has, in another case pending before it, referred to the Court of Justice a question for a preliminary ruling concerning the compatibility with EU law of national measures which, for economic reasons, provide for the reimbursement of medicines prescribed off label, such as Avastin. (17)

50. Some, like the applicants in the main proceedings, argue in substance that national policies which authorise, or even encourage, the off-label prescribing of medicines for budgetary reasons run counter to the logic which underlies the EU regulatory framework for the placing of medicinal products on the market. (18) Since only the uses stipulated in the MA will have been the subject of the preclinical tests and clinical trials necessary for obtaining the MA, (19) uses which have not been validated by such trials should, at least, remain the exception.

51. Others, such as the Region of Emilia-Romagna and the Irish Government in the present case, consider that the off-label use of a medicinal product for certain therapeutic indications is necessary where, despite evidence of the efficacy and safety of such use, the holder of the MA for the medicine does not take the necessary steps to extend the MA to cover it. The Region of Emilia-Romagna, the AGCM, SOI-AMOI and the Italian Government claim that off-label use is necessary, sometimes even when another medicine exists the MA for which covers the indications in question, in order to ensure access to care and to avoid excessively burdening the budgets of social security systems.

52. It is not for me, in the context of the present case, to take a position in this debate or to express my thoughts on the merits of the policies of the Member States regarding the regulation of the off-label use of medicinal products. I shall therefore confine myself to examining whether, and if so to what extent, Article 101 TFEU protects the market dynamics which have resulted from off-label use.

53. In this connection, it would seem useful to me to begin by outlining the main issues raised by the five questions referred by the national court.

54. To begin with, the purpose of the second, third and fourth questions is to enable the national court to determine whether the legal barriers which arise from the provisions governing the placing on the market of medicinal products for off-label use preclude the substitutability of Avastin and Lucentis for the treatment of eye diseases and, consequently, their belonging to the same product market.

55. In its reasoning relating to these questions, Roche argues that, having regard to those legal barriers, such products are not part of the same market and, more generally, are not in competition with each other. Accordingly, there could be no question of a restriction on competition resulting from the collusive conduct identified by the AGCM (*'the collusive conduct at issue'*).

56. Next, by its first question, the national court seeks to establish whether Genentech and Novartis must be regarded as competing undertakings in the context of the licensing agreement relating to Lucentis. If they are not, the national court questions the Court of Justice about the relevance, for the purposes of the application of Article 101 TFEU, of the fact that the collusive conduct at issue arose in the context of a licensing agreement between undertaking that are not in competition.

57. The line of argument put forward by the applicants in the main proceedings highlights the issues raised by this question. According to them, the licensing agreement relating to Lucentis binds undertakings that are not in competition. The restrictions on the off-label use of Avastin pursued by means of the collusive conduct at issue (*'the restrictions at issue in the main proceedings'*), while not expressly provided for in the licensing agreement, arose in the course of the agreement's implementation. They allege that, in the case of licensing agreements between non-competing undertakings, the elimination of competition between licensor and licensee falls outside the scope of application of Article 101(1) TFEU or is, at least, exempted under Article 101(3) TFEU.

58. Lastly, the fifth question invites the Court to clarify whether the collusive conduct at issue may, in any event, be classified as a restriction of competition by object, even though the scientific debate concerning the comparative safety and efficacy of Avastin and Lucentis in the field of ophthalmology had not been decided at the material time.

59. It is in that order that I propose to analyse the questions referred for a preliminary ruling, after dismissing the main objections of inadmissibility that have been raised against them.

B. Admissibility

60. The AGCM, Aiudapds and the Region of Emilia-Romagna dispute the admissibility of the questions referred, essentially on the ground that the statement of facts and law set out in the order for reference is deficient and incomplete, merely describing the arguments advanced by the applicants in the main proceedings, which are contested by other interested parties, and omitting important factual elements.

61. The AGCM emphasises in particular that the order for reference fails to mention that Avastin has been used in the field of ophthalmology worldwide since 2005, without any adverse events of statistical relevance having been notified, so much so that the World Health Organisation (WHO) considers bevacizumab (the active substance in Avastin) as the only anti-VEGF medicine essential in ophthalmology. (20) The order for reference also says nothing about the fact that, in 2014, AIFA reinstated Avastin on List 648 for the treatment of ocular vascular pathologies.

62. According to the AGCM and the Region of Emilia-Romagna, the Court of Justice is not in a position to

give a useful answer to the referring court. The AGCM also submits, as does Aiudapds, that, given the incomplete and partly incorrect presentation of the facts, the questions referred are hypothetical.

63. I would recall in this connection that, according to settled case-law, the Court may refuse to rule on a question submitted 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 subject matter, 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. (21)

64. As for the last of those grounds for refusing to rule on a request for a preliminary ruling, the Court has stated that the information provided to it in an order for reference serves not only to enable it to provide answers which will be of use to the national court, but also to enable the governments of the Member States and other interested parties to submit observations in accordance with Article 23 of the Statute of the Court of Justice of the European Union. To that end, the national court must define the factual and legislative context of the questions which it is asking or, at the very least, explain the factual assumptions on which those questions are based. (22)

65. As regards, first of all, the arguments alleging the incomplete nature of the statement of facts and law set out by the national court, the Court considers that, even where there are gaps in the order for reference, it does have sufficient information to reply usefully to the questions referred if the order for reference enables it to determine the scope of the questions referred. (23) The order for reference in the present case satisfies that condition in my view. The Court is, therefore, in a position to provide answers which will be of use to the referring court and the interested parties have been able to submit their observations to the Court, as is clear from the pleadings that have been lodged. (24)

66. Secondly, as regards the arguments alleging the incorrect nature of the description of the material facts, it is not for the Court of Justice but for the national court to ascertain the facts which have given rise to the dispute. (25) It is not for the Court of Justice to verify the accuracy of the legal and factual background which the national court is responsible for defining. (26) It is, in principle, required to base its considerations on the premisses which the national court regards as having been established. (27)

67. Consequently, I consider that the questions referred for a preliminary ruling are admissible.

C. The second, third and fourth questions concerning the definition of the relevant product market

68. The second, third and fourth questions concern the extent to which the regulatory framework for the placing of medicinal products on the market must be taken into account in the definition of the relevant product market. By its second and third questions, which I propose to examine together, the referring court asks, in substance, whether, in the pharmaceutical sector, the definition of the relevant market is necessarily circumscribed by the content of MAs. By its fourth question, the referring court asks the Court of Justice about the relevance, in this context, of uncertainty regarding the lawfulness of marketing medicinal products which have been repackaged with a view to their off-label use.

69. In the present case, the AGCM has defined the relevant product market as including all medicinal products for the treatment of ocular vascular pathologies. (28) That definition is not called into question in the present case. The only point under discussion is whether Avastin belongs to that market or not.

70. It is clear from both the legislation (29) and the case-law (30) that a relevant product market comprises all those products which are regarded as interchangeable or substitutable by the consumer, by reason of their characteristics, their prices and their intended use. (31)

71. According to the case-law, it is also necessary, when making such an assessment, to take into account not only the objective characteristics of the products, by virtue of which they are particularly suitable for satisfying the constant needs of consumers, but also the conditions of competition and the structure of supply and demand. (32)

72. In accordance with those principles, the definition of the relevant product market depends not on criteria established in advance by the legal rules governing the conduct of economic actors, but on the objective characteristics of the products and on the actual competitive conditions surrounding such conduct. Those conditions will include legal rules to the extent that they are capable of affecting the degree of interchangeability of the goods in question, but are not limited to such legal rules. Other circumstances can, as the case may be, indicate the existence of effective competitive constraints.

73. In this case, the legal framework governing the placing on the market — and the prescribing (33) — of medicinal products may entail certain legislative obstacles to the substitutability of a medicine used off label for a medicine used on label for the same therapeutic indications. (34) Nevertheless, such obstacles are not insurmountable, nor therefore are they necessarily decisive in the definition of the relevant market.

74. In light of those considerations, I think that, where the competitive conditions actually observed indicate that there is effective demand-side substitutability between a medicinal product used off label for certain therapeutic indications and another medicinal product that has received an MA in respect of the same therapeutic indications, the two products belong to the same product market (section 1 below). That applies even where the lawfulness of prescribing and marketing the first medicinal product with a view to off-label use is uncertain (section 2 below).

1. The relevance, in the definition of the relevant product market, of the content of MAs (the second and third questions)

75. As has been argued by all of the interested parties, with the exception of the applicants in the main proceedings, the fact that the MA for a medicinal product does not cover certain therapeutic indications does not mean that that medicine cannot have a degree of interchangeability with medicines which are authorised for those indications that is sufficient to create an effective competitive constraint on them.

76. Certainly, the content of an MA will, in principle, influence the substitutability of different medicinal products for the same therapeutic use. In so far as prescription medicines are concerned, demand is generally determined not by the preferences of final consumers (that is to say, patients) but by the decisions of medical practitioners, and an MA is likely, at the very least, to guide medical practitioners in their choice of appropriate treatment for their patients. That is especially true where national law limits the possibilities for prescribing medicinal products off label or for obtaining reimbursement and lays down specific rules governing medical liability in the event that harm is caused by the off-label use of a medicinal product.

77. However, the practice of medical practitioners in prescribing medicines, coupled, as the case may be, with administrative decisions concerning the approval for reimbursement of medicines prescribed off label, may be at the origin of competitive dynamics which demonstrate the actual interchangeability of two medicinal products independently of the content of their respective MAs. Indeed, if the content of an MA is limited by the application that was made by its holder to the pharmaceutical regulatory authorities, (35) that application will not necessarily cover all the possible uses to which medical practitioners may put the medicine in question in the exercise of their therapeutic freedom. (36)

78. In the present case, it is apparent from the order for reference that Avastin was, at the time of the collusive conduct at issue, very often prescribed for ophthalmological indications. Moreover, when the concerted practices identified by the AGCM began (that is to say, in June 2011), Avastin was still included in the list of medicinal products which the SSN reimbursed for the treatment of neovascular glaucoma and all exudative macular diseases with the exception of AMD. (37)

79. Those circumstances reveal that Avastin, when used off label, exerted an effective competitive constraint on Lucentis. In accordance with the principles mentioned in points 70 and 71 of this Opinion, that constraint must be taken into consideration in the definition of the relevant product market.

80. This approach reflects the approach that the Commission adopted in certain merger control decisions in which it took into account medicinal products used off label in its analysis of the actual competitive dynamics for the purposes of defining the relevant product market. (38)

81. Moreover, if the definition of the relevant product market were systematically limited by the content of MAs, pharmaceutical companies would, in practice, have carte blanche to reach agreements, prior to the placing of their medicines on the market, to share markets by ensuring that there was no overlapping of the therapeutic indications covered by their respective MA applications, as indeed Aiudapds, SOI-AMOI, Altroconsumo, Condacons and the Italian Government have argued. The market would then be defined with no account being taken of the interchangeability of medicinal products on the demand side, in breach of the principles set out in points 70 and 71 of this Opinion.

2. The relevance, in the definition of the relevant product market, of uncertainty regarding the lawfulness of prescribing and marketing medicines (the fourth question)

82. The words *'establish ... whether'* used in the fourth question reflect the uncertainty surrounding the lawfulness of marketing Avastin once it has been repackaged with a view to its use in ophthalmology. That issue has been hotly debated in the written and oral submissions of the interested parties. According to the applicants in the main proceedings, that activity is unlawful in numerous cases, or even most of the time. Other interested parties, such as the AGCM, SOI-AMOI, the Region of Emilia-Romagna and the Italian Government, dispute that allegation. (39)

83. The applicants in the mains proceedings have also raised the question of the impact on the definition of the relevant market of the alleged infringement of the provisions of Italian law which limit the freedom of medical practitioners to prescribe off-label medicines.

84. Under Italian law, that practice is, they allege, permitted only where, on the basis of an individual assessment, there is no authorised medicinal product with which a given patient can be treated effectively. (40) A medicinal product prescribed off label would therefore not be interchangeable with a medicinal product prescribed on label for the same indications, but subsidiary to it. The AGCM, SOI-AMOI, Condacons, the Region of Emilia-Romagna and the Italian Government do not share that view and suggest a different interpretation of Italian law. (41)

85. Since this particular question could also be relevant to the resolution of the dispute in the main proceedings, (42) I shall read the fourth question referred for a preliminary ruling as asking whether or not there is any need, when defining the relevant product market, to verify not only whether the marketing of medicinal products for off-label use, but also whether prescribing them for off-label use is in accordance with the applicable legal framework.

86. In my view, the principles recalled in points 70 and 71 above imply that uncertainty regarding the lawfulness of prescribing or marketing medicinal products with a view to their off-label use for certain therapeutic indications does not, in itself, mean that

such medicines do not form part of the same market as medicines authorised for those indications.
87. Of course, the competition authorities and the courts responsible for applying the competition rules should take account of any such uncertainty where it is capable of precluding the interchangeability of such medicinal products. Nevertheless, if they find that a medicinal product is in fact widely used off label in spite of such uncertainty, they may validly find that such a medicine is interchangeable with medicines used on label for the same indications and therefore belongs to the same product market as them.
88. They need not, in order to justify such a conclusion, remove that uncertainty by themselves assessing the lawfulness of prescribing and marketing medicinal products used off label. Indeed, such an exercise is unrelated to the application of the competition rules and does not normally fall within the competence of the authorities entrusted with their application. (43) As the AGCM, SOI-AMOI, the Italian Government and the Commission have emphasised, EU competition law pursues independent objectives distinct from those which pharmaceutical legislation seeks to achieve.
89. The approach I advocate is also consistent with that taken in the judgment in Slovenská sporiteľňa, (44) in which the Court offered certain points of clarification concerning the application of Article 101 TFEU to a cartel between undertakings the purpose of which was to remove from the market in question a third undertaking whose activity on that market was alleged to be unlawful. Without first verifying whether the services offered by the eliminated undertaking belonged to the same market as those offered by the undertakings party to the cartel, the Court held that the fact that the eliminated undertaking was allegedly operating unlawfully on the market in question at the time when the cartel was concluded was irrelevant to the application of Article 101(1) TFEU. To support that conclusion, the Court emphasised that it was for the public authorities, and not private undertakings, to ensure compliance with statutory provisions, the application of which could call for complex assessments not within the area of responsibility of private undertakings. (45) The Court then considered whether that fact could justify the grant of an exemption under Article 101(3) TFEU. (46)
90. That reasoning presupposes that the alleged unlawfulness of the offer of certain goods or services does not, in itself, prevent them from belonging to the same market as other goods or services the lawfulness of whose supply is not in question. (47)

D. The first question, concerning the nature of the relationship between the parties to a licensing agreement and the consequences thereof for the application of Article 101 TFEU to collusion postdating such an agreement

91. By its first question, the referring court asks whether the parties to a licensing agreement are to be regarded as competing undertakings when the licensee operates on the relevant market only by reason of that agreement. If that question is answered in the negative, the referring court asks the Court of Justice, essentially, about the consequences, for the analysis with regard to Article 101(1) and (3) TFEU of collusive conduct such as that at issue in the main proceedings, of the fact that the conduct occurred in the context of a contractual licensing relationship between undertakings that are not in competition.

1. The first part of the first question

92. An agreement for the grant of a licence concerning intellectual property rights, such as the agreement between Genentech and Novartis relating to Lucentis, is, in principle, a *'technology transfer agreement'* within the meaning of Article 1(1)(b) of Regulation No 772/2004. (48)
93. As is clear from Article 1(1)(j)(ii) of that regulation, the parties to a technology transfer agreement are regarded as competing undertakings in the market in which the goods manufactured with the aid of the technology transferred under the licence (referred to as *'contract products'* (49)) are sold if, absent the agreement, they would have been actual or potential competitors in that market.
94. Consequently, the parties to a licensing agreement are not regarded as competing undertakings when the licensee operates on the relevant market only by virtue of the agreement, in the absence of which it would have been neither an actual competitor nor a potential competitor of the licensor.
95. In the present case, no party disputes that, in the absence of the licensing agreement relating to Lucentis, Novartis would not have been an actual or potential competitor of Genentech in the market for medicinal products for the treatment of ocular vascular pathologies. Indeed, there is nothing in the file submitted to the Court to show that Novartis would even have commenced research and development with a view to creating a medicinal product for the treatment of such pathologies.
96. Thus, the collusive conduct at issue occurred in the context of a contractual licensing relationship between non-competing undertakings, in the absence of which there would have been no reason for it, as Roche emphasises.
97. That said, for reasons which I shall set out below, the collusive conduct at issue cannot be excluded from the prohibition laid down in Article 101(1) TFEU or benefit from exemption under Article 101(3) TFEU on the ground that the restrictions at issue in the main proceedings are allegedly similar to restrictions of competition that is exerted by a licensor with regard to a licensee set out in a licensing agreement between non-competing undertakings.

2. The second and third parts of the first question

98. As is clear from their wording, the second and third parts of the first question concern the application of Article 101(1) and (3) TFEU to *'restrictions of competition between ... licensor and ... licensee'*. In order to provide the national court with a useful answer, it seems to me necessary to clarify somewhat the nature and scope of the restrictions at issue in the main proceedings, to which this question refers, in the

light of the factual context described in the order for reference.

99. I would emphasise, in the first place, that the restrictions at issue were, more specifically, restrictions of the competition that is exerted with regard to a licensee by means of the demand for and use by third parties, in a form and for purposes not contemplated by the licensor, of a product initially manufactured and marketed by the licensor. (50)

100. In the second place, the interested parties disagree as to whether those restrictions related to competition between two products which rely on the same technology (*'intra-technology competition'*) or between two products which rely on different technology (*'inter-technology competition'*).

101. The significance of that distinction is that certain restrictions of intra-technology competition, in so far as they are deemed necessary for the dissemination of a new technology and, consequently, for the strengthening of inter-technology competition, fall outside the scope of Article 101(1) TFEU. (51)

102. Altroconsumo maintains that Avastin and Lucentis do not rely on the same technologies and that the collusive conduct at issue accordingly restricted inter-technology competition between those two products. The facts to which the referring court draws the attention of the Court of Justice do not permit the accuracy of that allegation to be verified. Roche disputes the allegation and argued at the hearing that Avastin and Lucentis are manufactured on the basis of the same patents, which thus cover both the anti-VEGF medicines developed by Genentech.

103. Subject to verification by the referring court, I shall assume that the two medicinal products were both produced on the basis of rights to the technology that was licensed under the licensing agreement relating to Lucentis, and indeed the answers which I shall suggest will be all the more valid if it proves that the medicines do not in fact rely on the same technology. (52)

(a) The applicability of Article 101(1) TFEU

104. In so far as concerns the second part of the first question, I consider that, even if they had been set out expressly in the licensing agreement relating to Lucentis, the restrictions at issue in the main proceedings could not escape the prohibition laid down in Article 101(1) TFEU on the ground that, as the applicants in the main proceedings contend, they restricted competition exerted by a licensor with regard to a licensee.

105. The doubts which the referring court has in this regard reflect a certain line of case-law according to which, where the conclusion or implementation of an agreement which is in itself pro-competitive, or at least neutral as regards competition, requires the insertion into that agreement of certain restrictions on the commercial independence of the parties, those restrictions do not fall within the scope of Article 101(1) TFEU. While the Court has not always used this terminology, this case-law upholds the doctrine of 'ancillary restrictions'.

106. This doctrine may be seen as drawing its origins from the judgment in LTM, (53) in which the Court emphasised the necessity, when considering the lawfulness of collusion, of analysing the situation which would have existed in the absence of the collusion. It held, with regard to the grant by a manufacturer to a distributor of an exclusive retailing right in a given territory, that *'it may be doubted whether there is an interference with competition if the ... agreement [in question] seems really necessary for the penetration of a new area by an undertaking'*. The Court subsequently applied and developed that doctrine in a series of judgments, (54) including Nungesser and Eisele v Commission (55) and, most recently, MasterCard and Others v Commission. (56)

107. Indeed, the applicants in the main proceedings refer to paragraph 57 of the judgment in Nungesser and Eisele v Commission (57) in support of their argument that Article 101(1) TFEU does not apply to the collusive conduct at issue. In that judgment, the Court examined a so-called *'open'* territorial exclusivity clause under which a licensor undertook not to grant other licences in respect of the territory granted and not to compete itself with the licensee in exploiting the rights relating to the licensed technology. According to the Court, the clause was necessary for the very existence of the licensing agreement since, without it, the licensee might have been deterred from accepting the risks associated with the exploitation of the licensed technology. In substance, the Court thus considered that, in order to promote the inter-technology competition which results from the dissemination of a new technology by means of a licensing agreement, (58) certain restrictions of intra-technology competition between undertakings capable of exploiting that technology may prove necessary. (59)

108. In that judgment, the Court also examined a so-called *'closed'* exclusivity clause by which the parties to the licensing agreement proposed to eliminate all competition from third parties, such as parallel importers and licensees in other territories. The parties to the agreement were criticised for having initiated proceedings and exerted pressure on parallel importers in pursuance of that clause. The Court did not hold that that clause was necessary for the dissemination of a new technology. The closed exclusivity clause did not, therefore, escape the application of Article 101(1) TFEU (60). Nor could it be exempted under Article 101(3) TFEU, because it manifestly went beyond what was indispensable for achieving the gains in efficiency. (61)

109. According to Roche and Roche Italia, the restrictions at issue in the main proceedings are comparable to an exclusive licence under which the licensor undertakes not to compete with the licensee by producing under the technology rights transferred or selling products which rely on that technology. Consequently, the approach adopted in paragraph 57 of the judgment in Nungesser and Eisele v Commission (62) can be applied in the present case.

110. I do not share that view.

111. Indeed, as is clear from the observations made by the AGCM which are set out in the order for reference, and as the Italian Government and the Commission have emphasised, the purpose of the collusive conduct at issue was not to restrict the production or sale by Genentech or other companies in the Roche group of products which incorporate the technology licensed to Novartis. On the contrary, its purpose was to influence the actions of parties unconnected with the licensing agreement relating to Lucentis, that is to say, the pharmaceutical regulatory authorities and medical practitioners, so as to limit the use of Avastin in ophthalmology. In other words, the applicants in the main proceedings intended not to alter the supply of Avastin, but to alter the demand from medical practitioners (on whose judgment patients rely) who were prescribing Avastin off label. Indeed, it was as a result of that demand that Avastin entered into competition with Lucentis.
112. Inasmuch as its purpose was to impede competitive dynamics independent of the wishes of the licensor and arising from sources not within the licensor's control, (63) the collusive conduct at issue raises different issues from those raised by open exclusive licenses such as that examined by the Court in paragraph 57 of its judgment in Nungesser and Eisele v Commission. (64)
113. In my view, the restrictions at issue in the main proceedings should instead be treated similarly to the closed exclusive licence at issue in that judgment (65) in so far as Article 101(1) TFEU is concerned. Admittedly, what underpinned the Court's approach was the objective of achieving the integration of geographic markets, which is not relevant in the present case. (66) However, I would observe that EU competition law focuses on combating the partitioning not only of the geographic markets, but also of the product markets on which undertakings are active. (67) At the very least, it cannot be inferred from that judgment that the elimination of all competitive pressure connected with products incorporating the licensed technology, including pressure from independent sources not under the control of the licensor, is ancillary to the conclusion or implementation of a licensing agreement.
114. The conclusion which I advocate also follows from an examination of the restrictions at issue in the main proceedings in the light of the most recent case-law, which is the judgment in MasterCard and Others v Commission, (68) in which the Court summarised and refined the theory of ancillary restrictions.
115. The Court first of all pointed out that, *'if a given operation or activity is not covered by the prohibition rule laid down in Article [101(1) TFEU], owing to its neutrality or positive effect in terms of competition, a restriction of the commercial autonomy of one or more of the participants in that operation or activity is not covered by that prohibition rule either if that restriction is objectively necessary to the implementation of that operation or that activity and proportionate to the objectives of one or the other'*. (69)
116. Next, the Court stated that the condition of objective necessity was fulfilled only where it was not possible to dissociate the restriction at issue from the main operation without jeopardising its existence and aims. That was the case where it would be impossible to carry out the operation in the absence of the restriction. On the other hand, the fact that the operation would, in the absence of the restriction, simply be more difficult to implement, or less profitable even, did not confer on the restriction the objective necessity required for it be classified as ancillary. (70)
117. Thus, in that judgment, a narrow interpretation was given of the doctrine of ancillary restrictions: without undermining the effectiveness of the prohibition laid down in Article 101(1) TFEU it could only apply to restrictions that are *'strictly indispensable to the implementation of the main operation'*. (71)
118. I doubt that restrictions such as those at issue in the main proceedings — even if they had been inserted into the licensing agreement — would constitute ancillary restrictions according to that case-law.
119. First of all, they are not restrictions *'of the commercial autonomy of one or more of the participants'* in a main operation, within the meaning of the judgment in MasterCard and Others v Commission. (72) Indeed, the restrictions which the Court classified as ancillary in that judgment and in its earlier case-law were invariably restrictions on the conduct of the parties to the principal operation themselves. (73)
120. According to the AGCM, the collusive conduct at issue, which admittedly involved the adoption by Roche and Roche Italia of a certain course of action in relation to the communication concerning the off-label use of Avastin, was aimed not at restricting the commercial independence of the parties to the licensing agreement relating to Lucentis, but to impede the competitive dynamics resulting from the actions of parties unconnected with that agreement. (74)
121. In the second place, I am not convinced that restrictions such as those at issue in the main proceedings are *'objectively necessary to the implementation'* of a licensing agreement, again within the meaning of the judgment in MasterCard and Others v Commission. (75)
122. It seems to me difficult to contend that it would be impossible to conclude a licensing agreement granting technology rights for the production and/or marketing of a medicinal product that is authorised for certain therapeutic indications without an undertaking from the licensor to impede the competition that arises from the demand expressed by medical practitioners for a different medicinal product which incorporates the same technology but is prescribed off label for such indications. The fact that, in some cases, the demand for a medicine used off label may alter the demand for a medicine covered by a licensing agreement and thus render the exploitation of the rights to the licensed technology less profitable is not sufficient to establish that such a restriction is objectively necessary. (76)

123. That is all the more true where, as in the present case, the restrictions were agreed upon not in the licensing agreement, but under a concerted practice post-dating the conclusion of the licensing agreement by several years. In my view, that last fact serves to indicate that the restrictions at issue were not objectively necessary for the implementation of the licensing agreement. Moreover, where a licensee has already made the necessary investments for launching the contract products — such as those required in order to obtain an MA — I fail to see how the implementation of the agreement could not be continued without such restrictions.

124. Should it be the case that Avastin and Lucentis do not incorporate the same technology, the collusive conduct at issue, a fortiori, will likewise not escape the application of Article 101(1) TFEU. (77) While restrictions relating to the exploitation of licensed technology by a licensor may fall outside the scope of that provision if they are objectively necessary for the conclusion of a licensing agreement, (78) that reasoning does not in any event apply to restrictions on the exploitation by a licensor of a different technology. On the contrary, the weakening of the competition arising from that other technology could erase the beneficial effect for competition which results from the dissemination of the new technology by means of a licensing agreement.

(b) The application of Article 101(3) TFEU

125. In my opinion, the nature of the restrictions at issue in the main proceedings, and the fact that they occurred in the context of a licensing agreement between non-competing undertakings, as such, is no more likely to justify the grant of an exemption under Article 101(3) TFEU.

126. In support of the opposing view, the applicants in the main proceedings argue that the restrictions at issue in the main proceedings are similar to certain restrictions which a licensor typically undertakes to give to a licensee. Such restrictions benefit from a block exemption if the market shares of the parties do not exceed certain thresholds or generally call for individual exemption even where those thresholds are exceeded.

127. In particular, Roche emphasises that the restrictions whereby a licensor undertakes not to exploit licensed technology or not to sell, actively and/or passively, products incorporating that technology in the exclusive territory of the licensee or to an exclusive group of purchasers reserved to the licensee benefit from the block exemption provided for by Regulation No 772/2004 and by Regulation No 316/2014 which succeeded it. That is equally true, Roche alleges, whether the restrictions appear in an agreement between non-competing undertakings (79) or are inserted into an agreement between competing undertakings. (80)

128. It alleges that, even in cases where a block exemption cannot be granted because the applicable market-share thresholds are exceeded, according to the Guidelines, the said restrictions usually fulfil the conditions for individual exemption under Article 101(3) TFEU. (81)

129. I am unconvinced by that line of argument. Indeed, for the reasons which I set out in points 111 to 113 above, the restrictions at issue in the main proceedings cannot be reduced to the types of clauses, mentioned in the preceding points of this Opinion, to which those regulations and the Guidelines refer. That conclusion applies a fortiori if it is the case that the medicinal products concerned incorporate different technologies. Indeed, there could then be no question of the exploitation of licensed technology or the sale of products incorporating that technology.

130. More generally, I doubt that restrictions such as those at issue in the main proceedings fall within the scope ratione materiae of those regulations, even in situations where, contrary to the AGCM's findings in this case, the market-share thresholds beyond which block exemption may not be granted have not been exceeded. (82)

131. According to recital 9 of Regulation No 772/2004, so that the benefits of technology transfers may be attained, the regulation must cover provisions contained in technology transfer agreements that do not constitute the primary object of the agreement where they are *'directly related to the application of the licensed technology'*. Recital 9 of Regulation No 316/2014 states, more explicitly, that that regulation covers the provisions of such agreements only to the extent that they are *'directly related to the production or sale of the contract products'*. The restrictions at issue in the main proceedings, however, concern neither the production nor the sale of anti-VEGF medicines. They relate to the use and purchase of one of those medicines by parties unconnected with the licensing agreement relating to Lucentis.

132. In light of all the foregoing considerations, I consider that the collusive conduct at issue does not fall outside the scope of Article 101(1) TFEU and does not benefit from exemption under Article 101(3) TFEU on the ground that the restrictions at issue in the main proceedings are similar to restrictions of competition that is exerted by a licensor with regard to a licensee that are included in a licensing agreement between non-competing undertakings.

133. However, that conclusion does not decide the question of whether the collusive conduct at issue actually falls foul of the prohibition laid down in Article 101(1) TFEU. Nor does it imply that that conduct cannot be exempted under Article 101(3) TFEU once compliance with the conditions laid down in that provision has been individually analysed, (83) which is a matter for the parties who invoke that exemption to prove. (84) I shall deal with those aspects below, in the context of my analysis of the fifth question referred for a preliminary ruling.

E. The fifth question, concerning the concept of 'restriction of competition by object'

1. The scope of the fifth question

134. By its fifth question, the referring court asks whether collusion intended to *'emphasise that [one]*

medicinal product is less safe or less efficacious' than another may constitute a restriction of competition by object if, at the material time, there is neither *'reliable'* scientific evidence to support the idea that that medicinal product is less efficacious or less safe, nor scientific knowledge to exclude that idea *'indisputably'*.

135. In order better to focus my analysis, it seems to me that three preliminary points of clarification are needed in connection with the scope of that question in the light of the facts described in the order for reference.

136. First of all, as is suggested by its wording, the fifth question is based on the premiss that, as the applicants in the main proceedings maintain, the equivalence of the safety and efficacy profiles of Avastin used off label and of Lucentis was the subject of scientific uncertainty at the time of the collusive conduct at issue.

137. That premiss is disputed by the AGCM, Aiudapds, SOI-AMOI, the Region of Emilia-Romagna, Altroconsumo and the Italian Government. Those parties essentially argue that, while medical science is never such that the therapeutic equivalence of two medicinal products can be proven indisputably, the evidence available at the material time, which was subsequently corroborated by other evidence, (85) indicated the therapeutic equivalence of Avastin and Lucentis much more strongly than it called it into question. SOI-AMOI also emphasises that the safety and efficacy of Avastin in ophthalmology had already been demonstrated at the material time by means of a long-standing, worldwide medical practice. (86)

138. Given that it is not for the Court of Justice to call into question the factual context described by the national court, (87) my analysis of the fifth question must, I think, be based on that premiss. I shall therefore start from the premiss that the scientific debate concerning the therapeutic equivalence of the two medicines in question was, in any event, still ongoing.

139. Secondly, the words *'emphasise that a medicinal product is less safe or less efficacious'* may lead to confusion. I would prefer the neutral formulation of the *'communication'* or *'dissemination'* of *'allegations'* in that regard.

140. Indeed, the Italian word *'enfatizzare'* that is used in the order for reference may also be translated into French by the expressions *'mettre l'accent sur'* or *'insister sur'*, which do not suggest the exaggeration of information in terms of its content. (88) Moreover, as SOI-AMOI has observed, the exaggeration of or insistence on the lesser security or efficacy of one product by comparison with another presupposes that that lesser security or efficacy actually exists. The wording of the fifth question however indicates, on the contrary, that that lesser security or efficacy is the subject of a scientific debate. (89)

141. Thirdly, the order for reference and the case file submitted to the Court of Justice do not indicate that the AGCM criticised the applicants in the main proceedings for having disseminated not only opinions on the risks associated with the off-label use of Avastin but also allegations of the lesser efficacy of such use by comparison with the use of Lucentis.

142. More precisely, the AGCM criticised the applicants in the main proceedings for having agreed upon a communication strategy to be adopted by Roche and Roche Italia with regard to the pharmaceutical regulatory authorities, medical practitioners and the general public. That strategy had allegedly consisted in insisting on the risks associated with the off-label use of Avastin and in spreading allegations of the lesser safety of that product by comparison with Lucentis. In particular, it was agreed that those companies would, on the basis of such allegations, request the EMA to amend the SPC for Avastin and to authorise the sending of a DHPC to ophthalmologists.

143. In order to give a useful answer to the referring court, I shall therefore focus my analysis on an assessment of whether or not collusion in the communication of allegations of the lesser safety of one medicinal product compared to another is a restriction by object. (90) That said, the approach which I shall recommend on completion of that analysis will also apply to the concerted dissemination of allegations concerning both the comparative safety and the comparative efficacy of the two medicines.

144. Bearing this in mind, I shall now address the question of whether, and if so to what extent, collusion in the communication to third parties of allegations of the lesser safety of one medicinal product used off label for certain therapeutic indications by comparison with a medicinal product that has been authorised for those indications constitutes a restriction of competition by object where the comparative safety of the two medicinal products is the subject of scientific uncertainty.

2. The framework for analysing whether there is a restriction of competition by object

145. According to settled case-law, the concept of *'restriction of competition by object'* designates agreements and concerted practices which, in themselves, reveal a *'sufficient degree of harm'* to competition to render the examination of their effects on competition superfluous. (91)

146. That case-law is based on the fact that *'certain forms of coordination between undertakings can be regarded, by their very nature, as being harmful to the proper functioning of normal competition'*. (92)

147. In order to establish whether particular collusive *conduct is in the nature of a restriction by object, 'regard must be had … to the content of its provisions, the objectives it seeks to attain and the economic and legal context of which it forms a part'*. (93) That context also includes *'the nature of the goods or services affected, as well as the real conditions of the functioning and structure of the market or markets in question'*. (94)

148. In particular, this individual, detailed examination makes it possible to *'understand the economic function and the real significance'* of the coordination at issue. (95) It also makes it possible to check whether there is

a plausible alternative explanation for the coordination other than the pursuit an anticompetitive aim. (96)

149. In addition, the subjective intention of the parties, while not a necessary factor (97) or a sufficient factor (98) in order to find a restriction by object, may be a relevant factor for that purpose. (99)

150. I would add that, although the concept of restriction by object must be interpreted narrowly, (100) it is not limited to the forms of collusion expressly listed in Article 101(1) TFEU. (101) The atypical or novel form of a particular instance of collusion does not prevent the Court from concluding, after an individual, detailed examination, that that collusion, in itself, reveals a sufficient degree of harm to competition. (102)

3. Application to the present case

151. Having regard to the principles I have outlined, and for reasons which I shall set out below, there can, in my view, be little doubt that collusive conduct concerning the dissemination of allegations of the lesser safety of one medicinal product by comparison with another does reveal a sufficient degree of harm to competition where those allegations are misleading (section (a) below). The aim of such conduct is to distort competition by exploiting a scientific uncertainty for the purpose of excluding the first medicinal product from the market or, at least, redirecting demand toward the second medicinal product.

152. This first hypothesis corresponds to the version of the facts of the case presented to the Court by the AGCM, Aiudapds, SOI-AMOI, the Region of Emilia-Romagna, Altroconsumo and the Italian Government. Those parties argue, in substance, that the collusive conduct at issue involved the communication of allegations that did not reflect the state of scientific knowledge at the material time. (103) The aim of the conduct was to discourage the off-label use of Avastin in such a way as to alter demand in favour of Lucentis.

153. On the other hand, where the allegations communicated are not misleading, such collusive conduct will not fall foul of the prohibition set out in Article 101(1) TFEU (section (b) below). In such a situation, the aim of the conduct is, in reality, to ensure the transparency of information regarding the safety of the medicinal products in question, so as to enable the recipients of such communications to take decisions of a kind that will protect public health. Such an aim promotes both public health and the free play of competition.

154. This second hypothesis corresponds to the version of the material facts put forward by the applicants in the main proceedings. Spurred by genuine concerns about the safety of Avastin in ophthalmology, they merely exchanged information about the conduct that Roche and Roche Italia would adopt in order to fulfil their pharmacovigilance obligations. The applicants in the main proceedings add that the conduct had the more general aim of protecting public health and, in parallel with that, the reputation of the Roche group as manufacturer and distributor of Avastin. According to them, the concern was that the negative repercussions flowing from the risks associated with the off-label use of Avastin should not affect the on-label use of that medicinal product or the Roche group. (104)

155. Given that the examination of whether or not the allegations communicated were misleading calls for an appraisal of facts which falls within the exclusive jurisdiction of the referring court, it is for that court to choose between the various interpretations of the facts proposed by the interested parties and consequently to determine whether the collusive conduct at issue fits one or other of the two hypotheses I have described.

(a) The existence of a restriction of competition by object where the allegations communicated are misleading

156. To my mind, the concerted communication of misleading allegations of the lesser safety of one medicinal product compared to another is, by its very nature, harmful to the proper functioning of normal competition, so much so that an examination of its effects on competition is not necessary. (105)

157. First of all, where an examination of the content of the allegations in question reveals that they are misleading, the concerted communication of those allegations impairs the quality of the information available on the market and, consequently, adversely affects the decision-making process of those who create the demand for the two products concerned. Such concerted communication is, in itself, likely to reduce, if not suppress, demand for the first product to the advantage of the second.

158. In my view, the communication of misleading allegations includes the dissemination of information which is in itself correct but is presented selectively or incompletely where, because of that manner of presentation, the information disseminated is likely to mislead those who receive it. (106)

159. To similar effect, Article 49(5) of Regulation No 726/2004 also provides that the holder of an AM may not communicate information relating to pharmacovigilance concerns to the general public without notifying the EMA and must, in any event, ensure that such information *'is presented objectively and is not misleading'*. (107)

160. That is the case whether or not there is continuing scientific uncertainty regarding the safety of a medicinal products. In my opinion, omitting to state that the risks created by using the medicine are uncertain, or exaggerating such risks with a lack of objectivity with regard to the available evidence, may render the concerted communication of those risks misleading. (108)

161. In the present case, the order for reference does not suggest that the content of the information regarding the adverse reactions caused by Avastin in ophthalmology, which the applicants in the main proceedings concerted to disseminate, was in itself incorrect. (109) The AGCM criticises them, in substance, for having presented that information incompletely and selectively, downplaying the value of scientific evidence to the contrary. Consequently, the

allegations of the lesser safety of Avastin by comparison with Lucentis were lacking in objectivity and were therefore misleading.

162. It will be for the referring court to determine, in the light of the considerations set out in points 158 to 160 above, whether or not those allegations were misleading, having regard to all the information that was at the disposal of the applicants in the main proceedings at the material time.

163. Next, the objective of the concerted dissemination of misleading allegations of the lesser safety of one medicinal product by comparison with another is necessarily the exclusion of the first medicine to the advantage of the second, or at the very least a reduction in the demand for the first medicine. Given the misleading nature of such allegations, there can be no plausible alternative explanation for such collusion, in particular, one relating to the pursuit of legitimate aims concerning the transparency of the information available in the market and the protection of public health.

164. If it is the case that the collusion at issue also pursued certain additional objectives unrelated to the restriction of competition, those may be taken into account only in the context of the possible application of Article 101(3) TFEU. (110)

165. In particular, the question could arise of whether the aim of halting the allegedly unlawful prescribing and marketing of Avastin for off-label use justifies the grant of an exemption under that provision.

166. In this connection, I would mention in passing the guidance that may be drawn from the judgment in Slovenská sporiteľňa, (111) to which I have already referred, in which the Court analysed, with regard to Article 101(3) TFEU, an agreement to eliminate a competitor whose activities were supposedly unlawful (and which proved to be so after the agreement had been concluded). The Court left open the question of whether the removal of a competitor that is acting illegally could bring about gains in efficiency. In any event, the restriction of competition was not essential for achieving such gains in efficiency. The undertakings party to the agreement should have lodged a complaint against the competitor with the competent authorities, rather than take the law into their own hands and agree to exclude the competitor from the market. (112)

167. In my view, that reasoning also implies that, if the unlawfulness of prescribing or marketing a medicinal product for off-label use has not yet been made clear in a final decision of a competent court, (113) it is not for undertakings to assume that it is unlawful and act in concert to eliminate, by means of the dissemination of misleading opinions, the competitive pressure which those activities exert on the sale of another product.

168. Finally, an examination of the economic and legal context, and in particular of the nature of the products and the operating conditions in the market in question, tends to confirm that collusion in the communication of misleading information regarding the lesser safety of one medicinal product by comparison with another is a restriction by object.

169. As the AGCM, the Region of Emilia-Romagna, the French Government and the Commission have pointed out, medical practitioners are particularly sensitive to safety considerations surrounding medicinal products. Where those considerations concern the off-label use of a medicine, their aversion to risk is likely to increase in accordance with the legal provisions governing medical liability in force in the Member State in question. In this instance, according to the AGCM and the Italian Government, such liability does arise in Italy and is severe under civil and criminal law. Given that specific context, the widespread communication of alarming and misleading information about the risks associated with the off-label use of a medicinal product is inherently likely to discredit that product among doctors and stimulate demand for competing medicinal products.

170. Moreover, the misleading nature of the opinions communicated, if established, will in itself mean that the collusive conduct at issue cannot be explained by the pursuit of the legitimate aims of ensuring the transparency of the information available in the market and the protection of public health and the reputation of the Roche group. That conclusion is all the more evident in that the attainment of such objectives did not necessitate concertation between the applicants in the main proceedings, having regard to the economic and legal context in which that conduct occurred.

171. Indeed, while the manufacturer or MA holder (such as Roche) of a medicinal product (such as Avastin) must bear the risks, at least to its reputation, which arise from uncertainty regarding the off-label use of that medicine, such risks are in no way borne by other undertakings (such as Novartis) which market a competing medicinal product (such as Lucentis). It is not for the latter undertakings to help define the appropriate measures to attenuate the safety concerns associated with the off-label use of a medicinal product which they neither manufacture nor market. Similarly, as the AGCM, the Region of Emilia-Romagna, Altroconsumo and the Commission have argued, pharmacovigilance obligations fall solely upon the undertaking which holds the MA for the medicinal product in question.

172. The subjective intention of the applicants in the main proceedings, as suggested by the findings of the AGCM that are set out in the order for reference, if established, could corroborate the existence of an anticompetitive aim behind the collusive conduct at issue. According to the AGCM, the applicants in the main proceedings expressed in various documents the intention to *'generate and disseminate'* unjustified concerns relating to the safety of Avastin with a view to steering demand towards Lucentis. Thus, they sought to exploit uncertainty regarding the comparative safety of the two products in a manner favourable to their own commercial interests, but harmful to competition.

173. I would add that, in the event that the referring court concludes that the allegations in question were

misleading, a finding that the collusive conduct at issue was a restriction by object should be reached independently of the actual effects of that conduct.

174. As other Advocates General have already emphasised, (114) and as the Court essentially clarified in its judgment in CB v Commission, (115) the individual, detailed examination of collusion should not be confused with the examination of its actual or potential effects on competition. If it were, the concepts of anticompetitive *'object'* and of anticompetitive *'effects'* would be merged, thus blurring the distinction which Article 101(1) TFEU draws between those two concepts. It is in that context that, according to the case-law, coordination may constitute a restriction by object if it has the *'potential to'* have, or is *'capable in an individual case'* of having an injurious effect on competition, without it being necessary to examine its actual effects. (116)

175. It is therefore immaterial, first of all, that the EMA refused to authorise the sending of a DHPC and made a different amendment to the SPC for Avastin from that requested by Roche. (117) Indeed, the fact that collusion does not meet with success in a given case is irrelevant to the identification of a restriction by object. (118) That fact may, however, be taken into account in the context of determining the amount of any fine. (119)

176. Secondly, the specialist competence of the pharmaceutical and ophthalmological regulatory authorities, which, according to the applicants in the main proceedings, enabled them to take a critical approach to the opinions communicated, is equally incapable of precluding a finding of restriction by object. On the contrary, I consider that, even if well-informed recipients have the necessary qualifications to foil a concerted strategy to disseminate misleading allegations about the safety of a product in order to reduce demand for it, the capacity of such a strategy to restrict competition cannot be called into question.

(b) The absence of a restriction of competition by object where the allegations communicated are not misleading

177. The case of collusion relating to the communication of misleading allegations of the lesser safety of one medicinal product by comparison with another must be clearly distinguished from the case of concertation whereby the undertakings which hold the MAs for two medicines agree to communicate information about the comparative safety of those two medicines which, in light of scientific knowledge at the material time, is precise and objective.

178. In my opinion, such concertation does not restrict competition within the meaning of Article 101(1) TFEU.

179. Its aim, or its economic function and real meaning, is to improve the quality of the information available in the market so as to enable medical practitioners and pharmaceutical regulatory authorities to take enlightened decisions. Such an aim, as Roche emphasised at the hearing, promotes both the protection of public health and healthy competition. At the same time, the concerted communication of precise and objective information about the safety profile of a medicinal product enables the reputation of that medicine and of the undertakings which developed or manufactured it to be preserved.

180. Concertation whereby the undertakings which hold the MAs for two medicinal products agree to communicate precise and objective information about the lesser safety of one of those medicines by comparison with the other is not, it seems to me, likely to produce anticompetitive effects.

181. That conclusion follows logically from the counterfactual analysis which is required in order to identify a restriction of competition. Indeed, it is necessary to examine whether competition is restricted *'within the actual context in which it would occur in the absence of the agreement in dispute'*. (120) Concertation of this kind, rather that restricting the competition that would have existed in its absence, strengthens competition by ensuring the transparency of the information available in the market while at the same time endeavouring to protect public health.

182. Consequently, if it is the case that the allegations which the applicants in the main proceedings concerted to disseminate were not misleading, the collusive conduct at issue would fall outside the scope of Article 101(1) TFEU.

183. That is true despite the fact that the legitimate aims which I have just mentioned, relating to the transparency of information and the protection of public health and the reputations of Avastin and of the Roche group, could have been achieved unilaterally by the companies within that group. (121)

184. Admittedly, that fact affects the plausibility of the hypothesis of concertation aimed at achieving such legitimate objectives. It does not, however, render anticompetitive concertation to disseminate precise and objective information about the safety of a medicinal product. Once again, that conclusion follows from an examination of the situation which would have existed in the absence of the concertation. Indeed, assuming that the allegations at issue were not misleading, the actions taken by Roche and Roche Italia pursuant to the collusive conduct at issue would have been necessary even absent the collusion, so as to achieve the legitimate objectives I have mentioned and, in particular, to protect public health. (122)

185. I would add in this connection that, as the applicants in the main proceedings argue, the communication of precise, objective information about the safety profile of a medicinal product furthers the objectives which Regulation No 726/2004 pursues in instituting pharmacovigilance obligations. Notifying the pharmaceutical regulatory authorities of the presumed adverse reactions resulting from the off-label use of a medicinal product corresponds to the requirements laid down in Article 16(2) of that regulation and Article 104(1) of Directive 2001/83, to which Article 21(1) of the regulation refers. An application to amend the SPC of the medicinal product in question and for authorisation to issue a formal

communication to medical practitioners, like the development of a strategy for communication to the general public, might in themselves constitute *'appropriate measures'* to minimise any possible safety risks, in accordance with Article 104(2) of Directive 2001/83.

186. It matters little that Regulation No 726/2004, like Directive 2001/83 did not extend the pharmacovigilance obligations to off-label uses of medicinal products until July 2012, (123) that is to say, after the collusive conduct at issue began. Undertakings cannot be criticised for adopting conduct consistent with those obligations, given that such conduct is in accordance with the intention of the legislature, guided by public health considerations.

V. Conclusion

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

(1) Article 101 TFEU is to be interpreted as meaning that the relevant product market comprises all those products which are regarded by consumers as interchangeable or substitutable, by reason of their characteristics, their prices and their intended use.

In the pharmaceutical sector, the content of marketing authorisations for medicinal products is not necessarily decisive in the determination of the relevant product market. In particular, the fact that the marketing authorisation for a medicinal product does not cover certain therapeutic indications does not preclude that medicinal product from forming part of the market for medicinal products used for those indications, provided that it is actually used interchangeably with medicinal products whose marketing authorisation covers those indications.

That is true even where there is uncertainty regarding the compliance with the applicable regulatory framework for the prescribing and marketing of medicinal products with a view to their use for therapeutic indications and by methods of administration not covered by their marketing authorisations.

(2) Restrictions of the competition that is exerted with regard to a licensee by means of the demand for and use by third parties, in a form and for purposes not contemplated by the licensor, of a product incorporating the licensed technology, even where they take place in the context of a licensing agreement between non-competing undertakings, do not escape the prohibition rule laid down in Article 101(1) TFEU on the ground that they are ancillary to the implementation of the licensing agreement; nor do they necessarily benefit from exemption under Article 101(3) TFEU.

(3) Collusion whereby two undertakings agree to communicate to third parties allegations of the lesser safety of one medicinal product by comparison with another, without being in possession of reliable scientific evidence to support those allegations or scientific knowledge indisputably contradicting them, constitutes a restriction of competition by object, within the meaning of Article 101(1) TFEU, where those allegations are misleading, which it is for the national courts to verify.

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1 Original language: French.

2. Commission Regulation of 27 April 2004 on the application of Article [101(3) TFEU] to categories of technology transfer agreements (OJ 2004 L 123, p. 11). That regulation expired on 30 April 2014. The following day Commission Regulation (EU) No 316/2014 of 21 March 2014 on the application of Article 101(3) [TFEU] to categories of technology transfer agreements (OJ 2014 L 93, p. 17) came into force.

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).

4. 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).

5. See the second paragraph of Article 4 of Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, [Regulation No 726/2004] and Regulation (EC) No 1394/2007 on advanced therapy medicinal products (OJ 2010 L 348, p. 1).

6. See Article 3(1) of Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, [Directive 2001/83] (OJ 2010 L 348, p. 74).

7. The list is drawn up pursuant to Article 1(4) of decreto-legge 21 ottobre 1996, No 536, convertito con modificazioni dalla legge 23 dicembre 1996, No 648 (Legislative Decree No 536 of 21 October 1996, converted, with amendments, into Law No 648 of 23 December 1996).

8. The applicants in the main proceedings emphasise that the product which results from the decanting of a vial of Avastin into several syringes each of which contains only the necessary dose for an intravitreal injection is inconsistent with the SPC for Avastin not only in terms of therapeutic indications, but also in terms of dosage, pharmaceutical form, method of administration and presentation.

9. See the Commission's 2017 'Study on off-label use of medicinal products in the European Union', available at https://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf

10. See footnote 39 to this Opinion.

11. For medicines authorised on completion of the centralised procedure, see Articles 16(2), 24(1) and

49(5) of Regulation No 726/2004. For medicines authorised by the Member States, see the second subparagraph of Article 23(2) and the second subparagraph of Article 101(1) of Directive 2001/83.
12. See judgment of the General Court of 11 June 2015, Laboratoires CTRS v Commission (T‑452/14, not published, EU:T:2015:373, paragraph 79).
13. This power is recognised by Article 168(7) TFEU. On this point, see the Opinion of Advocate General Sharpston in Novartis Pharma (C‑535/11, EU:C:2013:53, point 79).
14. See the second subparagraph of Article 1 of Regulation No 726/2004, Article 4(3) of Directive 2001/83 and judgment of 22 April 2010, Association of the British Pharmaceutical Industry (C‑62/09, EU:C:2010:219, paragraph 36). The power of the Member States to organise their social security systems must nevertheless be exercised in compliance with EU law (see the 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, paragraph 20 and the case-law cited).
15. See, on this point, European Commission, 'Study on off-label use of medicinal products in the European Union', 2017, pp. 59 to 71, available at https://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf
16. See, in particular, the judgments of the Conseil d'État (Council of State, France) (First and Sixth Chambers combined) No 392459 of 24 February 2017 (FR:CECHR:2017:392459.20170224) (concerning the legality of temporary recommendations for the use of Avastin for the treatment of AMD) and of the Corte costituzionale (Constitutional Court, Italy) No 151/2014 of 29 May 2014 (concerning the legality of provisions on the approval for reimbursement of medicines prescribed off label).
17. Case C‑29/17, pending before the Court (see OJ 2017 C 195, p. 9).
18. See, to that effect, Forwood, G., and Killick, J., 'Promoting the off-label use of medicines: where to draw the line?' in European Journal of Risk Regulation, 2016, No 2, p. 431.
19. See Article 8(3)(i) of Directive 2001/83, to which Article 6(1) of Regulation No 726/2004 refers.
20. The AGCM refers to the inclusion, since 2013, of bevacizumab on the WHO's Model List of Essential Medicines for ophthalmological indications.
21. Judgment of 14 March 2013, Allianz Hungária Biztosító and Others (C‑32/11, EU:C:2013:160, paragraph 26 and the case-law cited).
22. See, to that effect, judgment of 14 March 2013, Allianz Hungária Biztosító and Others (C‑32/11, EU:C:2013:160, paragraph 27 and the case-law cited).
23. See, inter alia, judgment of 17 July 2008, Raccanelli (C‑94/07, EU:C:2008:425, paragraph 29).
24. See, on this point, judgment of 14 March 2013, Allianz Hungária Biztosító and Others (C‑32/11, EU:C:2013:160, paragraph 28).
25. Judgment of 13 March 2001, PreussenElektra (C‑379/98, EU:C:2001:160, paragraph 40 and the case-law cited).
26. See judgment of 6 October 2015, Târşia (C‑69/14, EU:C:2015:662, paragraph 12 and the case-law cited).
27. Judgment of 28 January 1999, van der Kooy (C‑181/97, EU:C:1999:32, paragraph 30).
28. See point 40 of this Opinion.
29. Article 1(1)(j)(ii) of Regulation No 772/2004. Article 1(1)(j) of Regulation No 316/2014 lays down a similar definition.
30. See, inter alia, judgments of 25 October 2001, Ambulanz Glöckner (C‑475/99, EU:C:2001:577, paragraph 33), and of 28 February 2013, Ordem dos Técnicos Oficiais de Contas (C‑1/12, EU:C:2013:127, paragraph 77).
31. See also paragraph 7 of the Commission Notice on the definition of relevant market for the purposes of Community competition law (OJ 1997 C 372, p. 5).
32. See, in particular, judgment of 1 July 2008, MOTOE (C‑49/07, EU:C:2008:376, paragraph 32 and the case-law cited).
33. See points 83 to 85 of this Opinion.
34. Paragraph 42 of the Commission Notice on market definition for the purposes of Community competition law mentions regulatory barriers among the criteria used to define the relevant product market.
35. See Article 8(3) of Directive 2001/83, to which Article 6(1) of Regulation No 726/2004 refers.
36. See points 47 to 49 of this Opinion.
37. According to the AGCM's findings, the cost of Avastin continued to be covered, for the treatment of AMD, by certain regional social security systems even after it was removed from List 648 for that therapeutic indication.
38. Commission Decisions of 17 July 2009 in Case COMP/M. 5476 — Pfizer/Wyeth, (paragraphs 24 and 25); of 13 October 2001 in Case COMP/M. 6258 — Teva/Cephalon (paragraphs 88 to 91); and of 4 February 2009 in Case COMP/M. 5253 Sanofi/Aventis/Zentiva (footnote 6).
39. In principle, in accordance with Article 3(1) of Regulation No 726/2004, the medicinal products covered by that regulation cannot be placed on the market for therapeutic indications or for methods of administration not covered by their MA. Moreover, under Article 40(2) of Directive 2001/83, to which Article 19(1) of the regulation refers, a manufacturing authorisation is required for the processes of dividing medicinal products up and repackaging them. Nevertheless, the provisions admit of certain derogations. In particular, Article 3(1) of the directive provides that the directive does not apply where the medicinal product is prepared in a pharmacy pursuant to a medical prescription for an individual patient (see, on this point, judgment of 11 April 2013, Novartis Pharma (C‑535/11, EU:C:2013:226, paragraph 43)). The Court has stated, in its judgment of 16 July 2015, Abcur (C‑544/13 and C‑545/13, EU:C:2015:481, paragraph 64), that that derogation presupposed that the

preparation is based on the individual needs of a patient to whom a prescription has been issued. According to the AGCM and the Region of Emilia-Romagna, the dividing up and repackaging of Avastin take place in hospital pharmacies on the basis of individual prescriptions, such that the derogation applies. Roche and Roche Italia allege, on the contrary, that those processes were mostly carried out in batches and in standard fashion, on the basis of prescriptions not tailored to the individual needs of patients. The applicability of Article 3(1) of the directive in such a situation is the subject of one of the questions which the Consiglio di Stato (Council of State) has referred to the Court for a preliminary ruling in Case C‑29/17, which is pending.

40. The applicants in the main proceedings refer to Article 3(2) of decreto-legge 17 febbraio 1998, No 23, convertito con modificazioni dalla legge 8 aprile 1998, No 94 (Legislative Decree No 23 of 17 February 1998, converted, with amendments, into Law No 94 of 8 April 1998, the so-called 'Di Bella Law').

41. They refer, in particular, to Judgment No 151/2014 of the Corte costituzionale (Constitutional Court) of 19 May 2014. In that case, the court interpreted Article 1(4) of decreto-legge 21 ottobre 1996, No 536, convertito con modificazioni dalla legge 23 dicembre 1996, No 648 (Legislative Decree No 536 of 21 October 1996, converted, with amendments, into Law No 648 of 23 December 1996), which makes the reimbursement by the SSN of medicines prescribed off label conditional on the absence of any viable alternative therapy, as meaning that that condition is fulfilled when, even though an authorised alternative therapy exists, it is not economically viable. Following that judgment, an amendment was made to the law in question so as to enable the reimbursement of medicines prescribed off label under certain conditions, even where there is an authorised alternative therapy (decreto-legge 20 marzo 2014, No 36, convertito con legge 16 mayo 2014, No 79 (Legislative Decree No 36 of 20 March 2013, converted into Law No 79 of 16 May 2014)). Novartis Italia disputes the conformity of that amendment with Directive 2001/83 in the case before the Consiglio di Stato (Council of State) which gave rise to the request for a preliminary ruling in Case C‑29/17, pending before the Court. In any event, at the hearing, SOI-AMOI called into question the mandatory nature of Article 3(2) of the Di Bella Law — pursuant to which medicinal products cannot be prescribed off label unless there is no authorised alternative therapy for treating the patient in question — the infringement of which is not penalised.

42. In so far as concerns the necessity of reading questions referred for a preliminary ruling in light of the context in which they are referred in order to be able to provide a helpful answer, see judgment of 7 March 1996, Merckx and Neuhuys (C‑171/94 and C‑172/94, EU:C:1996:87, paragraph 15) and the Opinion of Advocate General Ruiz-Jarabo Colomer in Gottardo (C‑55/00, EU:C:2001:210, point 36).

43. At the hearing, Roche argued that the competition authorities could nevertheless request the cooperation of the pharmacovigilance authorities in determining the lawfulness of the prescribing and placing on the market of medicines intended for off-label use. In the present case, however, the lawfulness of such practices depends on the interpretation — about which various actors in the sector strongly disagree — of certain provisions of Italian and EU law. Such questions can be finally settled only by the courts.

44. Judgment of 7 February 2013 (C‑68/12, EU:C:2013:71, paragraph 21).

45. Judgment of 7 February 2013, Slovenská sporiteľňa (C‑68/12, EU:C:2013:71, paragraphs 20 and 21).

46. See point 165 of this Opinion.

47. The approach taken by the Court in its judgment of 7 February 2013, Slovenská sporiteľňa (C‑68/12, EU:C:2013:71, paragraphs 20 and 21) also contradicts the argument put forward by Roche that the unlawfulness of the marketing and prescribing of Avastin for off-label use suggests the absence of any competitive relationship capable of being restricted by the collusive conduct at issue. In the same vein, in Decision 85/206/EEC of 19 December 1984 relating to a proceeding under Article 85 of the EEC Treaty (IV/26.870 — Aluminium imports from eastern Europe) (OJ 1985 L 92, p. 1, paragraph 12.2), the Commission refuted the argument that Article 101(1) TFEU cannot apply to a cartel to restrict the competition presented by allegedly dumped metal because that competition was not competition in the context of a lawful free enterprise economy and there was therefore no 'competition' within the meaning of that provision capable of being restricted. According to the Commission's decision, it is not for private persons to assume public duties and regulate trade by means of a cartel.

48. Pursuant to Article 1(1)(b) of Regulation No 772/2004, when a licensing agreement contains clauses relating to the purchase of products by the licensee it is a 'technology transfer agreement', provided that those clauses are not the primary object of the agreement and are directly related to the production of contract products (see also Article 2(3) of Regulation No 316/2014). On the other hand, when an agreement provides for both the sale of products to a distributor and the assignment to that distributor of intellectual property rights, and the assignment is not the primary object of the agreement, the agreement falls within the scope of Commission Regulation (EU) No 330/2010 of 20 April 2010 on the application of Article 101(3) [TFEU] to categories of vertical agreements and concerted practices (OJ 2010 L 102, p. 1) (see Article 2(3) of that regulation). Since none of the interested parties has disputed this classification, I base my analysis on the premiss that, subject to verification by the national court, the agreement between Genentech and Novartis is a 'technology transfer agreement' within the meaning of Regulation No 772/2004. In any event, Article 1(1)(c) of Regulation No 330/2010 contains a definition of 'competing undertaking'

comparable to the definition in Article 1(1)(j)(ii) of Regulation No 772/2004.
49. See Article 1(1)(f) of Regulation No 772/2004. Article 1(1)(g) of Regulation No 316/2014 contains a similar definition of contract product.
50. See point 111 of this Opinion.
51. See point 107 of this Opinion. The greater tolerance expressed by Regulations No 772/2004 and No 316/2014 toward restrictions contained in licensing agreements between non-competing undertakings may also be explained by the fact that, in principle, such restrictions solely concern intra-technology competition. See, to that effect, paragraph 27 of the Communication from the Commission, Guidelines on the application of Article 101 [TFEU] to technology transfer agreements (OJ 2014 C 89, p. 3, 'the Guidelines').
52. See points 124 and 129 of this Opinion.
53. Judgment of 30 June 1966 (56/65, EU:C:1966:38, p. 250).
54. See, in particular, judgments of 11 July 1985, Remia and Others v Commission (42/84, EU:C:1985:327, paragraphs 19 and 20); of 28 January 1986, Pronuptia de Paris (161/84, EU:C:1986:41, paragraphs 16 to 22); of 19 April 1988, Erauw-Jacquery (27/87, EU:C:1988:183, paragraph 10); of 15 December 1994, DLG (C‑250/92, EU:C:1994:413, paragraph 35); and of 12 December 1995, Oude Luttikhuis and Others (C‑399/93, EU:C:1995:434, paragraphs 12 to 14).
55. Judgment of 8 June 1982 (258/78, EU:C:1982:211). See Whish, R. and Bailey, D., Competition Law, 7th edition, Oxford University Press, Oxford, 2013, p. 128.
56. Judgment of 11 September 2014 (C‑382/12 P, EU:C:2014:2201, paragraph 89).
57. Judgment of 8 June 1982 (258/78, EU:C:1982:211).
58. In the same vein, as is clear from recital 5 of Regulation No 772/2004 and recital 4 of Regulation No 316/2014, the legislature has taken the view that technology transfer agreements generally bring about gains in efficiency and promote competition, in particular by facilitating the dissemination of technology. See also paragraphs 9 and 17 of the Guidelines.
59. The principle is mentioned, with a citation of that judgment, in paragraph 12(b) of the Guidelines. However, it does not mean that all restrictions on intra-technology competition escape the prohibition laid down in Article 101(1) TFEU merely because they might strengthen inter-technology competition (see, by analogy, the judgment of 13 July 1966, Consten and Grundig v Commission (56/64 and 58/64, EU:C:1966:41, p. 337)).
60. Similar, in its judgment of 30 June 1966, LTM (56/65, EU:C:1966:38, p. 250), the Court identified, among the criteria for determining whether an agreement containing an exclusivity clause restricted competition, 'the opportunities allowed for other commercial competitors in the same products by way of parallel re-exportation and importation'.
61. Judgment of 8 June 1982, Nungesser and Eisele v Commission (258/78, EU:C:1982:211, paragraphs 53, 60, 67, 77 and 78).
62. Judgment of 8 June 1982 (258/78, EU:C:1982:211).
63. Moreover, Roche Italia has stated that, in its view, the product resulting from the division and repackaging of Avastin in pharmacies for ophthalmological use is a product manufactured by those pharmacies different from the Avastin placed on the market by Roche.
64. Judgment of 8 June 1982 (258/78, EU:C:1982:211).
65. Judgment of 8 June 1982, Nungesser and Eisele v Commission (258/78, EU:C:1982:211, paragraph 67).
66. The Court has repeatedly held that agreements aimed at partitioning national markets, in particular by limiting parallel exports, are agreements whose object is to restrict competition, inasmuch as the integration of markets is a Treaty objective (see judgment of 6 October 2009, GlaxoSmithKline Services and Others v Commission and Others (C‑501/06 P, C‑513/06 P, C‑515/06 P and C‑519/06 P, EU:C:2009:610, paragraph 61 and the case-law cited)).
67. See, to that effect, judgment of 3 September 2009, Prym and Prym Consumer v Commission (C‑534/07 P, EU:C:2009:505, paragraph 68).
68. Judgment of 11 September 2014 (C‑382/12 P, EU:C:2014:2201).
69. Judgment of 11 September 2014, MasterCard and Others v Commission (C‑382/12 P, EU:C:2014:2201, paragraph 89).
70. Judgment of 11 September 2014, MasterCard and Others v Commission (C‑382/12 P, EU:C:2014:2201, paragraphs 90, 91 and 93).
71. Judgment of 11 September 2014, MasterCard and Others v Commission (C‑382/12 P, EU:C:2014:2201, paragraph 91).
72. Judgment of 11 September 2014, MasterCard and Others v Commission (C‑382/12 P, EU:C:2014:2201, paragraph 89).
73. The judgment of 11 July 1985, Remia v Commission (42/84, EU:C:1985:327) concerned a non-compete clause inserted into an agreement for the transfer of an undertaking, the purpose of which was to protect the purchasers from competition from the vendor. In its judgment of 28 January 1986, Pronuptia de Paris (161/84, EU:C:1986:41), the Court classified as ancillary restrictions clauses relating to the obligation of a franchisor to communicate know-how to and to provide assistance to franchisees and the obligations of the franchisees to maintain the identity and reputation of a network. The Court ruled similarly in its judgment of 19 April 1988, Erauw-Jacquery (27/87, EU:C:1988:183), which concerned a clause, inserted into a licensing agreement concerning a plant breeders' rights in respect of the propagation of basic seeds, prohibiting the export and sale by the licensee of such seeds. The judgment of 15 December 1994, DLG (C‑250/92, EU:C:1994:413) concerned a provision in the statutes of a cooperative purchasing association limiting the freedom of its members to participate in competing associations. At issue in the judgment of 12

December 1995, Oude Luttikhuis and Others (C‑399/93, EU:C:1995:434) were provisions in the statutes of an agricultural cooperative association governing relations between the association and its members.

74. The applicants in the main proceedings did not merely agree that Roche and Roche Italia should refrain from encouraging the off-label use of Avastin, for example, by portraying it to the authorities as a substitute for Lucentis. On the contrary, they sought the dissemination of opinions discouraging such use by third parties.

75. Judgment of 11 September 2014, MasterCard and Others v Commission (C‑382/12 P, EU:C:2014:2201, paragraph 89).

76. See point 116 of this Opinion.

77. See points 100 to 103 of this Opinion.

78. See point 107 of this Opinion.

79. See Articles 4(2) and 5(2) of Regulation No 772/2004 and Articles 4(2) and 5(2) of Regulation No 316/2014. Those provisions do not include clauses of this type among the 'hardcore restrictions' or among the restrictions which are excluded from the benefit of the block exemption. See also paragraph 120 of the Guidelines.

80. Article 4(1)(c)(ii) and (iv) of Regulation No 772/2004 and Article 4(1)(c)(i) of Regulation No 316/2014. See also paragraphs 107 and 108 of the Guidelines.

81. See paragraphs 194 and 202 of the Guidelines.

82. Article 3(2) of Regulations Nos 772/2004 and 316/2014.

83. See, to that effect, paragraph 43 of the Guidelines.

84. Judgment of 6 October 2009, GlaxoSmithKline Services and Others v Commission and Others (C‑501/06 P, C‑513/06 P, C‑515/06 P and C‑519/06 P, EU:C:2009:610, paragraph 82 and the case-law cited).

85. Those parties refer, in particular, to various independent scientific studies and to the inclusion of bevacizumab in the WHO's Model List of Essential Medicines for ophthalmological indications (see footnote 20 to this Opinion). They also mention the European Medicines Agency's refusal to amend the SPC for Avastin in the manner requested by Roche. On this point, it is clear from the AGCM's decision that that body noted that 'Roche had requested amendments to section 4.8 ('adverse reactions' …) of the SPC for Avastin, in particular, to indicate more adverse reactions in the case of the intravitreal use of Avastin than is the case for Lucentis. However, the [EMA's committee for medicinal products for human use] took the view, in its report on Avastin, that amendments should be made 'only' to section 4.4 ('Special warnings and precautions for use'), given that (1) according to the scientific evidence currently available, the differences between Avastin and Lucentis in terms of adverse reactions are not statistically significant, (2) systemic adverse reactions, that is to say, not limited to the eye that has been injected but concerning the patient's life, may be caused by anti-VEGF therapies generally.'

86. I would observe in this connection that Article 10a of Directive 2001/83, to which Article 6(1) of Regulation No 726/2004 refers, provides that, for the purposes of obtaining an MA, the existence of a long-standing medical usage and of scientific evidence of the efficacy and safety of a medicinal product may, under certain conditions, make good the absence of preclinical tests or clinical trials.

87. See point 66 of this Opinion.

88. Here, 'enfatizzare' has been translated into French as 'exagérer', which suggests an exaggeration of information in terms of its content that is not necessarily suggested by the English 'emphasise' or the German 'herausstellen'.

89. In reality, as is apparent from the order for reference (see point 35 of this Opinion), it was not the 'lesser efficacy or safety' of Avastin by comparison with Lucentis that the AGCM criticised the applicants in the main proceedings for exaggerating or emphasising, but rather the 'risks' associated with the off-label use of Avastin. Again, according to the AGCM, the applicants in the main proceedings had also 'alleged' that Avastin was supposedly less efficacious and safe than Lucentis.

90. See, in this connection, judgments of 23 March 2006, FCE Bank (C‑210/04, EU:C:2006:196, paragraph 21), and of 12 September 2013, Le Crédit Lyonnais (C‑388/11, EU:C:2013:541, paragraph 20).

91. See, inter alia, judgments of 30 June 1966, LTM (56/65, EU:C:1966:38, p. 249); of 11 September 2014, CB v Commission (C‑67/13 P, EU:C:2014:2204, paragraphs 49, 53 and 57); and of 27 April 2017, FSL and Others v Commission (C‑469/15 P, EU:C:2017:308, paragraph 103 and the case-law cited).

92. See, in particular, judgments of 11 September 2014, CB v Commission (C‑67/13 P, EU:C:2014:2204, paragraph 50 and the case-law cited), and of 27 April 2017, FSL and Others v Commission (C‑469/15 P, EU:C:2017:308, paragraph 103 and the case-law cited).

93. See, inter alia, judgment of 6 October 2009, GlaxoSmithKline Services and Others v Commission and Others (C‑501/06 P, C‑513/06 P, C‑515/06 P and C‑519/06 P, EU:C:2009:610, paragraph 58 and the case-law cited).

94. Judgments of 12 December 1995, Oude Luttikhuis and Others (C‑399/93, EU:C:1995:434, paragraph 10); of 14 March 2013, Allianz Hungária Biztosító and Others (C‑32/11, EU:C:2013:160, paragraph 36); and of 11 September 2014, CB v Commission (C‑67/13 P, EU:C:2014:2204, paragraph 53).

95. I am borrowing here the expression used by Advocate General Wathelet in his Opinion in Toshiba Corporation v Commission (C‑373/14 P, EU:C:2015:427, point 67).

96. In particular, in its judgment of 11 September 2014, CB v Commission (C‑67/13 P, EU:C:2014:2204, paragraphs 74, 75 and 86), the Court held, in substance, that an instance of collusion was not a restriction of competition by object because, in light of the context

and, in particular, the structure of and operating conditions in the market in question, its true aim was not anticompetitive. In that case, that aim consisted in the imposition of a financial contribution on the members of a grouping which benefit from the efforts of other members for the purposes of developing certain activities of the members of that grouping. See, to that effect, Ibañez Colomo, P., and Lamadrid, A., 'On the notion of restriction of competition: what we know and what we don't know we know', The Notion of Restriction of Competition, edited by Gerard, D., Merola, M. and Meyring, B., Bruylant, Brussels, 2017, pp. 353 to 358. See also judgment of 4 October 2011, Football Association Premier League and Others (C‑403/08 and C‑429/08, EU:C:2011:631, paragraph 143) and the Opinion of Advocate General Trstenjak in Beef Industry Development Society and Barry Brothers (C‑209/07, EU:C:2008:467, points 51 to 53).

97. See, in particular, judgments of 6 October 2009, GlaxoSmithKline Services and Others v Commission and Others (C‑501/06 P, C‑513/06 P, C‑515/06 P and C‑519/06 P, EU:C:2009:610, paragraph 58), and of 19 March 2015, Dole Food and Dole Fresh Fruit Europe v Commission (C‑286/13 P, EU:C:2015:184, paragraph 118).

98. Judgment of 11 September 2014, CB v Commission (C‑67/13 P, EU:C:2014:2204, paragraph 88).

99. See, in particular, judgments of 8 November 1983, IAZ International Belgium and Others v Commission (96/82 to 102/82, 104/82, 105/82, 108/82 and 110/82, EU:C:1983:310, paragraphs 23 and 24), and of 11 September 2014, CB v Commission (C‑67/13 P, EU:C:2014:2204, paragraph 54).

100. Judgment of 11 September 2014, CB v Commission (C‑67/13 P, EU:C:2014:2204, paragraph 58).

101. Judgment of 20 November 2008, Beef Industry Development Society and Barry Brothers (C‑209/07, EU:C:2008:643, paragraph 23).

102. See judgment of 20 November 2008, Beef Industry Development Society and Barry Brothers (C‑209/07, EU:C:2008:643, paragraph 31 et seq. and the Opinion of Advocate General Wathelet in Toshiba Corporation v Commission (C‑373/14 P, EU:C:2015:427, points 74, 89 and 90).

103. See point 137 of this Opinion.

104. Independently of the debate concerning the truth of the allegations concerning the comparative safety of Avastin and Lucentis, the applicants in the main proceedings also argue that the aim of the collusive conduct at issue was to enable the licensing agreement relating to Lucentis to be implemented. They maintain that the restrictions at issue in the main proceedings were ancillary to the conclusion of that main, pro-competitive agreement. I have already refuted that line of argument, in points 110 to 124 of this Opinion, in the context of my examination of the first question.

105. As the French Government has remarked, some French courts have taken this approach. In Judgment No 177 of 18 December 2014 Sanofi e.a. c. Autorité de la concurrence (RG No 2013/12370) and Judgment No 50 of 26 March 2015, Reckitt Benckiser e.a. c. Arrow Génériques (RG No 2014/03330), the Cour d'appel de Paris (Court of Appeal, Paris, France) held that the communication of information about the composition and safety profile of medicinal products which was not incorrect but was presented in a misleading manner infringed Article 101 TFEU or Article 102 TFEU. It considered, in substance, that such communication escapes the prohibitions laid down in those provisions if it is made on the basis of objective, verifiable findings, but falls within their scope when made on the basis of unverified, incomplete or ambiguous assertions. The Cour de cassation (Court of Cassation, France) upheld those two decisions in Judgment No 890 of 18 October 2016, Sanofi e.a. c. Autorité de la Concurrence e.a. and Judgment No 33 of 11 January 2017, Reckitt Benckiser e.a. c. Arrow Génériques e.a.

106. Such a definition of the misleading nature of an allegation is similar to that of the misleading nature of advertising laid down in Article 2(b) of Directive 2006/114/EC of the European Parliament and of the Council of 12 December 2006 concerning misleading and comparative advertising (OJ 2006 L 376, p. 21). In accordance with that provision, 'any advertising which in any way, including its presentation, deceives or is likely to deceive the persons to whom it is addressed or whom it reaches and which, by reason of its deceptive nature, is likely to affect their economic behaviour or which, for those reasons, injures or is likely to injure a competitor' is misleading. See also the decisions of the French courts cited in footnote 105 to this Opinion.

107. See also, with regard to medicinal products authorised by the Member States, the second subparagraph of Article 106a(1) of Directive 2001/83.

108. See, on this point, European Medicines Agency, Guideline on good pharmacovigilance practices (GVP), Module XV — Safety communication, of 22 January 2013 (EMA/118465/2012), p. 4: 'safety communication should address the uncertainties related to a safety concern. This is of particular relevance for emerging information which is often communicated while competent authorities are conducting their evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented.' See also Module VII — Periodic safety update report (Rev 1) (EMA/816292/2011 Rev 1), of 9 December 2013, p. 28, which states that the periodic safety update reports (which MA holders must submit pursuant to Article 28(2) of Regulation No 726/2004) must characterise the potential risks communicated, mentioning, in particular, the 'strength of evidence and its uncertainties, including analysis of conflicting evidence'.

109. The applicants in the main proceedings have argued, in particular, without any of the interested parties disputing the fact, that the independent study entitled 'Randomised controlled comparison of age-related macular degeneration treatment trial (CATT)', to which the AGCM's decision refers, gave a slightly

higher number of notifications of systemic adverse reactions for Avastin used off label than for Lucentis. It is only the interpretation of that data that is disputed. In particular, the AGCM has emphasised that that study states that that difference in the numbers of notifications is not statistically significant.

110. Judgments of 8 November 1983, IAZ International Belgium and Others v Commission (96/82 to 102/82, 104/82, 105/82, 108/82 and 110/82, EU:C:1983:310, paragraph 25 and paragraph 30 et seq.), and of 20 November 2008, Beef Industry Development Society and Barry Brothers (C‑209/07, EU:C:2008:643, paragraphs 21, 33 and 39). See also, on this point, judgment of 6 April 2006, General Motors v Commission (C‑551/03 P, EU:C:2006:229, paragraph 64).

111. Judgment of 7 February 2013 (C‑68/12, EU:C:2013:71, paragraph 21).

112. Judgment of 7 February 2013, Slovenská sporiteľňa (C‑68/12, EU:C:2013:71, paragraphs 29 to 36). The General Court adopted a similar approach in its judgment of 15 March 2000, Cimenteries CBR and Others v Commission (T‑25/95, T‑26/95, T‑30/95 to T‑32/95, T‑34/95 to T‑39/95, T‑42/95 to T‑46/95, T‑48/95, T‑50/95 to T‑65/95, T‑68/95 to T‑71/95, T‑87/95, T‑88/95, T‑103/95 and T‑104/95, EU:T:2000:77, paragraph 2558). In that case, the General Court held that, while undertakings have the right not only to notify the competent authorities of infringements of national law or EU law, but also to respond collectively to that end, they are not entitled to 'take the law into their own hands by substituting themselves for the authorities with competence to penalise any infringements' of those provisions.

113. In the present case, Roche stated at the hearing that it has never brought legal proceedings to challenge the lawfulness of prescribing Avastin off label. Moreover, the order for reference does not indicate whether or not the applicants in the main proceedings challenged in court the lawfulness of preparing and selling Avastin for off-label use prior to commencing the collusive conduct at issue. The AGCM's decision and the observations submitted by the interested parties however indicate the existence of litigation concerning the lawfulness of including Avastin, for ophthalmological indications, in the lists of medicinal products that may be reimbursed by national and regional social security systems.

114. See the Opinions of Advocate General Kokott in T-Mobile Netherlands and Others (C‑8/08, EU:C:2009:110, points 46 and 47); of Advocate General Wahl in CB v Commission (C‑67/13 P, EU:C:2014:1958, points 44 to 52) and in ING Pensii (C‑172/14, EU:C:2015:272, points 40 et seq.); and of Advocate General Wathelet in Toshiba Corporation v Commission (C‑373/14 P, EU:C:2015:427, points 68 and 69).

115. Judgment of 11 September 2014 (C‑67/13 P, EU:C:2014:2204, paragraph 81).

116. Judgments of 4 June 2009, T-Mobile Netherlands and Others (C‑8/08, EU:C:2009:343, paragraph 31); of 14 March 2013, Allianz Hungária Biztosító and Others (C‑32/11, EU:C:2013:160, paragraph 38); and of 19 March 2015, Dole Food and Dole Fresh Fruit Europe v Commission (C‑286/13 P, EU:C:2015:184, paragraph 122). See also the Opinions of Advocate General Kokott in Dole Food and Dole Fresh Fruit Europe v Commission (C‑286/13 P, EU:C:2014:2437, point 109), and of Advocate General Wathelet in Toshiba Corporation v Commission (C‑373/14 P, EU:C:2015:427, point 68).

117. See footnote 85 to this Opinion.

118. Judgments of 13 July 1966, Consten and Grundig v Commission (56/64 and 58/64, EU:C:1966:41, p. 342); of 8 July 1999, Hüls v Commission (C‑199/92 P, EU:C:1999:358, paragraphs 164 and 165); and of 13 December 2012, Expedia (C‑226/11, EU:C:2012:795, paragraphs 35 to 37).

119. Judgments of 4 June 2009, T-Mobile Netherlands and Others (C‑8/08, EU:C:2009:343, paragraph 31), and of 14 March 2013, Allianz Hungária Biztosító and Others (C‑32/11, EU:C:2013:160, paragraph 38).

120. Judgments of 30 June 1966, LTM (56/65, EU:C:1966:38, p. 250); of 28 May 1998, Deere v Commission (C‑7/95 P, EU:C:1998:256, paragraph 76); and of 6 April 2006, General Motors v Commission (C‑551/03 P, EU:C:2006:229, paragraph 72 and the case-law cited). See also, to that effect, judgments of 11 July 1985, Remia and Others v Commission (42/84, EU:C:1985:327, paragraph 18), and of 23 November 2006, Asnef-Equifax and Administración del Estado (C‑238/05, EU:C:2006:734, paragraph 55).

121. See points 170 and 171 of this Opinion.

122. Paragraph 127 of the Guidelines states that restrictions which are objectively necessary to protect public health do not fall within the scope of Article 101(1) TFEU. See also, Commission staff working document 'Guidance on restrictions of competition "by object" for the purpose of defining which agreements may benefit from the de minimis notice, accompanying the communication from the Commission, Notice on agreements of minor importance which do not appreciably restrict competition under Article 101(1) [TFEU] (de minimis notice)', SWD(2014) 198 final, p. 4, and the communications from the Commission, 'Guidelines on Vertical Restraints' (OJ 2010 C 130, p. 1, paragraph 60) and 'guidelines on the application of Article [101(3) TFEU] (OJ 2004 C 101, p. 97).

123. See points 12 to 14 of this Opinion. See also the second subparagraph of Article 23(2) and the second subparagraph of Article 101(1) of Directive 2001/83.