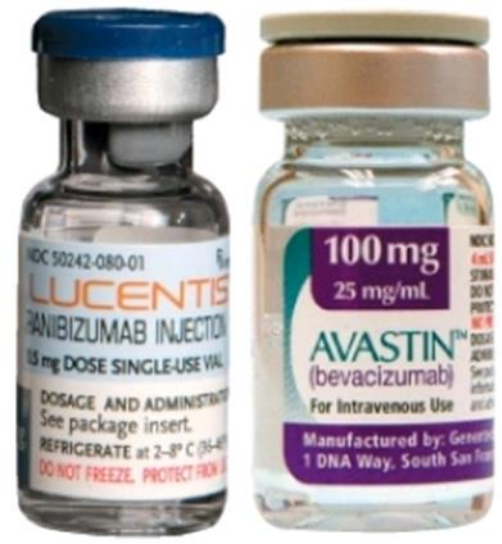
Court of Justice EU, 11 April 2013, Novartis v Apozyt



PHARMACEUTICAL LAW

No "new placement on the market" as a result of carrying out the preparation of ready-to-use syringes based on individual prescriptions

- **When it prepares ready-to-use syringes in order to respond to orders placed by pharmacies in which patients have handed in prescriptions for such syringes, a company such as Apozyt does not use any of the biotechnological processes listed in point 1 of the Annex to Regulation No 726/2004; nor, moreover, does it supply anything to those pharmacies in advance, either directly or indirectly through wholesalers. Furthermore, it is apparent from the order for reference, and in particular from the wording of the question raised, first, that the Landgericht Hamburg proceeds on the basis that the composition of the medicinal product is not modified. Second, the content of the syringes that have been pre-filled in that way is administered to the patient by the prescribing doctor who has thus himself decided to treat his patient using such syringes.**
- **In such circumstances, provided that the referring court does in fact find that the processes in question do not result in any modification of the medicinal product and that they are carried out solely on the basis of individual prescriptions making provision for them, there is no ground for considering that the activity thus carried out can be equated with a new placing on the market of a medicinal product included in point 1 of the Annex to Regulation No 726/2004; accordingly, the company concerned is, in that respect, not subject to the obligation to hold a marketing authorisation granted by the Community pursuant to Article 3 (1) of the regulation.**
- **In view of all the foregoing considerations, the answer to the question referred is that activities such as those at issue in the main proceedings, provided that they do not result in a modification of the medicinal product concerned and are carried out solely on the basis of individual prescriptions calling for processes of such a kind – a matter which falls to be determined by the referring court –, do not require a marketing authorisation under Article 3 (1) of Regulation No 726/2004 but remain, in any event, subject to Directive 2001/83.**

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Court of Justice EU, 11 April 2013
(L. Bay Larsen, J.-C. Bonichot, C. Toader (rapporteur), A. Prechal en E. Jarašiūnas)
JUDGMENT OF THE COURT (Fourth Chamber)
11 April 2013 (*)
(Reference for a preliminary ruling – Regulation (EC) No 726/2004 – Medicinal products for human use – Procedure for authorisation – Requirement for authorisation – Concept of medicinal products 'developed' by means of certain biotechnological processes, as referred to in point 1 of the Annex to that regulation – Repackaging process – Injectable solution distributed in single-use vials containing a larger quantity of the therapeutic solution than that actually used for the purposes of medical treatment – Part of the content of such vials drawn off, on prescription by a doctor, into syringes pre-filled with the prescribed dose, without any modification of the medicinal product)
In Case C-535/11,
REQUEST for a preliminary ruling under Article 267 TFEU from the Landgericht Hamburg (Germany), made by decision of 12 October 2011, received at the Court on 20 October 2011, in the proceedings
Novartis Pharma GmbH
v
Apozyt GmbH,
THE COURT (Fourth Chamber),
composed of L. Bay Larsen, acting as President of the Fourth Chamber, J.-C. Bonichot, C. Toader (Rapporteur), A. Prechal and E. Jarašiūnas, Judges, Advocate General: E. Sharpston, Registrar: A. Impellizzeri, Administrator, having regard to the written procedure and further to the hearing on 26 September 2012,
after considering the observations submitted on behalf of:
– Novartis Pharma GmbH, by L. Kröner, C. Schoonderbeek and I. Millarg, Rechtsanwälte, – Apozyt GmbH, by W. Prinz, Rechtsanwalt, and by C. Künzer,
– the German Government, by T. Henze and A. Wiedmann, acting as Agents,
– the Czech Government, by M. Smolek and D. Hadroušek, acting as Agents,
– Ireland, by E. Creedon, acting as Agent, and by S. Woulfe, Barrister-at-Law,

– the Greek Government, by I. Bakopoulos and O. Souropani, acting as Agents,
– the Portuguese Republic, by L. Inez Fernandes and A. Antunes, acting as Agents,
– the European Commission, by M. Šimerdová and B.-R. Killmann, acting as Agents,
after hearing the Opinion of the Advocate General at the sitting on 31 January 2013,
gives the following

Judgment

1 This request for a preliminary ruling concerns the interpretation of Article 3(1) 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).

2 The request has been made in proceedings between Novartis Pharma GmbH ('Novartis') and Apozyt GmbH ('Apozyt') concerning whether Apozyt may produce, distribute and promote ready-to-use syringes that are intended for the treatment of eye disease and contain doses of the medicinal products Lucentis and Avastin.

Legal context

European Union legislation

3 Recitals 7 and 13 in the preamble to Regulation No 726/2004 read as follows:

'(7) Experience gained since the adoption of Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology [OJ 1987 L 15, p. 38] has shown that it is necessary to create a centralised authorisation procedure that is compulsory for high-technology medicinal products, particularly those resulting from biotechnical processes, in order to maintain the high level of scientific evaluation of these medicinal products in the European Union and thus to preserve the confidence of patients and the medical professions in the evaluation. ...

(13) In the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. ...'

4 Under Article 3(1) of Regulation No 726/2004 'no medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation'.

5 Article 3(2) of the regulation adds:

'Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Community in accordance with the provisions of this Regulation, if:

(a) the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community; or

(b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community level.

...'

6 Point 1 of the Annex to Regulation No 726/2004, which concerns 'Medicinal products to be authorised by the Community', reads as follows:

'Medicinal products developed by means of one of the following biotechnological processes:

– recombinant DNA technology,

– controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,

– hybridoma and monoclonal antibody methods.'

7 As regards the content of an application for a marketing authorisation, Article 6(1) of Regulation No 726/2004 refers to the information in, inter alia, Article 8(3) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ 2001 L 311, p. 67), as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 (OJ 2010 L 348, p. 74) ('Directive 2001/83').

8 In that regard, it is apparent from Article 8(3) of Directive 2001/83 that the particulars and documents which must accompany an application for a marketing authorisation include, inter alia, the name of the medicinal product, the qualitative and quantitative particulars of all the constituents of that product, a description of the manufacturing method, posology, pharmaceutical form, method and route of administration and expected shelf life.

9 Under Article 16 of Regulation No 726/2004, the holder of a marketing authorisation is obliged to supply forthwith to the European Agency Medicines Agency (EMA), to the European Commission and to the Member States any new information which might entail the variation of the particulars or documents referred to in Article 8(3) of Directive 2001/83. If that holder proposes to make any variation of those particulars and documents, he is to submit the relevant application to the EMA.

10 Article 19(1) of Regulation No 726/2004 provides that the supervisory authorities are for their part to be responsible for verifying on behalf of the European Union that the holder of the marketing authorisation for a medicinal product for human use satisfies the requirements laid down in, inter alia, Title IV of Directive 2001/83, which contains Articles 40 to 53.

11 In that regard, Article 40 of Directive 2001/83 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. …
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.
…'

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

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

13 Article 3 of that directive provides:

'This Directive shall not apply to:
(1) Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).
(2) Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).
…'

14 Article 5(1) of the directive provides:

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

15 Article 6(1) of Directive 2001/83 reads as follows:

'No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation … No 726/2004 ….
When a medicinal product has been granted an initial marketing authorisation 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 marketing authorisation …'

German law

16 Paragraph 4 of the Law on the marketing of medicinal products (Gesetz über den Verkehr mit Arzneimitteln) provides:

'1. Finished medicinal products are medicinal products which are produced and marketed in particular packaging for sale to the consumer, or other medicinal products intended for consumers, in the preparation of which an industrial process is applied in another way or which, apart from in pharmacies, are produced industrially. Finished medicinal products are not intermediates intended for further processing by a manufacturer.
…
14. *Production shall include making, preparing, processing or working, transferring to other containers – including bottling –, packaging, marking and selling …'*

17 Paragraph 21 of the Law on the marketing of medicinal products, which concerns the requirement for authorisation, provides:

'1. Finished medicinal products … may be marketed, under this Law, only if they have been approved by the competent Federal authorities or if the Commission of the European Communities or the Council of the European Union has granted a marketing authorisation in accordance with Article 3(1) or (2) of Regulation No 726/2004 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 and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ 2006 L 378, p.1) … .
2. Authorisation is not required for medicinal products
…
1b. other than the medicinal products listed in point 1, or for medicinal products authorised outside the scope of this Law for pharmacies in possession of a prescription for a patient.
…
(c) put into a container without being modified …'

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

18 Novartis is the holder of a marketing authorisation for Lucentis. The marketing authorisation was granted by the Commission by decision of 22 January 2007 (C(2007) 237)), adopted under Article 3(1) of Regulation No 726/2004.

19 One of the therapeutic indications specifically mentioned in the marketing authorisation for Lucentis is treatment of wet age-related macular degeneration ('AMD'). The wet form of AMD involves the pathological growth of blood-vessels in the retina together with fluid and blood secretions which damage the tissue of the retina. The disease results in serious visual impairment.

20 Lucentis is distributed in perforable vials containing 0.23 ml which are sold for around EUR 1 200 per unit, each vial being supplied with a syringe authorised for that use, a filter cannula and an injection cannula. According to the instructions for health professionals, the product concerned should be drawn up from the vial using the 1 ml syringe and filter cannula supplied with the vial. The filter cannula placed on the syringe must then be replaced by an injection cannula and the

contents of the syringe must be discarded until the syringe contains only the recommended dose of 0.05 ml of the product. An injection into the eye may then be given. The content of the vial is intended for the administration of a single dose, even though ultimately only 0.05 ml out of 0.23 ml of the medicinal liquid is used.

21 Roche Pharma AG, which is not a party to the main proceedings, is the holder of a marketing authorisation for Avastin. That marketing authorisation was granted by the Commission by a decision of 12 January 2005 (C(2005) 97)), which was adopted under Article 3(1) of Regulation No 726/2004.

22 The marketing authorisation for Avastin covers, in essence, therapeutic indications connected to the treatment of metastatic cancers of the colon, breast and kidney. In Germany, Avastin is used, on a doctor's prescription, in the treatment of AMD, since it was already used for that purpose before Lucentis was authorised and since at that time there were no medicinal products specifically for the treatment of AMD. As in other Member States, Avastin continues to be used in ophthalmology because it costs substantially less than Lucentis. The referring court states that in Germany that use, which relates to the therapeutic freedom of medical practitioners, is lawful provided that the patient gives his consent. Avastin is sold in 4 ml or 16 ml vials. However, the concentrate contained in the vials must not be used in undiluted form but must be diluted with saline solution and administered by infusion.

23 Apozyt prepares, using the content of the medicinal products Lucentis and Avastin, syringes which contain only the dose necessary for an injection on the basis of the dose prescribed by a doctor. The pre-prepared syringes are filled in a sterile environment in a production unit with an isolation chamber. The pre-filled syringes are dispatched and delivered to the pharmacy which has ordered them. According to Apozyt, pharmacies place orders only when patients produce prescriptions to this effect. The decanting into the syringes carried out in that way allows the content of the vials of Lucentis and Avastin to be used for a number of injections, so that the final price of an injection is considerably lower than the price that would be paid for an injection using solely the medicinal products as they are marketed.

24 Novartis brought proceedings before the referring court seeking an order that Apozyt cease commercial activities of this kind, which, according to Novartis, amount to acts of unfair competition. In support of its action, Novartis asserts that the activity of filling ready-to-use syringes with doses of the unmodified medicinal product also requires a marketing authorisation, in particular because – as referred to in the first and third indents of point 1 of the Annex to Regulation No 726/2004 – the active substances in Lucentis and Avastin have been developed by means of recombinant DNA technology and are also obtained using hybridoma and monoclonal antibody methods.

25 Moreover, in Novartis' submission, the fact that the single-use vials contain a higher dose than necessary in therapeutic terms is accounted for by production procedures. The surplus content is also intended to ensure the safe application of Lucentis. Novartis maintains that there is a danger of infiltration of bacteria when the original product is transferred from one container to another, as well as a problem relating to the conservation of the product in ready -to-use syringes such as those produced by the defendant in the main proceedings.

26 Apozyt contends that a marketing authorisation is not required for the procedures it carries out, since the process of producing the medicinal product has already been completed at the time when it re-packages it, then distributes it in the form of ready-to-use syringes containing lower doses than those contained in the original medicinal products that are the subject of a marketing authorisation. Thus, the preparation of ready-to-use syringes, such as those at issue in the main proceedings, cannot be regarded as the 'development' of a medicinal product by means of one of the processes listed in the Annex to Regulation No 726/2004. Furthermore, Apozyt submits that the preparation of ready-to-use syringes under sterile conditions, such as those which obtain in its filling units, is a guarantee of a higher degree of safety, given that doctors who themselves transfer the product to another container prior to an injection are not operating under sterile conditions. The syringes used are the same as those supplied by the original manufacturer, so that issue cannot be taken with Apozyt for altering the process for administering the medicinal products in question.

27 The Landgericht Hamburg explains that under Articles 3 and 4 of the Law against unfair competition (Gesetz gegen den unlauteren Wettbewerb), any person who, by reason of his conduct, infringes a requirement for approval or authorisation acts unfairly. Furthermore, such conduct may be challenged by any competitor who may require the conduct to be prohibited. Thus, if Apozyt's business of packaging ready-to-use syringes was covered by the requirement for authorisation laid down in Article 3 of Regulation No 726/2004, that business would be unfair within the meaning of Articles 3 and 4 of that law. In that connection, the Landgericht Hamburg refers to the fact that the Hanseatisches Oberlandesgericht Hamburg (Hamburg Higher Regional Court) has held, in a previous judgment, that the term 'developed', which is used in the introductory words of point 1 of the Annex to Regulation No 726/2004, also covers the filling of syringes and that consequently a marketing authorisation was also required for that activity. The referring court tends to concur with view but points out that the issue has considerable significance for the pharmaceutical sector, particularly since such filling of syringes, in a sterile environment, on the basis of the recommended dose, could allow substantial savings to be made.

28 In those circumstances, the Landgericht Hamburg decided to stay the proceedings and to refer the following question to the Court for a preliminary ruling:

'Does the term "developed" in the introductory words of point 1 of the Annex to [Regulation No 726/2004] extend to processes in which portions only of a medicinal product which has been developed and produced on a ready-to-use basis in accordance with the above procedures are drawn off into another container, after being prescribed and ordered at the time concerned by a doctor, if as a result of the process the composition of the medicinal product is not modified, and therefore in particular to the production of pre-filled syringes which have been filled with a medicinal product which is authorised under the Regulation?'

The application for the reopening of the oral procedure

29 By letter of 25 February 2013, Apozyt requested that the Court order the reopening of the oral procedure pursuant to Article 83 of the Rules of Procedure, on the ground that the Opinion of the Advocate General was based on inaccurate factual and legal considerations, particularly in relation to, on the one hand, the conclusion that Apozyt's activities amounted to the placing on the market of a new medicinal product and, on the other, the conditions for Article 5(1) of Directive 2001/83 to apply.

30 In that regard, it should be recalled, first, 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 where the case must be decided on the basis of an argument which has not been debated between the parties (see order in **Case C-17/98 *Emesa Sugar* [2000] ECR I-665, paragraph 18**; judgments in **Case C-210/03 *Swedish Match*** [2004] ECR I-11893, paragraph 25, and **Case C-138/05 *Stichting Zuid-Hollandse Milieufederatie* [2006] ECR I-8339, paragraph 23).**

31 Second, under the second paragraph of Article 252 TFEU, it is the duty of the Advocate General, acting with complete impartiality and independence, to make, in open court, reasoned submissions on cases which, in accordance with the Statute of the Court of Justice of the European Union, require the Advocate General's involvement. In carrying out that task, the Advocate General may, where appropriate, analyse a request for a preliminary ruling by placing it within a context which is broader than that strictly defined by the referring court or by the parties to the main proceedings. Since the Court is not bound either by the Advocate General's Opinion or by the reasoning on which it is based, it is not absolutely necessary to reopen the oral procedure, under Article 83 of the Rules of Procedure, each time the Advocate General raises a point of law which was not the subject of debate between the parties (**Case C-361/06 *Feinchemie Schwebda and Bayer CropScience* [2008] ECR I-3865, paragraph 34**).

32 In the present case, since the Court considers that it has sufficient information to give a ruling and since the case does not have to be decided on the basis of arguments which have not been debated between the parties, there is no need to grant the request that the oral procedure be reopened.

The question referred for a preliminary ruling

33 By its question, the referring court asks, in essence, whether activities such as those at issue in the main proceedings require a marketing authorisation under Article 3(1) of Regulation No 726/2004 and, if not, whether those activities remain subject to Directive 2001/83.

34 Novartis and the Czech and Greek Governments submit that activities such as those at issue in the main proceedings amount to repackaging and are not covered by the marketing authorisation granted for the original medicinal products, with the result that those activities are unlawful. Novartis thus considers that, if Apozyt is to repackage the medicinal products in question in a pre-filled syringe, it should submit an application for a marketing authorisation to that effect to the EMA.

35 Apozyt, the German Government, Ireland and the Portuguese Government defend the contrary position, submitting that such activities do not require the grant of a marketing authorisation additional to those already granted.

36 The Commission contends that the question raised may be of no relevance for the resolution of the dispute in the main proceedings, since, in its view, the word 'hergestellt' (developed) in the introductory words of the German-language version of point 1 of the Annex to Regulation No 726/2004 cannot be construed as a means of determining whether the obligation to hold a marketing authorisation also applies to activities whereby portions of a medicinal product which has been developed and produced in accordance with authorised procedures are, on a doctor's prescription, subsequently transferred into another container. It also maintains that, in order to decide on the case before it, the referring court must in reality ascertain whether activities such as those at issue in the main proceedings, whereby ready-to -use syringes are filled with a medicinal product which is already authorised and is contained in perforable vials, must be regarded as processes involving dividing up or changes in packaging or presentation within the meaning of Article 40(2) of Directive 2001/83. If that is the case, Apozyt will not need a marketing authorisation to carry out such processes. If, however, such processes cannot be regarded as falling within Article 40 of that directive, that would be a strong indication that a marketing authorisation is necessary to carry them out.

37 In that regard, the Court observes that Article 3(1) of Regulation No 726/2004 establishes an obligation to submit an application for a marketing authorisation in the framework of the centralised procedure in which the EMA has mandatory competence so far as the granting of those authorisations is concerned. That obligation relates to the high-technology medicinal products included in the Annex to the regulation, in

particular medicinal products developed by means of one of the three biotechnological processes listed in point 1 of the Annex.
38 It follows from Article 3 of Regulation No 726/2004 in conjunction with Articles 2 and 6 of Directive 2001/83 that industrially produced medicinal products for human use intended to be placed on the market in Member States, other than those included in the Annex to Regulation No 726/2004, must as a rule have a marketing authorisation granted by the authorities of those Member States under that directive. There is an option – in the present case on the terms set out in Article 3(2) of Regulation No 726/2004 – whereby medicinal products not included in the Annex thereto may none the less be granted a marketing authorisation under the centralised procedure, thereby avoiding the need to submit multiple applications for marketing authorisations under the authorisation procedure established by Directive 2001/83.
39 Accordingly, in adopting Article 3 of Regulation No 726/2004, the European Union legislature established a test for determining whether a given medicinal product must, in order to be placed on the market in the European Union, be authorised under the centralised authorisation procedure established by that regulation or under the national procedures implementing Directive 2001/83.
40 In the main proceedings it is established that the medicinal products Lucentis and Avastin have been placed on the market in the European Union and have in that regard a marketing authorisation granted by the Community in accordance with Article 3(1) of Regulation No 726/2004, in their capacity as medicinal products 'developed' by means of one of the biotechnological processes mentioned in point 1 of the Annex to the regulation.
41 When it prepares ready-to-use syringes in order to respond to orders placed by pharmacies in which patients have handed in prescriptions for such syringes, a company such as Apozyt does not use any of the biotechnological processes listed in point 1 of the Annex to Regulation No 726/2004; nor, moreover, does it supply anything to those pharmacies in advance, either directly or indirectly through wholesalers. Furthermore, it is apparent from the order for reference, and in particular from the wording of the question raised, first, that the Landgericht Hamburg proceeds on the basis that the composition of the medicinal product is not modified. Second, the content of the syringes that have been pre-filled in that way is administered to the patient by the prescribing doctor who has thus himself decided to treat his patient using such syringes.
42 In such circumstances, provided that the referring court does in fact find that the processes in question do not result in any modification of the medicinal product and that they are carried out solely on the basis of individual prescriptions making provision for them, there is no ground for considering that the activity thus carried out can be equated with a new placing on the market of a medicinal product included in point 1 of the Annex to Regulation No 726/2004; accordingly, the company concerned is, in that respect, not subject to the obligation to hold a marketing authorisation granted by the Community pursuant to Article 3 (1) of the regulation.
43 It is true that in its judgment in **Case C-433/00 *Aventis* [2002] ECR I-7761** the Court held that where a medicinal product had been the subject of two separate central marketing authorisations, one for packs of five items and the other for packs of 10 items, the European Union rules precluded that product from being marketed in a package consisting of two packs of five items which had been joined together and relabeled, commonly known as 'bundling'. However, the circumstances of the present case can be distinguished from those at issue in *Aventis*, which concerned repackaging for the purposes of parallel trading, and the Court observes in particular, concurring with the Portuguese Government, that the activity carried out by a company such as Apozyt occurs after the medicinal products at issue in the main proceedings have been placed on the market. In particular, the drawing off of liquid medicinal products from the original vials, and the transfer into ready-to-use syringes of the portions so drawn off, without any modification of those products, is in reality analogous to actions which, in the absence of Apozyt's activities, could otherwise be, or have been, carried out, under their responsibility, by doctors prescribing the treatment or by pharmacies themselves in their dispensaries, or else in hospitals.
44 However, it should be observed that, even if the service provided by a company such as Apozyt to its customer-pharmacies does not in itself amount to a placing on the market requiring a marketing authorisation, that none the less does not mean that that activity is lawful, since it remains in any event subject to the provisions of Directive 2001/83, in particular the provisions laying down a requirement for authorisation to manufacture medicinal products.
45 The German Government points out that it has made use of the derogation provided for in Article 5(1) of Directive 2001/83 by excluding from the scope of that directive, in order to fulfill special needs, medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility. According to the German Government, an activity such as that at issue in the main proceedings falls within the scope of that derogation and therefore requires neither a specific authorisation nor, *a fortiori*, a marketing authorisation.
46 It should be borne in mind in that regard that Article 5(1) of Directive 2001/83 is a specific derogating provision, which must be interpreted strictly, applicable in exceptional cases where it is appropriate to meet special medical needs, in circumstances in which a doctor, following an actual examination of his patients and on the basis of purely therapeutic considerations, prescribes a medicinal product which does not have a valid marketing authorisation in the European Union

and for which there is no authorised equivalent on the national market or which is unavailable on that market (see, to that effect, **Case C-185/10 *Commission* v *Poland* [2012] ECR I-0000, paragraphs 35, 36 and 48**). The Court pointed out in particular, in paragraph 37 of that judgment, that Article 5(1) cannot be relied on where medicinal products having the same active substances, the same dosage and the same form as those which the doctor providing treatment considers that he must prescribe to treat his patients are already authorised and available on the national market.

47 Thus, in the circumstances of the case before the referring court, that provision cannot be relied on with regard to the use of a medicinal product such as Lucentis, since those circumstances do not entail prescription of a medicinal product different from the product which already has a marketing authorisation; the injection volumes used are no different from those provided for in the marketing authorisation and nor is the product used for a therapeutic indication not covered by the marketing authorisation.

48 However, the possibility remains that the Federal Republic of Germany may be able to rely on Article 5(1) of Directive 2001/83 as regards the making available of an authorised medicinal product, such as Avastin, for therapeutic indications not covered by the marketing authorisation, where such a formulation is in accordance with the specifications of an authorised practitioner and is for use by an individual patient under his direct personal responsibility. Indeed, in that regard, since the active ingredients of Avastin and Lucentis are different, a doctor, when faced with a particular condition and relying solely on therapeutic considerations specific to his patients, including considerations pertaining to how medicine is administered, may take the view that a treatment not covered by the marketing authorisation, in accordance with the pharmaceutical form and the dosage which he considers appropriate and using Avastin which has a Community marketing authorisation, is preferable to treatment with Lucentis.

49 Concerning the last point, it should, however, be recalled that a prescribing doctor is required, from the point of view of professional conduct, not to prescribe a given medicinal product if it is not appropriate for the therapeutic treatment of his patient, including from the point of view of how it is administered (see **Case C-62/09 *Association of the British Pharmaceutical Industry* [2010] ECR I-3603, paragraph 40**).

50 Such considerations do not, however, settle the question as to whether the activity of a company such as Apozyt, at least so far as Lucentis is concerned, requires a specific authorisation under the European Union rules.

51 With regard to the requirements applying to an activity such as that carried out by Apozyt, the referring court mentions Article 40 of Directive 2001/83. In that regard, it is indeed the case that, under the first subparagraph of Article 40(2) of the directive, authorisation, as referred to in that provision, is required for that activity in so far as it concerns the repackaging of medicinal products which have a marketing authorisation.

52 However, as Ireland and the Commission submit, under the second subparagraph of Article 40(2) of Directive 2001/83 such authorisation is not required for, inter alia, dividing up and changes in packaging where those processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes.

53 It will thus fall to the referring court to ascertain, in particular, on the one hand, whether Apozyt is 'legally authorised' in Germany to carry out such processes and, on the other, whether those activities are in fact included within a system for the retail supply of medicinal products by pharmacies. On the latter point, the referring court will in particular have to determine whether the processes in question are carried out only on the basis of individual prescriptions that call for them to be carried out.

54 In view of all the foregoing considerations, the answer to the question referred is that activities such as those at issue in the main proceedings, provided that they do not result in a modification of the medicinal product concerned and are carried out solely on the basis of individual prescriptions calling for processes of such a kind – a matter which falls to be determined by the referring court –, do not require a marketing authorisation under Article 3 (1) of Regulation No 726/2004 but remain, in any event, subject to Directive 2001/83.

Costs

55 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 (Fourth Chamber) hereby rules:

Activities such as those at issue in the main proceedings, provided that they do not result in a modification of the medicinal product concerned and are carried out solely on the basis of individual prescriptions calling for processes of such a kind – a matter which falls to be determined by the referring court –, do not require a marketing authorisation under Article 3(1) 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, but remain, in any event, subject to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010.

* Language of the case: German.

OPINION OF ADVOCATE GENERAL SHARPSTON
delivered on 31 January 2013 [1]
Case C-535/11
Novartis Pharma GmbH
v
Apozyt GmbH
[Reference for a preliminary ruling from the Landgericht Hamburg (Germany)]
(Public health – Procedures for the authorisation of medicinal products for human use – Medicinal product with marketing authorisation specifying the container in which the product is to be placed on the market – Product transferred into another container – Whether a new marketing authorisation is required)

1. By this reference for a preliminary ruling, the Court is asked to interpret the rules governing the placing of medicinal products for human use on the market in the European Union. The issue concerns a product for which company A has obtained a marketing authorisation under which, inter alia, the product is to be marketed in containers of a specified size. Company B then takes that product, draws it off into a smaller container and sells it against a medical prescription for an individual patient. The process does not lead to the product being changed in any way. Company B sells the product in that form without being in possession of a marketing authorisation. Is it entitled to do so?

Legal framework

European Union ('EU') legislation

2. The rules governing the granting of marketing authorisations in respect of medicinal products for human use are laid down in two principal measures. These currently comprise Regulation No 726/2004 [2] and Directive 2001/83. [3] The former lays down a centralised procedure, applicable to certain types of medicinal products; any authorisation granted under it will automatically be valid throughout the EU. The latter regulates the procedures to be observed by the Member States in the granting of authorisations in respect of medicinal products not subject to the Regulation.

3. Although the national court's question is framed by reference exclusively to the Regulation, any description of the relevant legislative provisions would be incomplete unless it also took into account the requirements laid down under Directive 2001/83. It would also be lacking if it did not provide a brief history of the legislation and it is with that that I begin. [4]

A brief history of the legislation

4. The first Community measure concerning the regulation of medicinal products was Directive 65/65. [5] The recitals in the preamble to that measure record the desire to approximate the relevant provisions within the (then) European Economic Community concerning the production and distribution of proprietary medicinal products. They note that such approximation had necessarily to be achieved progressively and that priority was to be given to eliminating the disparities liable to have the greatest effect on the functioning of the common market. [6] To that end, Article 3 of Directive 65/65 imposed, for the first time, a requirement that no proprietary medicinal product could be placed on the market in a Member State unless an authorisation (a 'marketing authorisation') had been issued by the competent authority of that Member State.

5. Directive 75/319 [7] both amended the provisions concerning marketing authorisations for medicinal products and added new rules as regards the manufacture of those products. In particular, Article 16(1) obliged Member States to take all appropriate measures to ensure that the manufacture of proprietary medicinal products was subject to the holding of an authorisation (a 'manufacturing authorisation'). According to Article 16(2), such an authorisation was required for 'both total and partial manufacture' and 'the various processes of dividing up, packaging [and] presentation'. At the same time, that provision laid down a derogation from the requirement to obtain an authorisation for 'preparation, dividing up [and] changes in packaging or presentation' where those processes were 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.

6. Directive 87/22 [8] introduced a Community mechanism for concertation, prior to any national decision relating to a high-technology medicinal product, with a view to arriving at uniform decisions throughout the Community. The list of products to which that procedure applied included, at Annex A, medicinal products developed by means of recombinant DNA technology and by hybridoma and monoclonal antibody methods.

7. The next significant measure was Directive 89/341. [9] Article 1 of that measure amended Article 3 of Directive 65/65 so as to include in the requirement for a marketing authorisation what were termed 'industrially produced medicinal products which do not comply with the definition of a proprietary medicinal product'. The same provision laid down a specific exclusion in respect of, inter alia, medicinal products prepared on the basis of a magistral or officinal formula and permission was given to Member States to exclude certain medicinal products in order to fulfil 'special needs'.

8. Directive 92/25 [10] further extended the scope of the controls relating to medicinal products. To that end, Article 3(1) provided that a wholesale distributor of medicinal products required an authorisation (a 'distribution authorisation') to that effect, subject to the proviso laid down in Article 3(3) that possession of a manufacturing authorisation pursuant to Article 16 of Directive 75/319 was to be deemed to include an authorisation for wholesale distribution. The effect of that measure was thus to apply controls to the entire chain of distribution of medicinal products leading to their supply to the public. It thus completed the process started with the provisions governing marketing authorisations introduced by Directive 65/65. I shall,

however, mention two further enactments before completing this summary.

9. The first is Directive 93/39, [11] Article 1(1) of which amended Article 3 of Directive 65/65 by removing the reference to 'proprietary' medicinal products.

10. The second is Regulation No 2309/93. [12] The recitals in the preamble narrate that the experience acquired as a result of Directive 87/22 had shown that it was necessary to establish a centralised Community authorisation procedure ('the centralised procedure') for technologically advanced medicinal products, in particular those derived from biotechnology, and to provide for the orderly introduction of Community procedures for the authorisation of medicinal products alongside the national procedures of the Member States. [13] To that end, Article 3(1) of Regulation No 2309/93 provided that no medicinal products referred to in Part A of the Annex might be placed on the market within the Community unless a marketing authorisation had been granted by the Community in accordance with the provisions of the same regulation. The products listed in Part A of the Annex included medicinal products developed by means of recombinant DNA technology and by hybridoma and monoclonal antibody methods.

11. This brief summary shows that this is not an area in which the law stands still. Directive 65/65 was amended, extended or partially repealed by 11 instruments prior to its repeal and Directive 2001/83 has likewise been amended 12 times since its enactment. Changes to the centralised procedure have been less frequent, but Regulation No 2309/93 was modified three times before being superseded and Regulation No 726/2004 has been amended six times since coming into force. The result has been that piecemeal changes have often been 'bolted on' to the existing legislation in a manner that has not always been entirely coherent. The Court has already had occasion to note a lack of consistency in the use of terminology in Directive 2001/83. [14] In its observations in the present case, the Commission has pointed out differences between the language versions that risk giving rise to confusion. [15] The legislation at issue must, in my view, above all be interpreted purposively.

12. Having set out that background, I now turn to Directive 2001/83 and Regulation No 726/2004 themselves.

Directive 2001/83

13. Recital 2 in the preamble to the Directive states that *'the essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health'*.

14. According to recital 35, *'it is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Community through to supply to the public'*.

15. Article 2(1) provides:

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

16. Article 3 states:

'This Directive shall not apply to:

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

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

…'

17. By virtue of Article 5(1):

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

18. According to the first subparagraph of Article 6(1):

'No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with [Regulation No 726/2004] …'

19. The second subparagraph of Article 6(1) concerns, inter alia, variations to a medicinal product which has been granted an initial marketing authorisation. Such variations may either be the subject of a new authorisation in accordance with the first subparagraph or be included in the authorisation as originally granted.

20. Article 8(3) states that an application for an authorisation to place a medicinal product on the market is to be accompanied by the particulars set out in that provision. Those particulars include:

'…

(j) A summary … of the product characteristics, a mock-up of the outer packaging … and of the immediate packaging of the medicinal product [16] …

…'

21. Article 11 lists the information that the summary of the product characteristics referred to in Article 8(3)(j) is to contain. That list includes, at paragraph 6.5, 'nature and contents of container' and, at paragraph 6.6, 'special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate'.

22. According to Article 21(1), when a marketing authorisation is issued, the competent authorities of the Member State to whom the application was made are to inform the holder of the summary of the product characteristics as approved by them.

23. Article 40 forms part of Title IV, entitled 'Manufacture and importation'. It 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.'

24. Article 46 specifies the obligations imposed on the holders of manufacturing authorisations. They essentially concern the manufacturing process as such; and include a duty to comply with the principles of good manufacturing practice for medicinal products.

25. Article 77 obliges the Member States to ensure that the wholesale distribution of medicinal products [17] is subject to a distribution authorisation. The duties of those who hold such an authorisation are set out in Article 80.

Regulation No 726/2004

26. Article 1 provides:

'The purpose of this Regulation is to lay down Community procedures for the authorisation, supervision and pharmacovigilance of medicinal products for human ... use ...'

27. By virtue of Article 2, the definitions specified in Article 1 of the Directive are to apply for the purposes of the Regulation.

28. Article 3(1) states:

'No medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation.'

29. Articles 4 to 10 set out the procedure relating to applications for the authorisation of a medicinal product. Applications are to be submitted to the European Medicines Agency established under the Regulation, [18] which will delegate responsibility for the examination of the application to the Committee for Medicinal Products for Human Use. [19] Article 6(1) provides that each application is to include the particulars and documents referred to in, inter alia, Articles 8(3) and 11 of and Annex I to Directive 2001/83. Where the Committee's opinion is favourable to the granting of the authorisation, Article 9(4)(a) provides that a draft summary of the product characteristics, as referred to in Article 11 of the Directive, is to be annexed to that opinion. By virtue of Article 10(1), the Commission must prepare a draft of the decision to be taken in respect of the application; that draft is to include or make reference to the documents mentioned in points (a) to (d) of Article 9(4). The draft decision is to be forwarded to the Member States and the applicant. The Commission will thereafter take a final decision in accordance with the procedure laid down in Articles 10(2) and 87(3) of the Regulation.

30. Article 13(1) provides:

'Without prejudice to Article 4(4) and (5) of [Directive 2001/83], a marketing authorisation which has been granted in accordance with this Regulation shall be valid throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 6 of [Directive 2001/83].'

31. Article 16(1) obliges the holder of a marketing authorisation to take account of scientific and technical progress and to introduce any changes that may be required to enable the medicinal product to be manufactured by means of generally accepted scientific methods. The holder is to apply for the approval of any resulting variations in accordance with the Regulation.

32. The Annex to the Regulation is entitled 'Medicinal products to be authorised by the Community'. Paragraph 1 states:

'Medicinal products developed by means of one of the following biotechnological processes:
– recombinant DNA technology,
– controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
– hybridoma and monoclonal antibody methods.'
...'

33. The Regulation says nothing about manufacturing or distribution authorisations. These are governed exclusively by the Directive.

German law

34. Paragraph 21(1) of the Gesetz über den Verkehr mit Arzneimittel (Law on the marketing of medicinal products) requires that a marketing authorisation be in place under Directive 2001/83 or Regulation No 726/2004 in order for a medicinal product to be marketed. Paragraph 21(2) of the same law exempts, inter alia, products intended for delivery to pharmacies in possession of a prescription for a patient and products which are put into a container without being modified.

Facts and the question referred for a preliminary ruling

35. Novartis is the holder of a marketing authorisation delivered under Regulation No 726/2004 for 'Lucentis', which it sells within the EU. [20] That product is used for treating wet age-related macular degeneration ('AMD'), a debilitating disease of the retina. Its active substance is ranibizumab. [21] It is injected intravitreally, that is to say, directly into the eye. Novartis sells the product in vials containing 0.23 ml at a price of approximately EUR 1 200. The recommended dose is 0.05 ml. According to the instructions for use, the contents of the vial are to be drawn off into a 1 ml syringe (supplied with the product and authorised for its use), then, before injection, the quantity exceeding 0.05 ml is to be

ejected in order, according to those instructions, to prevent infiltration of bacteria. Thus, for each dose, 0.18 ml is discarded. The summary of product characteristics annexed to the marketing authorisation states that the vial is for single use only, that re-use may lead to infection and/or other illness or injury and that any unused medicinal product or waste material is to be disposed of in accordance with local requirements.

36. Avastin is a medicinal product for the treatment of certain types of cancer, which is distributed in Germany by Roche Pharma AG and in respect of which that company has a marketing authorisation issued under the Regulation. [22] Its active substance is bevacizumab. It has not been authorised for the treatment of AMD, but may none the less be used for that purpose, since its active substance is an inhibitor of the type of growth which leads to AMD. Prior to Lucentis becoming available to patients, there was no medicinal product on the market specifically designed for the treatment of that disease. The use of Avastin for that purpose continues notwithstanding the authorisation of Lucentis, since it may be purchased at a very much lower price. [23] Such use is permitted under German law with the consent of the patient. It is sold in vials of 4 ml and 16 ml. [24] The instructions for use provide that the concentrate contained in the vials should be diluted with saline solution and administered as an infusion. The summary of product characteristics annexed to the marketing authorisation states that Avastin is for single use only, since the product contains no preservatives, and that any unused product or waste material is to be disposed of in accordance with local requirements.

37. Apozyt produces pre-filled syringes, containing only the dose of the medicinal product in question which is necessary for a single injection. Those products include Lucentis and Avastin. For that purpose, Apozyt draws off the contents from the original vials into several sterile syringes which are then supplied throughout Germany for injection by a doctor. The product itself is not modified. Production occurs under sterile conditions and, according to Apozyt, in each case on the instructions of a pharmacy which has a doctor's prescription for a specific patient. Since the vials in question are stated in the summary of product characteristics forming part of the marketing authorisation to be for single use, [25] Apozyt's activities appear to contravene those authorisations. Apozyt has no separate authorisation for the products it markets.

38. Novartis has brought proceedings before the Landgericht Hamburg (Regional Court, Hamburg) in which it seeks, inter alia, an order prohibiting Apozyt from developing, placing on the market and offering for sale pre-filled syringes intended for the treatment of eye disease containing a portion only of Lucentis or Avastin. It does so on the basis that an authorisation under Article 3(1) of the Regulation is required in order to undertake the activities in question and that no such authorisation exists. The order for reference states that, if Novartis can establish that Apozyt's activities require a marketing authorisation, the rules of national competition law will require the national court to make an order in the form requested.

39. Apozyt argues that no such authorisation is required, since its activities do not result in the products being 'developed' for the purposes of the Annex to the Regulation.

40. The parties are in dispute before the national court as regards the safety of the products concerned as a result of Apozyt's processes. Novartis claims that the fact that the vials it markets contain more than the necessary dosage is due to production-related issues and is also intended to ensure the safe application of Lucentis. [26] It argues that effectiveness is not ensured if the product is used other than as intended in the instructions for use by medical experts. There is also a risk that bacteria may penetrate. Since neither Lucentis nor Avastin contains a preservative agent, problems could also arise in relation to shelf life. Apozyt maintains that safety may, in fact, be enhanced if the product is supplied in ready-to-use doses. In particular, the drawing-off into the syringe takes place at its premises under sterile conditions which do not necessarily exist at doctors' surgeries.

41. Since the national court is uncertain as to the proper construction to be given to Regulation No 726/2004, it has referred the following question for a preliminary ruling:

'Does the term "developed" in the introductory sentence of the Annex to [Regulation No 726/2004] extend to processes in which portions only of a medicinal product which has been developed and produced on a ready-to-use basis in accordance with the above procedures are drawn off into another container, after being prescribed and ordered at the time concerned by a doctor, if as a result of the process the composition of the medicinal product is not modified, and therefore in particular to the production of pre-filled syringes which have been filled with a medicinal product which is authorised under the Regulation?'

Analysis

The scope of Regulation No 726/2004

42. The Court is asked to construe the meaning of the term 'developed' in the introductory sentence of the Annex to Regulation No 726/2004. It is implicit in the question referred that the issue of whether Apozyt's activities require it to have a marketing authorisation can be decided on the basis of the Court's answer in that regard.

43. The Commission submits that, by asking its question in that way, the national court is misconstruing the nature of the Regulation as a legislative measure. Since its purpose is essentially procedural, consideration of its wording will not provide an answer to the substantive question which must be resolved in order for the national court to give a ruling in the dispute before it.

44. I agree.

45. Prior to the enactment of Regulation No 2309/93 [27] (the predecessor to Regulation No 726/2004) the position was, in summary, that the (then) Community rules governing the authorisation of medicinal products were contained exclusively in Directive 65/65, as amended. That was the case whatever the nature of the product concerned. There was, it is true, the requirement laid down by Directive 87/22 for concertation at Community level prior to taking national decisions in relation to a high-technology medicinal product, but there was no Community-wide authorisation procedure.

46. That procedure was introduced by Regulation No 2309/97 and has been carried forward to its successor, Regulation No 726/2004. Thus, in Title I ('Definitions and scope'), Article 1 of the latter provides that its purpose is 'to lay down Community procedures' for, inter alia, the authorisation of medicinal products for human use and to establish a European Medicines Agency. Article 3 goes on to provide that no medicinal product appearing in the Annex may be placed on the market in the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of the Regulation. The Annex, for its part, sets out a brief description of the types of products that are to be authorised under the centralised procedure. Leaving aside the provisions concerning veterinary medicinal products, with which this Opinion is not concerned, the remainder of the body of the Regulation essentially deals with the consequences that arise from the instigation of Community-wide rules for the authorisation of medicinal products. It does not, in other words, seek to establish new procedures going beyond those which are necessary having regard to its purpose.

47. I addressed the interrelationship between Directive 2001/83 and Regulation No 726/2004 in my Opinion in *Commission* v *Lithuania*, [28] where I observed that the two sets of rules cannot properly be read in isolation from one another, but must instead be considered together. The substantive requirements are set out in the Directive, while the Regulation contains rules that are essentially procedural. [29] I see no reason to change those views.

48. Given that the purpose of the Annex to Regulation No 726/2004 is to delineate those products that require authorisation under the centralised procedure, it can have no substantive effect. It serves as a point of reference in order to determine whether a product falls to be authorised under that procedure (failing which, the product will require authorisation under the national procedures legislated for by Directive 2001/83). But it does not determine whether a particular product, or a particular process applied to a product, requires authorisation as such.

49. While the above analysis may provide a technical answer to the national court's question, it does not provide a useful one. It is, however, settled case-law that, in the procedure laid down by Article 267 TFEU, it is for the Court of Justice to provide the national court with an answer which will be of use to it and enable it to determine the case before it. To that end, this Court may have to reformulate the question or questions referred to it. [30]

50. To that end, I propose reformulating the national court's question as follows:

'Where a medicinal product falling within paragraph 1 of the Annex to Regulation No 726/2004 has been developed and produced on a ready-to-use basis and has been granted a marketing authorisation specifying the containers in which the product is to be marketed, can a process which (1) involves portions only of that product being drawn off into another container, after being prescribed and ordered at the time concerned by a doctor, but which (2) does not involve any modification to the composition of the product, be carried out without requiring a separate marketing authorisation, or a variation of the existing marketing authorisation, under the Regulation?'

The scope and objectives of the legislation

51. The overarching requirement which must be satisfied if a medicinal product [31] is to be placed on the market in a Member State is laid down in the first subparagraph of Article 6 (1) of Directive 2001/83. In accordance with that provision, a marketing authorisation must first have been issued in respect of the product concerned, either under the Directive or in accordance with the procedure laid down under Regulation No 726/2004.

52. The second subparagraph of Article 6(1) of Directive 2001/83 makes it clear that the requirement to obtain authorisation covers not only the initial placing of the product on the market but also, essentially, *any modifications* to the product, including any 'additional … presentations, as well as any variations and extensions'. Article 16(1) of the Regulation also requires that variations to the product, as authorised, must be approved.

53. The extent of the obligation to have in place a marketing authorisation was confirmed by the Court in *Aventis Pharma*, [32] when it noted the requirement (in what are now Article 6(1) of the Regulation and Articles 8(3) and 11 of Directive 2001/83) that the application for authorisation be accompanied by the particulars and documents specified there and, in relation to the details concerning the packaging of the products, the associated objective that these were 'intended to protect consumers from being misled and thereby to protect public health'. [33] Those observations extend, I suggest, to all of the particulars and documents that must accompany the application.

54. That the legislation extends to all aspects of a medicinal product, as covered by its marketing authorisation, is therefore clear. At what point, though, do the obligations concerning the authorisation cease to apply? Can it, for example, be said that, since the first subparagraph of Article 6(1) of Directive 2001/83 refers to a medicinal product being 'placed on the market', a third party may then modify the product without requiring any form of authorisation? That the legislation is, in other words, spent once the product has reached the market place?

55. I do not believe that it can.
56. It is true that, as regards the related concept of goods being 'put on the market', the Court has held that the rights conferred by a trade mark in those goods are to be exhausted once the goods have been put into circulation for the first time. [34] It is also true that, in the context of medical devices, the legislature has defined 'placing on the market' by reference to the point at which a device is first made available on the market. [35]
57. It seems to me, however, that the present case is different. I have already noted the Court's view that the use of terminology in Directive 2001/83 is inconsistent. [36] To interpret the expression 'placed on the market' in a particular manner purely on the basis that it is defined in that way in *other* (relatively) closely-related legislation would not be satisfactory. Moreover, the expression is *not* defined in the legislation governing the authorisation of medicinal products, whilst it *is* so defined in that relating to medical devices. As regards the putting of goods on the market and the associated doctrine of the exhaustion of trade mark rights, the context is entirely different from the present one.
58. Here it seems to me that context is everything. Recital 35 in the preamble to Directive 2001/83 plainly states that 'it is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Community through to supply to the public'. In my view, the requirement that a marketing authorisation be in place (and thus, by definition, be complied with) does not cease at the point at which the product in question is *first* placed on the market (so that the terms of the authorisation could be disregarded thereafter). It is spent only when the marketing process can be said to have terminated. An authorisation must therefore be in place on *every* occasion on which the product concerned is made available on the market until the point at which that product has, in fact, been disposed of by being supplied to the public.
59. Any other interpretation would fail to satisfy the requirement that control be exercised over the entire chain of distribution.
60. It would also fail to reflect the general scheme of the legislation. By virtue of Article 6(1) of Directive 2001/83 and Article 16(1) of Regulation No 726/2004, the holder of a marketing authorisation in respect of a medicinal product is under a duty to apply to the competent authority for a new, or a modified, authorisation if he varies the product from the form in which it was authorised. For it to be possible for a third party to alter the equivalent product without being required to apply for an authorisation would make no sense.
61. I therefore consider that the first subparagraph of Article 6(1) of Directive 2001/83 falls to be interpreted so that it reads 'no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State … *and the product is marketed in accordance with that authorisation*'. Such an interpretation also accords with the 'essential aim' of the rules, as clearly expressed in recital 2, which 'must be to safeguard public health'.
62. It is, of course, possible that the activities carried out by a particular party fall within one of the exceptions provided for under the legislation and it is to these that I now turn.

The exceptions

Article 3(1) and (2) of Directive 2001/83

63. Article 3 of Directive 2001/83 sets out a series of situations to which the Directive does not apply. The first two paragraphs merit particular consideration. They apply to medicinal products 'prepared in a pharmacy'.
64. Article 3(1) excludes those products where the preparation in question is carried out in accordance with a medical prescription for an individual patient. By virtue of Article 3(2), a similar exclusion applies where preparation is undertaken in accordance with a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question. The purpose of the exceptions is clear. They remove from the complicated, not to say expensive, system of marketing authorisations the supply of medicinal products to the public in circumstances that arise, if not on a daily basis, at least regularly throughout the Member States. They presuppose that the preparation of the product in question will be carried out in a pharmacy – that is, by, or under the supervision of, a pharmacist. The public is therefore protected, in so far as preparation will be the responsibility of a qualified medical professional with expertise in the dispensing of the products concerned. The additional limitations imposed by those provisions ensure that the pharmacist is supplying the products on an individual basis. If that were not the case, there would be a risk that the preparation would not be carried out with the necessary degree of supervision.
65. Where a pharmacist is not involved, the exceptions laid down in Article 3(1) and (2) cannot apply.
66. Can it be argued that a further exception should be implied, so that the preparation of medicinal products on a non-industrial basis but not in a pharmacy should also fall outwith the application of Directive 2001/83 by virtue of those provisions?
67. I do not believe so.
68. Article 2(1) states that the Directive 'shall apply to medicinal products … either prepared individually or manufactured by a method involving an industrial process'. Article 3 then defines those medicinal products that can be described as *not* being so prepared. It is not intended that there should be some kind of 'gap' between the two provisions that falls to be filled by an implied exception of the kind I have just described.

Article 5(1) of Directive 2001/83

69. Article 5(1) of Directive 2001/83 provides that Member States may, in order to fulfil special needs, exclude from the application of the Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications

of an authorised health-care professional and for use by an individual patient under his direct personal responsibility. The Court has held that that provision applies only where there is no authorised equivalent on the national market or where the authorised product is unavailable on that market. [37] Since the activities at issue in the present case concern products that *are* available on that market, I shall not consider that exception further.

Article 40 of Directive 2001/83

70. Article 40(1) of Directive 2001/83 requires Member States to ensure that the manufacture of medicinal products manufactured within their territory be subject to a manufacturing authorisation. By virtue of the first subparagraph of Article 40(2), 'manufacturing' includes 'both total and partial manufacture and … the various processes of dividing up, packaging [and] presentation'.

71. The second subparagraph, however, exempts from the obligation to hold a manufacturing authorisation activities which involve the 'preparation, dividing up, changes in packaging or presentation', where those processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes. The Commission suggests that the exemption in question may be applicable in the present case.

72. The manufacturing authorisation forms part of the series of controls which the legislation lays down in the form (depending on the precise activity carried out) of requirements relating to manufacturing authorisations, distribution authorisations and marketing authorisations. Whilst there is a degree of overlap, inasmuch as the possession of a manufacturing authorisation will generally exempt the holder from the need to have a distribution authorisation in respect of the products concerned (although not vice versa), [38] the fact remains that the types of activity in question are essentially discrete.

73. In the present case, the national court's question is directed to the holding of a *marketing* authorisation. There seems to be no real doubt that the activities that are being challenged in the main proceedings extend to the marketing of the products in question. There is nothing in the legislation which provides that exemption from the requirement to hold a manufacturing authorisation automatically means that the person so exempted will not require to hold a marketing authorisation if, and to the extent that, he chooses to engage in that activity and is not exempted from the need to hold a marketing authorisation by some other provision. [39] For those reasons, it seems to me that the Commission's argument is fatally flawed.

Other considerations

Economic factors

74. Ireland notes the widespread use of 'drawing off' procedures in its health care system, particularly in hospital pharmacies. It points out that the use of those procedures in respect of AMD results in savings of at least EUR 2 million a year and invites the Court not to construe the legislation in a manner which it considers would lead to an unacceptable result.

75. Both Directive 2001/83 and Regulation No 726/2004 are drafted with a view to ensuring the safety of medicinal products. They are not concerned with economic factors, a point which is reinforced in recital 13 in the preamble to the Regulation, which refers to decisions being taken 'on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations'. As regards the Directive, in ***Commission v Poland*** the Court refused to take financial considerations into account when construing the derogation laid down in Article 5 (1) of the Directive. [40]

76. I would, however, add this. The derogation laid down in the second subparagraph of Article 40(2) of Directive 2001/83 excludes from the requirement to obtain a manufacturing authorisation, inter alia, dividing up or changing the packaging of a product, provided that such activities are carried out by pharmacists in dispensing pharmacies or by persons legally authorised to that effect in a Member State. They must also be undertaken solely for retail supply. It seems to me that that would include such activities where they are carried out on behalf of patients in a hospital pharmacy. As regards the obligation to be in possession of a marketing authorisation, Article 3(1) of the Directive exempts products which have been prepared in a pharmacy in accordance with a medical prescription for an individual patient. While I cannot express a concluded view, since the precise nature of the procedures concerned was not discussed in detail before the Court, it seems to me that the exemptions I have just described will, in the normal course, allow health care services to prepare medicines on behalf of individual patients, even if those activities would otherwise require a marketing authorisation to be in place.

The therapeutic freedom of medical practitioners

77. Ireland raises the issue of the therapeutic freedom of medical practitioners to prescribe for their patients as they, in their professional judgment, think most appropriate. That freedom, it argues, implies that medicinal products to which processes have been applied in the manner, for example, undertaken by Apozyt may be placed on the market without the requirement for an authorisation, provided that such activities are carried out against a prescription signed by a medical practitioner in respect of an individual patient.

78. Such an argument seems to me to be too widely expressed to be correct. It is true that medical practitioners' ability to prescribe for their patients as they best think fit is an important aspect of their professional freedom. Equally, however, that freedom is not unconstrained. Practitioners are likely to be restricted, for example, by the provisions of national legislation in the manner in which they may prescribe controlled narcotic drugs for their patients.

79. However, it seems to me that once a product has been validly placed on the market in accordance with the legislation, the fact that the authorisation has been granted in respect of a particular form of treatment will have no impact on the relationship between the medical practitioner and his client. The practitioner will thus be free, with his patient's consent as appropriate, to prescribe for him a product notwithstanding that the product has been authorised for an ailment other than that from which the patient is suffering. [41] The practitioner's therapeutic freedom to prescribe in the best interests of his patient is preserved.

Postscript: the competent authority for delivering marketing authorisations

80. I have referred above to the interrelationship of Directive 2001/83 and Regulation No 726/2004. [42] I have also noted that the marketing authorisation procedure extends to variations of the authorisation originally granted. Plainly, it seems to me, an entity which has been granted an authorisation under one procedure should make an application for a variation to the authority which delivered the first authorisation.

81. Where a different entity seeks to place on the market a product for human use which is the subject of an existing authorisation, but in a different form, the same reasoning should, in my view, apply. As I have explained, that legislation allocates the responsibility for delivering authorisations either centrally, under Regulation No 726/2004, or to the Member States, under Directive 2001/83. [43] It does so on the basis, in particular, that the expertise relating to products which fall to be authorised centrally under the Regulation will lie with the authority designated for that purpose under that measure rather than with the competent authorities of the Member States. It follows that such an entity should, in a procedure for application for a marketing authorisation, also deal with that authority. While it is true that Article 3(3) of the Regulation makes provision for certain generic products to be authorised under the Directive notwithstanding that the reference product on which they are based was authorised under the centralised procedure, that is an exception to the general rule, which applies only in respect of the simplified arrangements relating to that type of product. There is no reason to extend that exception.

Conclusion

82. In the light of all the foregoing considerations, I am of the opinion that the Court should answer the question raised by the Landgericht Hamburg to the following effect:

Where a medicinal product for human use falling within paragraph 1 of the Annex to Regulation No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency has been developed and produced on a ready-to-use basis and has been granted a marketing authorisation specifying the containers in which the product is to be marketed, a process which (1) involves portions only of that product being drawn off into another container, after being prescribed and ordered at the time concerned by a doctor, but which (2) does not involve any modification to the composition of the product, cannot be carried out without requiring a separate marketing authorisation, or a variation of the existing marketing authorisation, under the Regulation.

There is an exception to that rule where the provisions of Article 3(1) or (2) or Article 5(1) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use apply. However, Article 3(1) and (2) of the Directive will be inapplicable where the product in question is not prepared in a pharmacy and Article 5(1) will be applicable only where there is no authorised equivalent to the product concerned on the market of the Member State in question or where the product which is authorised is unavailable on that market. The exemption laid down in the second subparagraph of Article 40(2) of the Directive relates to manufacturing authorisations and does not apply to marketing authorisations in respect of those medicinal products.

1 – Original language: English.

2 – 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 most recently by Regulation (EU) No 1027/2012 of 25 October 2012 (OJ 2012 L 316, p. 38) ('Regulation No 726/2004' or 'the Regulation').

3 – 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 most recently by Directive 2012/26/EU of 25 October 2012 (OJ 2012 L 299, p. 1) ('Directive 2001/83' or 'the Directive').

4 – It is not my intention to conduct a full review of every item of legislation governing the authorisation of medicinal products. What follows is merely a description of those measures which are most relevant to the case in the main proceedings.

5 – Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ, English Special Edition 1965-1966, p. 20).

6 – See the 4th and 5th recitals in the preamble.

7 – Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ 1975 L 147, p 13).

8 – Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology (OJ 1987 L 15, p. 38).

9 – Council Directive 89/341/EEC of 3 May 1989 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ 1989 L 142, p. 11).
10 – Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use (OJ 1992 L 113, p. 1).
11 – Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products (OJ 1993 L 214, p. 22).
12 – Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (OJ 1993 L 214, p. 1).
13 – See the 2nd and 18th recitals in the preamble.
14 – See Case C-7/11 *Caronna* [2012] ECR I-0000, paragraph 32.
15 – The particular issue highlighted by the Commission involves the use, in the German language version of the word '*hergestellt*' in the introductory part of the wording in the Annex to Regulation No 726/2004, coupled with the use of the equivalent term '*Herstellung*' in Article 16 of the same regulation. Other language versions use different expressions. For example, the French language version uses the words '*issus de*' and '*fabrication*', respectively, while its English equivalent uses 'developed' in the introductory part of the Annex and 'manufacture' in Article 16. The German reader is thus encouraged to think that the two parts of the legislation may be linked, while French and English readers may be led to believe that no connection is intended.
16 – See the definitions of 'immediate packaging' and 'outer packing' in Article 1(23) and (24), respectively.
17 – As defined in Article 1(17).
18 – See Articles 1 and 4(1).
19 – Established under Article 5(1).
20 – The marketing authorisation was issued on 22 January 2007 under number EU/1/06/374/001.
21 – Both ranibizumab (for Lucentis) and bevacizumab (for Avastin) fall within the Annex to the Regulation, since they are medicinal products developed by means of recombinant DNA technology (first indent) and also by means of hybridoma and monoclonal antibody methods (third indent).
22 – The marketing authorisation was issued on 12 January 2005 under number EU/1/04/300/001. Roche Pharma is not a party to the main proceedings.
23 – Apozyt claims in its written observations that the use of its products results in a saving of approximately 50% with respect to the price of Lucentis.
24 – The order for reference does not provide details of the appropriate dose for Avastin. In its written observations, Ireland states that it understands that it ranges between 0.04 ml and 0.1 ml for the treatment of AMD.
25 – See points 22 and 29 above, as regards the Directive and the Regulation, respectively.
26 – The position as regards Avastin is unclear.
27 – Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (OJ 1993, L 214, p. 1).
28 – Case C-350/08 [2010] ECR I-10525.
29 – See points 90 and 92.
30 – See, inter alia, Case C-98/06 *Freeport* [2007] ECR I-8319, paragraph 31.
31 – As defined in Article 1(2) of Directive 2001/83. By virtue of Article 2 of Regulation No 726/2004, that definition will also apply for the purposes of the latter measure.
32 – Case C-433/00 [2002] ECR I-7761.
33 – Paragraphs 23 and 25. See also the Opinion of Advocate General Jacobs in that case at point 45, where he observed that 'a … marketing authorisation relates to more than the constituents of the medicinal product concerned'.
34 – See Case 3/78 *Centrafarm* [1978] ECR 1823, paragraph 11.
35 – See Article 1(2)(h) of Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, as amended (OJ 1990 L 189, p. 17), Article 1(2)(h) of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, as amended (OJ 1993 L 169, p. 1) and Article 1(2)(i) of Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices (OJ 1998 L 331, p. 1).
36 – See point 11 above.
37 – See, to that effect, Case C-185/10 *Commission* v *Poland* [2012] ECR I-0000, paragraph 36.
38 – See, now, Article 77(3) of Directive 2001/83.
39 – See point 76 below.
40 – Cited in footnote 37 above, paragraph 38.
41 – Indeed, it appears that the prescription of Avastin to treat patients suffering from AMD falls into this category: see point 36 above.
42 – See point 42 et seq. above.
43 – See point 48 above.