Case C-165/21

Request for a preliminary ruling

Date lodged:

11 March 2021

Referring court:

Københavns Byret (Denmark)

Date of the decision to refer:

24 November 2020

Applicant:

Orion Corporation

Defendant:

Lægemiddelstyrelsen

KØBENHAVNS BYRET

(COPENHAGEN DISTRICT COURT)
ORDER

made on 24 November 2020

Case BS-6241/2017-KBH

Orion Corporation
…
v
Lægemiddelstyrelsen (the Danish Medicines Agency)
…

Intervener: Teva Danmark A/S
…

and

Case BS-31735/2018-KBH

Orion Corporation
…
v
Lægemiddelstyrelsen
…

REQUEST FOR A PRELIMINARY RULING

pursuant to Article 19(3)(b) of the Treaty on European Union and Article 267 of the Treaty on the Functioning of the European Union. **[OR. p. 2]**

1. The dispute in the main proceedings and the relevant facts

1 The main proceedings before the referring court concern an issue relating to the validity of two marketing authorisations for generic medicines with the active substance ‘dexmedetomidine’ (dexmedetomidine hydrochloride), that were granted by the defendant, the Lægemiddelstyrelsen (the Danish Medicines Agency), which is the competent regulatory authority for medicinal products in Denmark.

2 Those authorisations were granted in accordance with the national rules transposing Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (‘the Medicinal Products Directive’).

3 The marketing authorisations at issue were both granted in accordance with the abridged procedure provided for in Article 10 of the Medicinal Products Directive, applying the decentralised procedure provided for in Article 28 thereof. One marketing authorisation was granted by the Danish State in its capacity as a reference Member State under Article 28(1) of the Medicinal Products Directive, whilst the other was granted by the Danish State in its capacity as Member State concerned under Article 28(5) thereof.

4 As a reference medicinal product for clinical and pre-clinical data, reference was made in the applications for both products to the Community marketing authorisation of 16 September 2011 for the medicinal product Dexdor, which is owned by the applicant, Orion Corporation.

5 However, as regards the calculation of the regulatory data protection period, reference was made to the medicinal product Precedex, which was authorised in the Czech Republic on 21 November 2002, before the Czech Republic became a member of the European Union, but after that product had received an unfavourable assessment from the European Medicines Evaluation Agency (EMEA) under the centralised procedure.

6 When granting the generic marketing authorisations at issue, the Lægemiddelstyrelsen relied on information provided by the Czech authorities showing that Precedex could be used as a reference medicinal product and provide the basis for a 'global marketing authorisation' under Article 6[(1)] of the Medicinal Products Directive, and therefore the data protection period for Dexdor should be calculated from 1 May 2004, when the Czech Republic acceded to the European Union.

7 In the main proceedings, Orion Corporation claims that Precedex does not satisfy the conditions for being a reference medicinal product within the meaning of the Medicinal Products Directive and cannot provide the basis for a global marketing authorisation with Dexdor, and therefore the data protection period **[OR. p. 3]** must be calculated only as from the authorisation of Dexdor on 16 September 2011.

8 The Lægemiddelstyrelsen, on the other hand, contends that it was entitled and required to rely on the information from the Czech authorities to establish that Precedex was authorised under the Medicinal Products Directive on 1 May 2004, when the Czech Republic acceded to the European Union, and Precedex could therefore be used as a reference medicinal product.

9 The following is stated regarding the course of events

10 Orion developed dexmedetomidine at the beginning of the 1990s. On 9 September 1994 Orion entered into an agreement with Abbott Laboratories ('Abbott') granting Abbott an exclusive licence to place dexmedetomidine on the market in countries which were members of the European Union at that time and in European countries outside the European Union.

11 On 18 December 1998 Abbott submitted to the European Medicines Evaluation Agency (EMEA) an application for a Community marketing authorisation for dexmedetomidine. In the application Abbott's product originally bore the trade name Primadex, but it was changed to Precedex for trade mark reasons.

12 With the application Abbott submitted the results of a number of clinical trials in support of the evaluation of the risks and benefits of Precedex. Information on the manufacture and quality of the product was provided through the 'European Drug Master File' ('EDMF') procedure since Abbott was not the producer of the medicinal product and therefore some commercially confidential and protected information, and expert assessments thereof, was provided directly by the producer (Fermion) to the EMEA in the form of a 'restricted part of the ASM'.

13 The application was assessed by the Committee for Proprietary Medicinal Products ('CPMP'), which expressed serious concerns about the clinical documentation.

14 In its preliminary assessment of the application at a meeting held from 18 to 20 May 1999, the CPMP expressed the view that the application should be

rejected in the light of the information provided since the risk-benefit balance was not positive. This assessment was repeated at a hearing before the CPMP held from 14 to 16 March 2000 at which Abbott was informed that all the members of the CPMP supported rejection of the application.

15 As a result of the CPMP's conclusions, Abbott withdrew its application on 15 March 2000 and subsequently abandoned attempts to obtain marketing authorisation in the European Union. **[OR. p. 4]**

16 On 29 August 2000 Abbott submitted an application for market authorisation in the Czech Republic, which was not a member of the European Union at that time. The dossier submitted by Abbott as a basis for the Czech application was, as regards the pre-clinical and clinical data, identical to the dossier submitted with the application to the EMEA. The Czech dossier contained no information on quality and manufacture or the pharmaceutical expert assessment thereof from the restricted part of the ASM in the EDMF.

17 In March 2002 Abbott returned to Orion the rights to market the product in the countries of the European Union at that time.

18 On 23 October 2002, the Czech agency for medicinal products, the SUKL, granted Abbott marketing authorisation for Precedex on the basis of the Czech rules at that time.

19 On 1 May 2004 the Czech Republic acceded to the EU. There is no information as to whether an updating of the dossier or a re-assessment of the marketing authorisation for Precedex was carried out at the time of the Czech Republic's accession to the EU.

20 In May 2004 Abbott transferred its rights under the licence agreement with Orion, including the Czech marketing authorisation, to Hospira Inc. According to the information provided, no Precedex has been sold in the Czech Republic since 2006.

21 After re-acquiring in 2002 the rights to market dexmedetomidine in the countries of the European Union at that time, Orion initiated a clinical programme to address the shortcomings which the CPMP had identified in Abbott's application for Precedex. On 18 December 2005, the Committee for Medicinal Products for Human Use (CHMP) confirmed to Orion that the centralised procedure could be used for Dexdor because Orion was able to show, in accordance with Article 3 of Regulation (EC) No 726/2004, that Dexdor constituted a 'significant therapeutic … innovation', and in the period between 2005 and 2010 Orion carried out inter alia three new phase III trials to address the shortcomings which the CPMP had identified in relation to Abbott's application for Precedex.

22 In September 2008 Hospira Inc. transferred the rights to dexmedetomidine in the countries which had acceded to the European Union after 2002, including the Czech Republic, to Orion, and therefore Orion then had the rights in all EU

countries. In July 2010 Orion abandoned the Czech marketing authorisation for Precedex.

23 In September 2010 Orion then submitted an application to the European Medicines Agency (EMA) for a Community market authorisation for dexmedetomidine under the name Dexdor. Orion's application for marketing authorisation for Dexdor received a positive assessment from the CHMP on 21 July 2011 and was authorised by Commission **[OR. p. 5]** decision of 16 September 2011. [The marketing authorisation] was granted by the European Commission with authorisation number EU/1/11/718/001-007 in accordance with the centralised procedure provided in 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 (Medicinal Products Regulation).

24 On 23 October 2015 Teva submitted an application for marketing authorisation for the product 'Teva' Dexmedetomidine in accordance with the decentralised procedure with the Czech Republic as the reference country and with, inter alia, Denmark as the Member State concerned. In the application, Dexdor was stated as the reference medicinal product with regard to the data on the product's safety and efficacy, whilst Precedex was stated as the reference medicinal product with regard to determining the expiry of the data protection period, and therefore it was to be calculated from 1 May 2004.

25 In the proceedings the Czech authorities concurred with that calculation of the data protection period since the Czech marketing authorisation for Precedex was, in their view, granted in accordance with EU law and Precedex and Dexdor were consequently covered by the same global marketing authorisation under the second subparagraph of Article 6(1) of the Medicinal Products Directive.

26 In a letter of 9 December 2015, Orion submitted objections to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) concerning the justification for using the marketing authorisation for Precedex as the starting point for the data protection period for Dexdor. Orion claimed that that period should instead be calculated on the basis of the central marketing authorisation for Dexdor as from 16 September 2011.

27 The CMDh addressed the issue at a meeting held from 14 to 16 December 2015. The Committee declared that Precedex and Dexdor had to be regarded as part of the same global marketing authorisation since the Czech authorities had stated that the national, Czech, marketing authorisation for Precedex was consistent with Community law in force and could therefore be used as a reference medicinal product within the meaning of Article 10 of the Medicinal Products Directive.

28 In addition to the application from Teva, the Lægemiddelstyrelsen examined an application submitted on 31 March 2016 for marketing authorisation for generic

dexmedetomidine from EVER Valinject GmbH. In that application Dexdor and Precedex were stated as reference medicinal products in the same way as in the Teva application. Unlike in the Teva application, in that application Denmark was stated as the reference Member State. **[OR. p. 6]**

29 As regards the calculation of the data protection period, in examining both applications the Lægemiddelstyrelsen relied on information from the Czech authorities. Therefore, in relation to both 'EVER Pharma' Dexmedetomidine and 'Teva' Dexmedetomidine, the Lægemiddelstyrelsen relied on the fact that the Czech Republic's market authorisation for Precedex was consistent with EU law as at 1 May 2004, and that the regulatory data protection period for Dexdor should be calculated from the Czech Republic's accession to the European Union on 1 May 2004.

30 On that basis, the Lægemiddelstyrelsen granted a marketing authorisation for 'Teva' Dexmedetomidine on 1 February 2017 and a marketing authorisation for 'EVER Pharma' Dexmedetomidine on 26 October 2017.

2. The relevant provisions of national and EU law

31 Marketing authorisations for medicinal products are governed by the Lægemiddelloven (Law on medicinal products), as codified by Lovbekendtgørelse (Consolidating Law) No 99 of 16 January 2016. That law provides inter alia as follows:

'Paragraph 7. A medicinal product may be marketed or supplied [in Denmark] only if a marketing authorisation has been granted either by the Sundhedsstyrelsen (Health Authority) pursuant to this law or by the European Commission pursuant to the provisions of EU law laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use etc. (Community marketing authorisation), subject to subparagraph 2 and Paragraphs 11 and 29 to 32.

Subparagraph 2. A medicinal product may be marketed online to users in other EU/EEA countries only if, in addition to being covered by a marketing authorisation as referred to in subparagraph 1, it is covered by a marketing authorisation valid in the country of destination in accordance with Article 6(1) of Directive 2001/83/EC or Article 6(1) of Directive 2001/82/EC.

Paragraph 8. Upon application, the Health Authority shall grant a marketing authorisation for a medicinal product where the risk-benefit balance of the medicinal product is favourable and, moreover, there are no grounds for refusal as referred to in Paragraphs 12 and 13.

Subparagraph 2. When weighing up the risk-benefit balance of a medicinal product, the positive therapeutic effects of the medicinal product shall be evaluated in relation to the risks with regard to the quality, safety and efficacy of

the medicinal product and risks of adverse effects on the environment, subject to Paragraph 12(2).'

32 The detailed provisions on consideration of applications for marketing authorisations for medicinal products etc. are to be found in bekendtgørelse (Order) No 1239 of 12 December 2005 on marketing authorisation for medicinal products etc. **[OR. p. 7]**

33 Paragraph 3 of that order lists the requirements applicable to the content of applications for marketing authorisations. It states inter alia:

'Paragraph 3. An application under Paragraph 8 of the Law on Medicinal Products must contain the following information and documents:

...

(10) The results of physico-chemical, biological or microbiological tests, pharmacological and toxicological tests and clinical trials.'

34 Paragraphs 9 to 17 of the order contain detailed provisions on generic medicines.

Paragraphs 9 to 10 state inter alia, as regards the requirements relating to toxicological, pharmacological and clinical documentation:

'Generic medicinal products

Paragraph 9. The applicant is not required to submit the toxicological, pharmacological and clinical documentation referred to in Paragraph 3(10) if the applicant can demonstrate that the medicinal product is a generic of a reference medicinal product that is authorised or has been authorised in Denmark or in another EU/EEA country for not less than eight years (the abridged procedure).

Subparagraph 2. A generic medicinal product authorised under subparagraph 1 may be marketed only after the expiry of a period of ten years from the date on which the marketing authorisation for the reference medicinal product was granted.

Subparagraph 3. In respect of applications under subparagraph 1 the applicant shall indicate the name of the Member State in which the reference medicinal product is authorised or has been authorised.

Paragraph 10. Reference medicinal product shall mean a medicinal product authorised under Paragraph 7 of the Law on medicinal products and Paragraph 3 of this Order.'

35 The Lægemiddelloven and Order No 1239 of 12 December 2005 implement 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

humans (Medicinal Products Directive). Under Article 6(1) of the Medicinal Products Directive:

'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 (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 1394/200.

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. **[OR. p. 8]** *All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).'*

36 Article 8(3)(i) of Directive 2001/83 provides that the application for marketing authorisation is to be accompanied by the results of pharmaceutical (physico-chemical, biological or microbiological) tests, pre-clinical (toxicological and pharmacological) tests, and clinical trials.

37 Article 10 of that directive provides:

'1. By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product

…

The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

2. For the purposes of this Article:

(a) "reference medicinal product" shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;

(b) "generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. ...

...'

38 Article 19(1) of the Medicinal Products Directive provides that, in order to examine the application submitted in accordance with Articles 8, 10, 10a, 10b and 10c, the competent authority of a Member State must verify whether the particulars submitted in support of the application comply with those articles and examine whether the conditions for issuing an authorisation to place medicinal products on the market are complied with.

39 According to Article 26(2) of that directive, marketing authorisation is to be refused if any particulars or documents submitted in support of the application do not comply with Articles 8, 10, 10a, 10b and 10c.

40 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 **[OR. p. 9]** and veterinary use and establishing a European Medicines Agency (Medicinal Products Regulation) contains rules on applications for Community marketing authorisation. Under Article 12(2) of that regulation:

'The refusal of a Community marketing authorisation shall constitute a prohibition on the placing on the market of the medicinal product concerned throughout the Community.'

3. Reason for the questions

41 It is apparent from the material in the file that in 2000 the EMEA considered that Precedex did not satisfy the conditions for authorisation in the European Union and therefore the application for it was withdrawn. It can further be concluded that in 2002 the Czech Republic authorised Precedex in accordance with the rules of national Czech law then in force and that the Czech Republic was not a member of the European Union at that time.

According to the information provided, this authorisation was maintained on the Czech Republic's accession to the European Union on 1 May 2004 without any updating. Therefore, there is clearly a conflict between the EMEA's evaluation and the Czech authorities' evaluation of the medicinal product.

42 Under Article 12[2] of the Medicinal Products Regulation, a refusal of a Community marketing authorisation is to constitute a prohibition on the placing on the market of the medicinal product concerned throughout the Community.

43 In addition, according to the EU Commission's guidelines entitled 'Notice to Applicants, Medicinal products for human use: Procedures for marketing authorisation', 5th edition, February 2007, (Chapter 2: Mutual Recognition, paragraph 2.3), the decentralised procedure cannot be applied to medicinal products where Community marketing authorisation has been applied for under the Medicinal Products Regulation and the applicant has, for example, withdrawn its application following the EMEA's evaluation of the data provided.

44 The referring court seeks to ascertain whether Article 12(2) of the Medicinal Products Regulation has relevance – and, if so, what relevance – to the use of the national Czech authorisation for Precedex as a reference medicinal product and the basis of a global marketing authorisation with Dexdor in the light of the previous negative evaluation of Precedex by the EMEA.

45 Furthermore, it follows from the judgment of the Court of Justice of 18 June 2009, *Generics*, Case C-527/07, EU:C:2009:379, that a medicinal product which was authorised only under the legislation in force in a country prior to its accession to the European Union and whose authorisation was never updated in accordance with Community law following the accession of the country concerned cannot be considered to be a reference medicinal product within the meaning of Article 10(2)(a). **[OR. p. 10]**

46 The referring court seeks to ascertain whether this in itself means that the national Czech authorisation for Precedex cannot be considered to be a reference medicinal product within the meaning of the Medicinal Products Directive, when that authorisation was never updated with, inter alia, the information and assessments in the restricted part of the ASM in the EDMF and in connection with or after the Czech Republic's accession to the European Union.

47 Finally, the referring court seeks to ascertain whether there may be restrictions – and, if so, what restrictions – on a national competent authority's power to verify whether a marketing authorisation issued in another Member State, before its accession to the European Union, can be used as a reference medicinal product in the abridged procedure under Article 10 of the Medicinal Products Directive.

48 In that connection, the referring court notes that it is clear from Article 19(1) of the Medicinal Products Directive, that, in order to examine the application submitted in accordance with Article 10(1), the competent authority of the Member State must examine whether the conditions for issuing a marketing authorisation are fulfilled. According to Article 26(2) of the Medicinal Products Directive, market authorisation must be refused if the information and documents submitted in support of the application do not comply with Article 10.

49 This means, according to the judgment of the Court of Justice of 14 March 2018 in Case C-557/16, *Astellas Pharma*, EU:C:2018:18, […], paragraph 29, that that the expiry of the data exclusivity period for the reference medicinal product is a precondition for the granting of a marketing authorisation for a generic medicinal product and that, in the decentralised procedure for marketing authorisations, compliance with that condition must be verified by all the Member States participating in that procedure. It is, therefore, for those Member States, after the application has been submitted, and in any event before the agreement of all parties is recorded, to oppose that application if that precondition is not satisfied.

50 It also appears to follow from the judgment in the abovementioned judgment in *Generics* (Case C-527/07), that the UK medicinal products authority was entitled to refuse use of the Austrian marketing authorisation as a reference medicinal product.

51 On the other hand, it is apparent from paragraphs 39 to 40 of the judgment of the Court of Justice in *Astellas Pharma* [C-557/16] that the holder of a marketing authorisation for a medicinal product that is used as a reference medicinal product for a generic medicine in accordance with a procedure under Article 10 of the Medicinal Products Directive has a right to effective judicial protection, but that does not mean that the holder of that marketing authorisation must be able to call into question [before the same national court] the validity of a marketing authorisation granted in another Member State. **[OR. p. 11]**

52 In this respect, the referring court wishes to ascertain whether paragraph 40 of the judgment in *Astellas Pharma* is to be interpreted as meaning that the national competent medicinal products authority is precluded from refusing the use of a national marketing authorisation from another Member State as a reference medicinal product where that marketing authorisation was granted before the Member State acceded to the European Union, under circumstances such as those in the main proceedings.

4. The questions referred

53 In the light of the foregoing, the following questions are referred to the Court of Justice for a preliminary ruling:

(1) In the light of Article 12(2) of Regulation No 726/2004 (formerly Article 12[2] of Regulation No 2309/1993) and Section 2.3 of Chapter 2 of the EU Commission's Notice to Applicants, can a medicinal product, such as Precedex at issue in this case, which was granted a marketing authorisation in a Member State in accordance with its national rules prior to the Member State's accession to the European Union, but after the medicinal product received a negative evaluation from the CPMP [now CHMP] under Regulation No 2309/1993 on the same clinical basis, in a situation where the national marketing authorisation has not been updated with new clinical documentation or related expert report, after the Member State's accession to the European Union, be considered to be a reference

medicinal product within the meaning of Article 10(2)(a) of Directive 2001/83 and can therefore provide the basis for a 'global marketing authorisation' under Article 6[1] of Directive 2001/83?

(2) Can a medicinal product, such as Precedex at issue in this case, which is authorised in a Member State under its national rules prior to the Member State's accession to the European Union, without the competent authority of the Member State having access to the restricted part of the ASM in the European Drug Master File procedure (now the Active Substance Master File procedure), in a situation where the national marketing authorisation has not been updated with the restricted part of the ASM after the Member State's accession to the European Union, be considered to be a reference medicinal product within the meaning of Article 10(2)(a) of Directive 2001/83 and can therefore provide the basis for a 'global marketing authorisation' under Article 6[1] of Directive 2001/83?

(3) Is the answer to Question 1 or 2 affected by the fact the national marketing authorisation concerned cannot provide the basis for mutual recognition under Article 28 of Directive 2001/83?

(4) Is the national competent authority of a reference Member State or a Member State concerned under the decentralised procedure provided for in Article 28 of Directive 2001/83 for a generic medicinal product, entitled or required **[OR. p. 12]** to refuse the use of a medicinal product as a reference medicinal product if the medicinal product in question is authorised in another Member State before its accession to the European Union, under the circumstances set out in Question 1 and/or 2?

(5) Is the answer to Question 4 affected by the fact that the national competent national authority of a reference Member State or Member State concerned had information showing that the medicinal product in question had received a negative evaluation from the CPMP under Regulation No 2309/1993 prior to authorisation in another Member State before that Member State's accession to the European Union?

…