Reports of Cases

JUDGMENT OF THE GENERAL COURT (Seventh Chamber, Extended Composition)

5 May 2021 *

(Medicinal products for human use – Application for marketing authorisation for a generic version of the medicinal product Tecfidera – Decision of the EMA not to validate the application for marketing authorisation – Previous decision of the Commission taking the view that Tecfidera – Dimethyl fumarate was not covered by the same global marketing authorisation as Fumaderm – Plea of illegality – Admissibility – Previously authorised combination medicinal product – Subsequent marketing authorisation for a component of the combination medicinal product – Assessment of the existence of two different global marketing authorisations – Manifest error of assessment)

In Case T-611/18,

Pharmaceutical Works Polpharma S.A., established in Starogard Gdański (Poland), represented by M. Martens and N. Carbonnelle, lawyers, and by S. Faircliffe, Solicitor,

applicant,

v

European Medicines Agency (EMA), represented by T. Jabłoński, S. Drosos and R. Pita, acting as Agents,

defendant,

supported by

European Commission, represented by A. Sipos and L. Haasbeek, acting as Agents,

and by

Biogen Netherlands BV, established in Badhoevedorp (Netherlands), represented by C. Schoonderbeek, lawyer,

interveners,

APPLICATION, first, for a declaration that the plea of illegality raised in respect of Commission Implementing Decision C(2014) 601 final of 30 January 2014 granting marketing authorisation for Tecfidera – Dimethyl fumarate, a medicinal product for human use, is admissible and well founded in so far as, in that implementing decision, the Commission considers that Tecfidera – Dimethyl fumarate is not covered by the same global marketing authorisation as Fumaderm, and, second, based on

* Language of the case: English.

Article 263 TFEU seeking annulment of the decision of the EMA of 30 July 2018 not to validate the application submitted by the applicant with a view to obtaining a marketing authorisation for a generic version of the medicinal product Tecfidera,

THE GENERAL COURT (Seventh Chamber, Extended Composition),

composed of R. da Silva Passos (Rapporteur), President, V. Valančius, I. Reine, L. Truchot and M. Sampol Pucurull, Judges,

Registrar: S. Spyropoulos, Administrator,

having regard to the written part of the procedure and further to the hearing on 13 July 2020,

gives the following

Judgment

I. Background to the dispute

1 The applicant, Pharmaceutical Works Polpharma S.A., is a pharmaceutical company that develops and markets various medicinal products, including generic medicinal products.

2 On 9 August 1994, the Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices; 'the BfArM') granted Fumapharm AG two marketing authorisations concerning two strengths of a medicinal product known as 'Fumaderm'. Fumaderm contains dimethyl fumarate ('DMF') and various monoethyl fumarate ('MEF') salts. First, Fumaderm prae, or Fumaderm initial, is intended to be used during a three-week initial phase to improve tolerance to treatment. It is available as tablets containing, inter alia, 30 mg of DMF, 67 mg of calcium MEF salt, 5 mg of magnesium MEF salt and 3 mg of zinc MEF salt. Second, Fumaderm is intended to be used at the end of the initial phase and is available as tablets containing, inter alia, 120 mg of DMF, 87 mg of calcium MEF salt, 5 mg of magnesium MEF salt and 3 mg of zinc MEF salt. Fumaderm is indicated for the treatment of psoriasis.

3 Those two marketing authorisations were successively transferred to Almirall Hermal GmbH, to Fumedica AG, and, finally, to Biogen Idec. In addition, in October 2003, Fumapharm granted Biogen Idec an exclusive licence to develop and market products containing DMF, then, in 2006, Biogen Idec acquired Fumapharm.

4 On 8 June 2011, Biogen Idec Ltd lodged with the European Medicines Agency (EMA) a request for eligibility for the grant of a marketing authorisation under the centralised procedure at EU level in accordance with Article 3(2)(b) 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). Article 3(2)(b) of Regulation No 726/2004 provides:

'Any medicinal product not appearing in the Annex [to Regulation No 726/2004] may be granted a marketing authorisation by the [Union] in accordance with the provisions of [that] Regulation, if … the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with [that] Regulation is in the interests of patients or animal health at [Union] level.'

5 The request referred to in paragraph 4 above concerned a product containing DMF and intended for the treatment of multiple sclerosis. In the letter that accompanied that request, Biogen Idec set out the following information. First, it stated that DMF was an active substance which had not previously been approved or assessed as a mono-substance, namely as a single component of a medicinal product, for any indication. Second, it stated that it intended to submit a 'full' application for marketing authorisation, that is to say, an application accompanied by all the data referred to in 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) and, in particular, the results of pre-clinical tests and clinical trials. Third, it stated that it was the holder of the marketing authorisation granted to Fumapharm in 1994 for Fumaderm, which contained DMF and MEF salts (see paragraph 2 above).

6 In those circumstances, first, Biogen Idec requested confirmation that the product for which it sought a marketing authorisation and which contained DMF did not fall within the scope of the global marketing authorisation for Fumaderm within the meaning of the second subparagraph of Article 6(1) of Directive 2001/83.

7 Article 6(1) of Directive 2001/83 provides:

'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 …

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. 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).'

8 Article 10(1) of Directive 2001/83 provides:

'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 [European Union].

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 first subparagraph shall also apply if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.

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.'

9 Second, and in the light of the foregoing, Biogen Idec, on 8 June 2011, also requested the EMA to confirm that, if it was approved on the basis of a full application, the product for which it sought a marketing authorisation would benefit from the data-protection period provided for in Article 14(11) of Regulation No 726/2004, irrespective of whether or not the active substance it contained, DMF, was classified as a 'new active substance'.

10 Article 14(11) of Regulation No 726/2004 provides:

'Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an eight-year period of data protection and a ten-year period of marketing protection, in which connection the latter period shall be extended to a maximum of 11 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.'

11 On 21 July 2011, the Committee for Medicinal Products for Human Use ('the CHMP'), established by Article 5(1) of Regulation No 726/2004, considered that Biogen Idec's product, containing DMF, was eligible for submission of an application for marketing authorisation under the centralised procedure on the ground that it constituted a significant therapeutic innovation within the meaning of Article 3(2)(b) of Regulation No 726/2004 (see paragraph 4 above).

12 By letter dated 3 August 2011, the EMA informed Biogen Idec that the CHMP considered that its product, containing DMF, was eligible for submission of an application for marketing authorisation under the centralised procedure. In that letter, the EMA explained that the authorisation for a combination medicinal product was not regarded as being covered by the global marketing authorisations for the different individual active substances in accordance with Article 6(1) of Directive 2001/83. The EMA added that, in the light of that assessment and the fact that a full development had been carried out by the applicant for its product containing DMF, the medicinal product at issue would, in principle, benefit from the data exclusivity provided for in Article 14(11) of Regulation No 726/2004, irrespective of whether or not the active substance was classified as a 'new active substance'.

13 On 28 February 2012, Biogen Idec submitted to the EMA an application for marketing authorisation for Tecfidera – Dimethyl fumarate ('Tecfidera – Dimethyl fumarate' or 'Tecfidera'), a medicinal product for human use, in accordance with Article 4(1) of Regulation No 726/2004. That application for marketing authorisation contained all the data referred to in Article 8(3) of Directive 2001/83. In that application, Biogen Idec stated, in essence, that Tecfidera was indicated for the treatment of multiple sclerosis. That application concerned gastro-resistant capsules containing 120 mg and 240 mg of DMF. The proposed dose consisted in a starting dose of 120 mg twice a day for seven days and then increasing that dose to reach the recommended dose of 240 mg twice a day. Moreover, in the form accompanying its application, Biogen Idec declared that its application concerned a known active substance and did not declare that Tecfidera contained a new active substance that had never been authorised in the European Union.

14 On 21 March 2013, in the light of all the data provided and the scientific discussions that had taken place within its organisation, the CHMP gave a positive opinion recommending that Tecfidera be granted a marketing authorisation.

15 Following that opinion, Biogen Idec contacted the European Commission and requested that the decision granting marketing authorisation indicate that the data exclusivity provided for in Article 14(11) of Regulation No 726/2004 applied to Tecfidera, in accordance with the position expressed by the EMA in its letter of 3 August 2011 (see paragraph 12 above).

16 On 16 May 2013, a meeting was held between the Commission and Biogen Idec. At that meeting, the Commission noted that, in the decisions granting marketing authorisation, no statement was made with regard to data exclusivity, on the ground that data exclusivity was a dynamic concept subject to change in the event of a transfer of assets between companies. The Commission added that the decisions granting marketing authorisation contained only, on the basis of the scientific assessment carried out by the CHMP, a statement regarding 'new active substance' status within the meaning of point 3 of Part II of Annex I to Directive 2001/83. That point provides, inter alia, that, 'where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the pharmaco-kinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/efficacy profile shall be [provided]' and that, 'should this not be the case, this association shall be considered as a new active substance'. Moreover, the Commission expressed reservations with regard to the EMA's interpretation concerning data exclusivity for Tecfidera, irrespective of 'new active substance' status (see paragraph 12 above). Accordingly, the Commission told Biogen Idec that it had a choice. On the one hand, Biogen Idec could have allowed the Commission to adopt a decision granting marketing authorisation without a statement on 'new active substance' status. Since that subject was not addressed in the CHMP's assessment report, if an application for marketing authorisation for a generic version of Tecfidera were validated, Biogen Idec would have to defend its case before the courts. On the other hand, Biogen Idec could have sent a request to the Commission asking it to suspend the process of adopting the decision granting marketing authorisation and request an assessment of 'new active substance' status. The Commission stated that that process could take a long time and emphasised that it was impossible to predict the outcome of the scientific assessment. In conclusion, the Commission requested Biogen Idec to inform it of its preference as soon as possible.

17 By letter to the EMA of 17 May 2013, the Commission stated, inter alia, that its decision granting marketing authorisation for Tecfidera could not include a statement regarding 'new active substance' status in the present case as the matter had not been addressed in the CHMP's assessment report.

18 By letter of 18 September 2013 to the Chair of the CHMP, the Commission stated that Biogen Idec had requested that the question of whether the active substance DMF could be classified as a new active substance be analysed. Moreover, the Commission stated that a new active substance was defined as a chemical substance that had not previously been authorised as a medicinal product in the European Union. In that regard, it referred to Annex I to the 'Notice to applicants, Volume 2A, Procedures for marketing authorisation, Chapter 1, Marketing authorisations' ('the Notice to Applicants') in the version of June 2013. Furthermore, it noted that DMF had not previously been authorised as a medicinal product in the European Union, but was part of the medicinal product Fumaderm, which had been authorised in Germany in 1994. Therefore, in order to assess whether DMF was a new active substance, the Commission requested the CHMP to assess whether DMF differed from Fumaderm, which contained DMF and MEF salts. Accordingly, the Commission requested the CHMP to reconsider its assessment report with a view to including an assessment of the DMF in Tecfidera in the light of the 'new active substance' status.

19 On 23 September 2013, the EMA received the request from Biogen Idec for the DMF in Tecfidera to be classified as a 'new active substance'.

20 In an assessment report dated 9 October 2013 on the 'new active substance' status of the DMF in Tecfidera, a CHMP rapporteur took the view that DMF differed from Fumaderm, which contained DMF and MEF. However, for reasons of consistency with previous similar cases, the rapporteur requested the opinion of the Quality Working Party, that is, a permanent working group that, inter alia, provides advice to the CHMP on the quality of medicinal products, with regard to whether or not DMF and MEF could be considered to be derivatives of each other.

21 In a second assessment report dated 9 October 2013, the CHMP's co-rapporteur concluded that Tecfidera, which contained DMF, differed from Fumaderm, which contained DMF and MEF. However, he requested the opinion of the Quality Working Party in order to ascertain whether the latter agreed, first, that DMF and MEF were chemically different and, second, that DMF and MEF were not derivatives of each other.

22 In a joint report dated 18 October 2013, the CHMP's rapporteur and co-rapporteur (together, 'the rapporteurs') considered that additional information had to be provided in support of the argument that DMF differed from Fumaderm, which contained DMF and MEF. In those circumstances, the rapporteurs raised a number of objections with Biogen Idec. First, they took the view that Biogen Idec had to justify why MEF and DMF could not be regarded as esters and derivatives of one another. Second, they requested Biogen Idec to address potential significant differences in terms of safety and/or efficacy, from the point of view of their properties, between the DMF in Tecfidera, on the one hand, and the mixture of DMF and MEF salts contained in Fumaderm, on the other.

23 At a meeting on 24 October 2013, the CHMP raised two major objections to the request for DMF to be awarded 'new active substance' status. Those objections concerned, first, establishing whether DMF and MEF were esters or derivatives of one another and, second, addressing the relevant clinical differences in terms of safety and/or efficacy between DMF, on the one hand, and DMF combined with MEF, on the other.

24 On 4 November 2013, Biogen Idec provided its responses to the objections raised by the CHMP.

25 In a joint report dated 11 November 2013, the rapporteurs analysed Biogen Idec's responses and considered that the active substance DMF contained in the medicinal product Tecfidera could not be classified as a 'new active substance', on the ground that it was not clear from the data provided that DMF's properties differed significantly, in terms of safety and/or efficacy, from the product Fumaderm, which was already authorised and contained a mixture of DMF and MEF salts.

26 On 21 November 2013, the CHMP delivered an opinion that was revised in relation to the opinion that had been adopted on 21 March 2013 (see paragraph 14 above). In that revised opinion, the CHMP noted that, in the Commission's request of 18 September 2013 to have the status of the DMF in Tecfidera as a 'new active substance' assessed (see paragraph 18 above), the Commission had stated, first, that a 'new active substance' within the meaning of Directive 2001/83 was a chemical substance which had not previously been authorised as a medicinal product in the European Union, and, second, that DMF formed part of the medicinal product Fumaderm, which was authorised in Germany in 1994, but had not previously been authorised as a medicinal product in the European Union.

27 In the same opinion, the CHMP, pursuant to Article 7 of Regulation No 726/2004, recommended, by consensus, that a marketing authorisation be granted for Tecfidera. Moreover, on the basis of an examination of the scientific evidence and in line with the clarification provided by the Commission on 18 September 2013 (see paragraph 18 above), the CHMP took the view that DMF differed from Fumaderm, which contained DMF and MEF salts. The CHMP inferred from this that the active substance in Tecfidera, DMF, was a 'new active substance'.

28 On 26 November 2013, the CHMP adopted the European Public Assessment Report ('the EPAR') for Tecfidera. The EPAR was published in accordance with Article 13(3) of Regulation No 726/2004. It contains a summary, written in a manner that is understandable to the public, of the characteristics of the medicinal product, together with the reasons for the CHMP's opinion in favour of granting marketing authorisation. The EPAR for Tecfidera comprises four parts. In the first part, the CHMP set out the background to the procedure. In the second part, the CHMP conducted a scientific discussion concerning, inter alia, qualitative aspects, non-clinical aspects, clinical aspects and the 'new active substance' status of the DMF contained in Tecfidera. In the third part, the CHMP assessed the risk-benefit ratio of Tecfidera and concluded that that ratio was positive for the treatment of 'patients suffering from relapsing-remitting multiple sclerosis'. In the fourth part, the CHMP recommended that a marketing authorisation be granted subject to certain conditions.

29 With regard specifically to the 'new active substance' status of the DMF in Tecfidera, the CHMP noted the clarification provided by the Commission on 18 September 2013 referred to in paragraph 18 above. Moreover, the CHMP highlighted that, to assess whether DMF differed from Fumaderm, which contained DMF and MEF salts, it had taken into consideration Article 10(2)(b) of Directive 2001/83, which provides, inter alia, that 'the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy'. Lastly, the CHMP considered that MEF and DMF were both active and were not the same active substance, since they did not share the same therapeutic moiety. In that regard, the CHMP referred to point 3 of Part II of Annex I to Directive 2001/83, referred to in paragraph 16 above. The CHMP inferred from this that there was no need for further investigation concerning potential significant differences with regard to the safety/efficacy profile. The CHMP concluded that the active substance in Tecfidera, DMF, was a new active substance.

30 On 19 December 2013, the Commission submitted a draft implementing decision granting marketing authorisation for 'Tecfidera – Dimethyl fumarate', a medicinal product for human use, to the Standing Committee on Medicinal Products for Human Use, established by Article 121(1) of Directive 2001/83 and referred to in Article 87(1) of Regulation No 726/2004, in order to receive an opinion from that committee by written procedure.

31 On 10 January 2014, one of the members of the Standing Committee on Medicinal Products for Human Use requested that a plenary meeting of that committee be held in accordance with Article 10(3)(c) of Regulation No 726/2004. That member agreed that a marketing authorisation should be granted for Tecfidera on the basis of the risk-benefit ratio. However, he disagreed with the assessment that the DMF in Tecfidera was a new active substance, since DMF was already used – in combination with another active substance – in Fumaderm. Despite that disagreement, he considered that Tecfidera was covered by a new global marketing authorisation, since it would not have constituted an additional strength, pharmaceutical form, administrative route or presentation of Fumaderm, or an extension thereof.

32 On 28 January 2014, a plenary meeting of the Standing Committee on Medicinal Products for Human Use was held in Brussels (Belgium) in order to discuss the draft Commission implementing decision granting marketing authorisation under Regulation No 726/2004 for 'Tecfidera – Dimethyl fumarate', a medicinal product for human use.

33 At that meeting, many members expressed the view that 'new active substance' status could not apply to a substance that was already included in a medicinal product that had already been authorised and that, consequently, DMF was not a new active substance.

34 In those circumstances, recital 3 of the draft Commission implementing decision was amended in order, first, to remove the reference to 'new active substance' status and, second, to state the fact that the application for marketing authorisation for Tecfidera was based on Article 8(3) of Directive 2001/83. The Standing Committee on Medicinal Products for Human Use then gave a positive opinion on that amended draft.

35 On 30 January 2014, the Commission adopted Implementing Decision C(2014) 601 final granting marketing authorisation under Regulation No 726/2004 for 'Tecfidera – Dimethyl fumarate', a medicinal product for human use ('the implementing decision of 30 January 2014'). A summary of that implementing decision was published in the *Official Journal of the European Union* on 28 February 2014 (OJ 2014 C 59, p. 1).

36 In recital 1 of the implementing decision of 30 January 2014, the Commission states that the medicinal product Tecfidera – Dimethyl fumarate complies with the requirements of Directive 2001/83.

37 In recital 2 of that implementing decision, the Commission states that it is therefore appropriate to authorise its placing on the market.

38 Recital 3 of that implementing decision is worded as follows:

'[DMF], the active substance of "Tecfidera – Dimethyl fumarate", is part of the composition of the authorised medicinal product Fumaderm which [consists] of DMF and calcium salt of ethyl fumarate, magnesium salt of ethyl hydrogen fumarate and zinc salt of ethyl hydrogen fumarate (MEF salts), belonging to the same marketing authorisation holder. The Committee for Medicinal Products for Human Use concluded that MEF and DMF are both active and are not the same active substance since they do not share the same therapeutic moiety. Therefore, it is considered that Tecfidera containing DMF is different from Fumaderm the other already authorised medicinal product composed of DMF and MEF salts. Therefore "Tecfidera – Dimethyl fumarate", the application of which was based on Article 8(3) of Directive 2001/83/EC, and the already authorised medicinal product Fumaderm do not belong to the same global marketing authorisation as described in Article 6(1) of Directive 2001/83/EC.'

39 Following the adoption of the implementing decision of 30 January 2014, a note was added to the EPAR (see paragraph 28 above) in order to indicate that, 'in view of [the] evolution of the regulatory considerations, as reflected in [recital 3] of the [implementing decision of 30 January 2014], the final statement in the CHMP opinion that "the active substance of Tecfidera, namely dimethyl fumarate, [was] a new active substance" [was] obsolete'. However, the CHMP stated that all the other scientific considerations and conclusions relating to its assessment remained valid.

40 On 22 June 2015, the applicant submitted a request to the BfArM for access to documents under the relevant German law. That request concerned, in essence, all the documents held by the BfArM relating to the application for marketing authorisation for the medicinal product Fumaderm. On 20 February 2017, the BfArM rejected that request on the ground that the information to which access was requested came under Biogen Idec's trade and business secrets and Biogen Idec was opposed to such access.

41 On 22 November 2017, the applicant sent a new request to the BfArM for access to documents. That request concerned all the documents held by the BfArM relating to the application for marketing authorisation for the medicinal product Fumaderm. That request for access to documents also concerned a product called Panaclar 120 mg, which was intended to treat psoriasis. That product had been the subject of an application for marketing authorisation which had been filed in 2005 by Fumapharm with the BfArM and which had subsequently been withdrawn.

42 On 27 November 2017, the applicant submitted a request to the EMA. By that request, it sought confirmation that it was eligible to submit an application for marketing authorisation under the centralised procedure in accordance with Article 3(3) of Regulation No 726/2004 for a generic medicinal product known as Dimethyl Fumarate Pharmaceutical Works Polpharma. Article 3(3) of Regulation No 726/2004 provides that a generic medicinal product of a reference medicinal product authorised by the European Union may, under certain conditions, be authorised by the competent authorities of the Member States in accordance with, inter alia, Directive 2001/83.

43 By letter of 14 December 2017, the EMA acknowledged receipt of the request referred to in paragraph 42 above. Moreover, it informed the applicant that, on the basis of the documentation provided, Dimethyl Fumarate Pharmaceutical Works Polpharma was eligible for submission of an application for marketing authorisation under the centralised procedure in accordance with Article 3(3) of Regulation No 726/2004. Furthermore, the EMA noted that the applicant's application for marketing authorisation would be accepted only after the expiry of the data-protection period, under Article 14(11) of Regulation No 726/2004, granted for the reference medicinal product 'Tecfidera', which had received an initial marketing authorisation on 30 January 2014. In that regard, the EMA referred to the implementing decision of 30 January 2014 (see paragraph 35 above). The EMA explained that, in that implementing decision, the Commission had considered that 'Tecfidera – Dimethyl fumarate', on the one hand, and the already authorised medicinal product known as Fumaderm, on the other, did not belong to the same global marketing authorisation within the meaning of the second subparagraph of Article 6(1) of Directive 2001/83 (see paragraph 7 above). In its letter of 14 December 2017, the EMA also noted that no rapporteur appointment would be made before it was possible to submit an application for marketing authorisation. Lastly, the EMA requested the applicant to inform it, no later than seven months beforehand, of its intention to submit an application for marketing authorisation in view of the data-protection period for Tecfidera.

44 On 19 March 2018, the BfArM rejected the request for access to documents referred to in paragraph 41 above.

45 By letter of 22 March 2018, the EMA referred to the applicant's letter of 27 November 2017 (see paragraph 42 above) and informed it that, during a meeting in March 2018, the CHMP and the Pharmacovigilance Risk Assessment Committee had jointly appointed a rapporteur for each of them.

46 On 19 April 2018, the applicant brought an appeal against the BfArM's decision referred to in paragraph 44 above, by which the BfArM had rejected the applicant's request for access to documents.

47 On 27 June 2018, the applicant submitted to the EMA an application for marketing authorisation for a generic medicinal product derived from Tecfidera. That application was amended on 5 and 18 July 2018. It concerned gastro-resistant capsules containing 120 mg and 240 mg of DMF. It was based on Article 10(1) of Directive 2001/83, which provides for the submission of an application for marketing authorisation under an 'abridged' procedure (see paragraph 8 above).

48 By letter of 11 July 2018, the EMA asked the applicant to provide additional information.

49 On 18 July 2018, the applicant replied to the EMA's request.

50 By letter of 30 July 2018 ('the contested decision'), the EMA stated, inter alia, that, according to recital 3 of the implementing decision of 30 January 2014, 'Tecfidera – Dimethyl fumarate', on the one hand, for which the application for authorisation was based on Article 8(3) of Directive 2001/83, and the already authorised medicinal product 'Fumaderm', on the other, did not belong to the same global marketing authorisation in accordance with Article 6(1) of Directive 2001/83, on the ground that MEF and DMF were both active and were not the same active substance since they did not share the same therapeutic moiety. Moreover, the EMA noted that, in accordance with Article 14(11) of Regulation

No 726/2004, without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with the provisions of that regulation are to benefit from an 8-year period of data protection and a 10-year period of marketing protection. Thus, the EMA considered that Tecfidera clearly benefited from its own independent eight-year period of data protection and that that protection period had not yet expired. In view of those findings, the EMA stated that the reference to data relating to the pre-clinical tests and clinical trials set out in the Tecfidera dossier was not currently authorised for the purpose of submitting an application for marketing authorisation under Article 10(1) of Directive 2001/83. The EMA concluded that it was unable to validate the applicant's application for the grant of a marketing authorisation for a generic medicinal product derived from Tecfidera.

51 On 8 October 2018, the BfArM dismissed the appeal brought by the applicant, referred to in paragraph 46 above, in so far as that appeal concerned the documents relating to the marketing authorisation for Fumaderm.

II. Procedure and forms of order sought

52 By application lodged at the Court Registry on 9 October 2018, the applicant brought the present action.

53 The EMA lodged its defence on 17 January 2019.

54 By documents lodged at the Court Registry on 21 December 2018 and 31 January 2019 respectively, Biogen Netherlands BV, namely the company to which the marketing authorisation for Tecfidera had been transferred ('Biogen'), and the Commission applied for leave to intervene in support of the form of order sought by the EMA.

55 By letters of 5, 7 and 25 February 2019, the EMA requested confidential treatment, vis-à-vis Biogen and the Commission, of certain information in the annexes to the defence.

56 The applicant lodged its reply on 11 March 2019.

57 By orders of the President of the Ninth Chamber of the General Court of 19 March 2019, Biogen and the Commission were granted leave to intervene in support of the form of order sought by the EMA. The decision on the merits of the requests for confidential treatment was reserved.

58 The EMA lodged its rejoinder on 29 April 2019.

59 On the basis of the non-confidential versions of the procedural documents, Biogen and the Commission lodged their statements in intervention on 16 and 17 May 2019 respectively.

60 The EMA and the applicant lodged their observations on the statements in intervention on 21 and 24 June 2019 respectively.

61 Following a change in the composition of the Chambers of the General Court, the Judge-Rapporteur was assigned, with effect from 4 October 2019, to the Seventh Chamber, to which the present case was consequently allocated, pursuant to Article 27(5) of the Rules of Procedure of the General Court.

62 Acting on a proposal from the Seventh Chamber, the Court decided, pursuant to Article 28 of the Rules of Procedure, to refer the case to a Chamber sitting in extended composition.

63 Acting on a proposal from the Judge-Rapporteur, the Court (Seventh Chamber, Extended Composition) decided to open the oral part of the procedure and, by way of the measures of organisation of procedure provided for in Article 89 of the Rules of Procedure, requested the parties to reply to a number of written questions and to produce certain documents. The parties complied with those requests within the prescribed periods.

64 After the hearing initially scheduled for 7 May 2020 was postponed, the parties presented oral argument and replied to the oral questions put by the Court at the hearing on 13 July 2020.

65 The applicant claims that the Court should:

– declare that the plea of illegality that it raises in respect of the implementing decision of 30 January 2014 is admissible and well founded in so far as, in that implementing decision, the Commission considers that 'Tecfidera – Dimethyl fumarate' is not covered by the same global marketing authorisation as Fumaderm;

– annul the contested decision;

– order the EMA to pay the costs.

66 The EMA contends, in essence, that the Court should:

– reject as inadmissible the plea of illegality directed against the implementing decision of 30 January 2014;

– in any event, dismiss the action for annulment as unfounded in its entirety;

– order the applicant to pay all the costs of the present proceedings.

67 The Commission contends that the Court should:

– reject as inadmissible the plea of illegality directed against the implementing decision of 30 January 2014 and, consequently, dismiss the action as unfounded;

– in any event, reject the plea of illegality directed against the implementing decision of 30 January 2014 as unfounded and, consequently, dismiss the action as unfounded.

68 Biogen contends that the Court should:

– reject as inadmissible the plea of illegality directed against the implementing decision of 30 January 2014;

– in any event, dismiss the action as unfounded in its entirety;

– order the applicant to pay the costs of the present proceedings, including those incurred by Biogen.

III. Law

69 By its first head of claim, the applicant requests the Court to declare that the plea of illegality that it raises in respect of the implementing decision of 30 January 2014 is admissible and well founded. By its second head of claim, the applicant requests the Court to annul the contested decision.

A. The first head of claim, seeking a declaration by the Court that the plea of illegality raised in respect of the implementing decision of 30 January 2014 is admissible and well founded

70 Under Article 277 TFEU, any party may, in proceedings in which an act of general application adopted by an institution, body, office or agency of the Union is at issue, plead the grounds specified in the second paragraph of Article 263 TFEU in order to invoke before the Court of Justice of the European Union the inapplicability of that act.

71 Article 277 TFEU gives expression to a general principle conferring upon any party to proceedings the right to challenge incidentally, with a view to obtaining the annulment of a decision addressed to that party, the validity of acts of general application which form the legal basis of that decision (see, to that effect, judgments of 6 March 1979, *Simmenthal* v *Commission*, 92/78, EU:C:1979:53, paragraph 39, and of 19 January 1984, *Andersen and Others* v *Parliament*, 262/80, EU:C:1984:18, paragraph 6).

72 The finding of illegality made by the court does not have *erga omnes* effect, but entails the illegality of the individual contested decision, whilst leaving the act of general application in the legal order without affecting the legality of other acts which have been adopted pursuant thereto and which were not challenged within the period for appeal (see judgment of 25 October 2018, *KF* v *SatCen*, T-286/15, EU:T:2018:718, paragraph 157 and the case-law cited).

73 Thus, the possibility of pleading the inapplicability of a measure of general application under Article 277 TFEU does not constitute an independent right of action and recourse may be had to it only as an incidental plea (see order of 8 July 1999, *Area Cova and Others* v *Council*, T-194/95, EU:T:1999:141, paragraph 78 and the case-law cited; judgment of 6 June 2013, *T & L Sugars and Sidul Açúcares* v *Commission*, T-279/11, EU:T:2013:299, paragraph 96).

74 Furthermore, in the context of a claim for annulment of an act of individual application having adverse effect, the Courts of the European Union do in fact have jurisdiction to declare, incidentally, the unlawfulness of a provision of general application on which the contested act is based. However, they do not have jurisdiction to make such declarations in the operative part of their judgments (see judgment of 14 December 2018, *GQ and Others* v *Commission*, T-525/16, EU:T:2018:964, paragraph 37 and the case-law cited).

75 In the present case, the applicant requests, by way of an independent head of claim, that the General Court declare that the plea of illegality which it raises in respect of the implementing decision of 30 January 2014 is admissible and well founded, in so far as the Commission considered in that implementing decision that Tecfidera – Dimethyl fumarate was not covered by the same global marketing authorisation as Fumaderm.

76 It follows from the case-law cited in paragraphs 70 to 73 above that the first head of claim is inadmissible and must be rejected.

77 However, in the light of the content of the application, that conclusion does not preclude the Court from examining, in the context of its response to the second head of claim of the action, which seeks annulment of the contested decision, the plea of illegality raised in respect of the implementing decision of 30 January 2014 (see, to that effect, judgments of 14 December 2018, *GQ and Others* v *Commission*, T-525/16, EU:T:2018:964, paragraphs 38 and 39, and of 12 December 2019, *Feral* v *Committee of the Regions*, T-529/16, not published, EU:T:2019:851, paragraphs 27, 33 and 58).

B. The second head of claim, seeking annulment of the contested decision

78 In support of its claim for annulment, the applicant raises a single plea in law, alleging that the implementing decision of 30 January 2014 is unlawful in so far as the Commission considered in that implementing decision that Tecfidera was not covered by the same global marketing authorisation as Fumaderm. In essence, the applicant submits that the implementing decision of 30 January 2014, which serves as the sole legal basis for the contested decision, is unlawful and must, in accordance with Article 277 TFEU, be declared inapplicable. Consequently, the applicant submits that the contested decision, which refuses to validate the application for marketing authorisation for a generic medicinal product derived from Tecfidera, has no legal basis and must be annulled, inter alia on the grounds of a failure to state reasons pursuant to Article 296 TFEU.

79 The EMA, supported by the Commission and by Biogen, raises a plea of inadmissibility.

1. Admissibility

80 The EMA, supported by the Commission and by Biogen, contends, in essence, that, even if the implementing decision of 30 January 2014 constitutes a regulatory act in so far as the Commission considered in that implementing decision that Tecfidera was not covered by the same global marketing authorisation as Fumaderm, the plea of illegality raised by the applicant should be rejected as inadmissible. The applicant would have been entitled to challenge that implementing decision on the basis of Article 263 TFEU and should therefore have brought an action for annulment of that implementing decision, which it failed to do.

81 First, the EMA contends that if, as the applicant claims, the implementing decision of 30 January 2014 is, in the light of recital 3 thereof, a regulatory act, that act directly, and without implementing measures, produces effects on the applicant's legal situation. According to the EMA, that implementing decision resulted in Tecfidera being granted a separate data-protection period and, consequently, resulted in the applicant being prevented from relying on the Tecfidera dossier until that period expired.

82 Second, the EMA, supported by Biogen, contends that the applicant had an interest in bringing proceedings against the implementing decision of 30 January 2014 in so far as the Commission confirmed in that implementing decision that Tecfidera and Fumaderm did not belong to the same global marketing authorisation. In that regard, the EMA states that an annulment of that implementing decision would have led to a finding that Tecfidera belonged to the same global marketing authorisation as Fumaderm and would thus have enabled the applicant immediately to submit an application for marketing authorisation for a generic version of Tecfidera.

83 According to the EMA, the applicant's legal situation had undoubtedly been adversely affected during the period between the publication of a summary of the implementing decision of 30 January 2014 in the *Official Journal of the European Union* on 28 February 2014 and the expiry of the period for bringing an action for annulment against that implementing decision.

84 For its part, the Commission also maintains that there is no direct legal connection between the contested decision and certain preparatory measures for the implementing decision of 30 January 2014.

(a) The classification of the implementing decision of 30 January 2014 as an 'act of general application'

85 It is clear from the wording of Article 277 TFEU that a plea of illegality may be raised only in respect of an act of general application (see paragraph 70 above).

86 Furthermore, the fourth paragraph of Article 288 TFEU provides that 'a decision shall be binding in its entirety' and that, where it 'specifies those to whom it is addressed[, it] shall be binding only on them'.

87 In the present case, the implementing decision of 30 January 2014 was adopted following an application for marketing authorisation submitted by Biogen Idec. Furthermore, that implementing decision grants a marketing authorisation to a specific company, namely Biogen Idec. Lastly, Biogen Idec is the sole addressee of that implementing decision.

88 Thus, from a formal point of view, the implementing decision of 30 January 2014 is an individual decision, and not an act of general application.

89 However, according to settled case-law, the choice of form cannot alter the nature of a measure, with the result that it must be ascertained whether the content of a measure is wholly consistent with the form attributed to it (judgment of 13 December 1989, *Grimaldi*, C-322/88, EU:C:1989:646, paragraph 14, and order of 27 October 2015, *Belgium* v *Commission*, T-721/14, EU:T:2015:829, paragraph 20). Furthermore, in order to determine the scope of a measure, the Courts of the European Union should not look merely at the official name of the measure but should first take account of its purpose and its content (judgment of 14 December 1962, *Confédération nationale des producteurs de fruits et légumes and Others* v *Council*, 16/62 and 17/62, not published, EU:C:1962:47, p. 918).

90 A measure is of general application if it applies to objectively determined situations and produces legal effects with respect to categories of persons envisaged in a general and abstract manner (judgment of 6 November 2018, *Scuola Elementare Maria Montessori* v *Commission*, *Commission* v *Scuola Elementare Maria Montessori* and *Commission* v *Ferracci*, C-622/16 P to C-624/16 P, EU:C:2018:873, paragraph 29).

91 The field of application of Article 277 TFEU must therefore include acts of the institutions which, although they are not in the form of a regulation, nevertheless produce similar effects (judgment of 6 March 1979, *Simmenthal* v *Commission*, 92/78, EU:C:1979:53, paragraph 40). In other words, the plea of illegality cannot be limited to acts in the form of an act of general application within the meaning of Article 277 TFEU, in order to ensure that those persons who are precluded from instituting proceedings directly in respect of acts of the institutions may obtain a genuine judicial review of such acts when they are affected by implementing decisions which are of direct and individual concern to them (see, to that effect, judgment of 26 October 1993, *Reinarz* v *Commission*, T-6/92 and T-52/92, EU:T:1993:89, paragraph 56).

92 In the present case, in recital 3 of the implementing decision of 30 January 2014, the Commission found that Tecfidera containing DMF differed from Fumaderm, the other already authorised medicinal product containing DMF and MEF salts. It concluded from this that Tecfidera – Dimethyl fumarate, for which the application for authorisation was based on Article 8(3) of Directive 2001/83, and the already authorised medicinal product Fumaderm did not belong to the same global marketing authorisation in accordance with Article 6(1) of that directive.

93 In that regard, it is important to note that the second subparagraph of Article 6(1) of Directive 2001/83 refers to Article 10(1) of that directive and therefore expressly connects the concept of a 'global marketing authorisation' with the regulatory data-protection period in Article 10(1), irrespective of the fact that that concept covers various developments of the initial medicinal product, in relation to which separate data have to be supplied at different points over the course of time (judgment of 28 June 2017, *Novartis Europharm* v *Commission*, C-629/15 P and C-630/15 P, EU:C:2017:498, paragraph 64). That finding is also valid as regards the regulatory data-protection period provided for in Article 14(11) of Regulation No 726/2004.

94 Thus, the result of the finding in recital 3 of the implementing decision of 30 January 2014 that Tecfidera and the previously authorised Fumaderm did not belong to the same global marketing authorisation within the meaning of the second subparagraph of Article 6(1) of Directive 2001/83 is that that implementing decision must be interpreted as meaning that a regulatory protection period for the data relating to Tecfidera was applicable.

95 Accordingly, the implementing decision of 30 January 2014 applies to objectively determined situations, on account of its finding as to the respective characteristics of Fumaderm and Tecfidera. Furthermore, in so far as the applicability of the regulatory protection period for the data relating to Tecfidera follows from that finding, that implementing decision is capable of producing legal effects with respect to categories of persons referred to in a general and abstract manner, that is to say, any operator whose activities may be linked to Tecfidera and, in particular, any operator that is capable of manufacturing a generic medicinal product derived from Tecfidera.

96 Consequently, the implementing decision of 30 January 2014 is, as the EMA and the Commission maintained at the hearing, an act of general application within the meaning of Article 277 TFEU, in so far as it states, in recital 3 thereof, that Tecfidera does not belong to the same global marketing authorisation as Fumaderm.

(b) The existence of a connection between the contested decision and the assessments disputed by the applicant

97 The Commission contends that there is a direct legal connection between the contested decision and the implementing decision of 30 January 2014, since the refusal in the contested decision is directly linked, first, to the finding that Tecfidera differs from Fumaderm and, second, to the independent data-protection period resulting from that classification. However, the Commission maintains that there is no direct legal connection between the contested decision and certain preparatory measures for the implementing decision of 30 January 2014, namely the CHMP's revised opinion of 21 November 2013 (see paragraph 26 above) and, a fortiori, the EPAR of 26 November 2013 relating to Tecfidera (see paragraph 28 above).

98 Since the purpose of Article 277 TFEU is not to enable a party to contest the applicability of any act of general application in support of any action whatsoever, the scope of a plea of illegality must be limited to what is necessary for the outcome of the proceedings. It follows that the general measure claimed to be illegal must be applicable, directly or indirectly, to the issue with which the action is concerned (see judgment of 25 October 2018, *KF* v *SatCen*, T-286/15, EU:T:2018:718, paragraph 156 and the case-law cited).

99 Thus, in actions for annulment brought against individual decisions, the Court of Justice has accepted that the provisions of an act of general application that form the basis of those decisions (see, to that effect, judgments of 28 October 1981, *Krupp Stahl* v *Commission*, 275/80 and 24/81, EU:C:1981:247, paragraph 32, and of 11 July 1985, *Salerno and Others* v *Commission and Council*, 87/77, 130/77, 22/83, 9/84 and 10/84, EU:C:1985:318, paragraph 36), or that have a direct legal connection with such decisions (see, to that effect, judgments of 31 March 1965, *Macchiorlati Dalmas* v *High Authority*, 21/64, EU:C:1965:30, p. 245; of 9 September 2003, *Kik* v *OHIM*, C-361/01 P, EU:C:2003:434, paragraph 76; and of 28 June 2005, *Dansk Rørindustri and Others* v *Commission*, C-189/02 P, C-202/02 P, C-205/02 P to C-208/02 P and C-213/02 P, EU:C:2005:408, paragraph 237), may legitimately form the subject matter of a plea of illegality.

100 In that regard, it is true that, in the judgment of 22 January 2015, *Teva Pharma and Teva Pharmaceuticals Europe* v *EMA* (T-140/12, EU:T:2015:41, paragraphs 52 and 53), relied on by the Commission, the Court rejected as inadmissible a plea of illegality raised in respect of a summary report and an opinion of the EMA's Committee for Orphan Medicinal Products. In that judgment, the

Court pointed out that those measures were preparatory measures and that the Commission could take a different view from that expressed in the committee's opinion. It inferred from this that those acts did not constitute general acts and were not, by their nature, capable of forming the legal basis of the contested decision or of having a legal connection with it, with the result that their purported illegality could not have any effect on the outcome of the proceedings.

101 However, first, it should be noted that, in its action, the applicant does not formally raise a plea of illegality in respect of the CHMP's opinion or the EPAR. The applicant submits that the CHMP's scientific assessment is manifestly incorrect inasmuch as it finds that there is a relevant difference between Tecfidera and Fumaderm. According to the applicant, it follows that the implementing decision of 30 January 2014, which endorses the CHMP's findings on that point, is unlawful and inapplicable.

102 Second, it follows from the case-law that where a decision purely and simply confirms the opinion of the EMA, the content of that opinion, and also that of the assessment report upon which it is based, are an integral part of the statement of reasons for that decision, as regards in particular the scientific assessment of the medicinal product in question (see judgment of 11 June 2015, *Laboratoires CTRS* v *Commission*, T-452/14, not published, EU:T:2015:373, paragraph 60 and the case-law cited).

103 In the implementing decision of 30 January 2014, the Commission did not reproduce the CHMP's conclusion that DMF, the active substance in Tecfidera, was a new active substance. However, in that implementing decision, the Commission relied explicitly, first, on the CHMP's assessment that MEF and DMF are both active and are not the same active substance because their therapeutic moiety is not the same, and, second, on the CHMP's conclusion that DMF differs from Fumaderm. The Commission inferred from this that Tecfidera and Fumaderm did not belong to the same global marketing authorisation. Thus, following the adoption of that implementing decision, a note was added to the EPAR, relating to Tecfidera, in order to indicate that, 'in view of [the] evolution of the regulatory considerations, as reflected in [recital 3] of the [implementing decision of 30 January 2014], the final statement in the CHMP opinion that "the active substance of Tecfidera, dimethyl fumarate, [was] a new active substance" [was] obsolete'. However, the CHMP stated that all the other scientific considerations and conclusions relating to its assessment remained valid.

104 It must therefore be held that the content of the CHMP's revised opinion, as well as the content of the EPAR on which it is based, is an integral part of the statement of reasons for the implementing decision of 30 January 2014, as regards in particular the scientific assessment of the existence of a difference between Tecfidera and Fumaderm.

105 Thus, the applicant is entitled, in order to demonstrate the unlawfulness of the implementing decision of 30 January 2014, to challenge the assessments that, first, appear in the CHMP's revised opinion and in the EPAR, and, second, form the basis of that implementing decision.

106 The line of argument put forward by the Commission to the effect that there is no direct legal connection between the contested decision and certain preparatory measures for the implementing decision of 30 January 2014 is therefore rejected.

(c) The applicant's right to bring a direct action against the implementing decision of 30 January 2014

107 Article 277 TFEU gives expression to a general principle conferring upon any party to proceedings the right to challenge, for the purpose of obtaining the annulment of a decision of direct and individual concern to that party, the validity of previous acts of the institutions which form the legal basis of the decision which is being attacked, if that party was not entitled under Article 263 TFEU to bring a direct action challenging those acts by which it was thus affected without having been in a position to

ask that they be declared void (judgments of 6 March 1979, *Simmenthal* v *Commission*, 92/78, EU:C:1979:53, paragraph 39, and of 17 June 1999, *ARAP and Others* v *Commission*, T-82/96, EU:T:1999:127, paragraph 46).

108 In so far as an applicant was entitled to bring an action for annulment of a measure which it subsequently claims to be unlawful by way of a plea of illegality, the plea of illegality raised in respect of that measure is to be rejected as inadmissible, on the ground that the fact that it was time-barred precludes it being a collateral challenge to a definitive measure (see, to that effect, judgment of 20 September 2011, *Regione autonoma della Sardegna and Others* v *Commission*, T-394/08, T-408/08, T-453/08 and T-454/08, EU:T:2011:493, paragraph 68). To accept that an applicant could, in an action for annulment of a decision, rely on irregularities in respect of an earlier act, annulment of which he or she could have sought, would make it possible indirectly to challenge earlier decisions which were not contested within the period for bringing proceedings prescribed in Article 263 TFEU, thereby circumventing that time limit (see, to that effect, judgment of 29 June 1995, *Spain* v *Commission*, C-135/93, EU:C:1995:201, paragraph 17).

109 It is therefore necessary to examine whether, in the light of the information in the file, an action brought by the applicant under the fourth paragraph of Article 263 TFEU against the implementing decision of 30 January 2014 would have been admissible.

110 In that regard, it should be noted that the fourth paragraph of Article 263 TFEU provides that 'any natural or legal person may, under the conditions laid down in the first and second paragraphs, institute proceedings against an act addressed to that person or which is of direct and individual concern to them, and against a regulatory act which is of direct concern to them and does not entail implementing measures'.

111 In the present case, it is common ground that the implementing decision of 30 January 2014 was not addressed to the applicant.

112 In that context, it should be borne in mind that the admissibility of an action brought by a natural or legal person against an act which is not addressed to them, in accordance with the fourth paragraph of Article 263 TFEU, is subject to the condition that they be accorded standing to bring proceedings, which arises in two situations. First, such proceedings may be instituted if the act is of direct and individual concern to them. Second, such persons may bring proceedings against a regulatory act not entailing implementing measures if that act is of direct concern to them (judgments of 17 September 2015, *Mory and Others* v *Commission*, C-33/14 P, EU:C:2015:609, paragraphs 59 and 91, and of 13 March 2018, *Industrias Químicas del Vallés* v *Commission*, C-244/16 P, EU:C:2018:177, paragraph 39).

113 In the first place, as regards the condition that the applicant must be individually concerned, it is settled case-law that persons other than those to whom a decision is addressed may claim to be individually concerned only if that decision affects them by reason of certain attributes which are peculiar to them or by reason of circumstances in which they are differentiated from all other persons, and by virtue of these factors distinguishes them individually just as in the case of the person addressed (judgments of 15 July 1963, *Plaumann* v *Commission*, 25/62, EU:C:1963:17, p. 223; of 3 October 2013, *Inuit Tapiriit Kanatami and Others* v *Parliament and Council*, C-583/11 P, EU:C:2013:625, paragraph 72; and of 19 December 2013, *Telefónica* v *Commission*, C-274/12 P, EU:C:2013:852, paragraph 46).

114 The possibility of determining more or less precisely the number, or even the identity, of the persons to whom a measure applies by no means implies that it must be regarded as being of individual concern to them as long as that measure is applied by virtue of an objective legal or factual situation

defined by the measure in question (see, to that effect, judgments of 22 November 2001, *Antillean Rice Mills* v *Council*, C-451/98, EU:C:2001:622, paragraph 52, and of 19 December 2013, *Telefónica* v *Commission*, C-274/12 P, EU:C:2013:852, paragraph 47).

115 In the present case, first, the fact that the applicant is a manufacturer of generic medicinal products and that it considered the possibility of placing a generic medicinal product derived from Tecfidera on the market is not, as such, capable of distinguishing the applicant individually, since other operators were likely to be in the same situation as it.

116 Next, it must be noted that the implementing decision of 30 January 2014 was adopted following an application for marketing authorisation submitted by Biogen Idec.

117 Under Directive 2001/83 or Regulation No 726/2004, the procedure for the grant of a marketing authorisation is conceived as a bilateral procedure involving only the applicant and the competent authority (see, to that effect, judgment of 23 October 2014, *Olainfarm*, C-104/13, EU:C:2014:2316, paragraph 34). It is a procedure between the applicant and the administration, during which the latter must take into account the applicant's interest in obtaining a marketing authorisation and the public interest in the protection of human health. Third parties, such as the applicant in the present case, are not entitled to participate in that procedure or set themselves up as interlocutors of the CHMP and of the Commission in regard to the assessment of the scientific data relating to the medicinal product in question (see, to that effect, judgment of 18 December 2003, *Olivieri* v *Commission and EMEA*, T-326/99, EU:T:2003:351, paragraph 94).

118 Lastly, it should be noted that, in the implementing decision of 30 January 2014, the Commission found that Tecfidera containing DMF differed from Fumaderm, the other already authorised medicinal product containing DMF and MEF salts, and that, consequently, Tecfidera – Dimethyl fumarate, for which the application for authorisation was based on Article 8(3) of Directive 2001/83, and the already authorised medicinal product Fumaderm did not belong to the same global marketing authorisation in accordance with Article 6(1) of Directive 2001/83.

119 Thus, it is apparent from the adoption procedure and the content of the implementing decision of 30 January 2014 that the applicant's individual situation was not taken into consideration when that implementing decision was adopted, including in so far as the Commission considered in that implementing decision that Tecfidera and the already authorised medicinal product Fumaderm did not belong to the same global marketing authorisation under Article 6(1) of Directive 2001/83.

120 The implementing decision of 30 January 2014 therefore concerned the applicant solely by reason of its objective capacity as a manufacturer of medicinal products, in particular generic medicinal products, in the same way as any other economic operator which was, at the same time and potentially, in the same situation.

121 Accordingly, it has not been established that the implementing decision of 30 January 2014 was of individual concern to the applicant.

122 In the second place, as regards the existence of a regulatory act not entailing implementing measures, it should be noted that the concept of 'regulatory act' within the meaning of the third limb of the fourth paragraph of Article 263 TFEU extends to all non-legislative acts of general application (judgment of 6 November 2018, *Scuola Elementare Maria Montessori* v *Commission*, *Commission* v *Scuola Elementare Maria Montessori* and *Commission* v *Ferracci*, C-622/16 P to C-624/16 P, EU:C:2018:873, paragraph 28).

123 In the present case, it should be noted that the implementing decision of 30 January 2014 is of general application as regards the assessments disputed by the applicant (see paragraphs 85 to 96 above). Furthermore, it is common ground that that implementing decision does not constitute a legislative act.

124 That implementing decision is therefore a regulatory act in so far as it states, in recital 3, that Tecfidera does not belong to the same global marketing authorisation as Fumaderm.

125 According to settled case-law, the expression 'does not entail implementing measures' within the meaning of the third limb of the fourth paragraph of Article 263 TFEU must be interpreted in the light of the objective of that provision, which, as is apparent from its drafting history, is to ensure that individuals do not have to break the law in order to have access to a court. Where a regulatory act directly affects the legal situation of a natural or legal person without requiring implementing measures, that person could be denied effective judicial protection if he or she did not have a legal remedy before the EU judicature for the purpose of challenging the lawfulness of the regulatory act. In the absence of implementing measures, a natural or legal person, although directly concerned by the act in question, would be able to obtain judicial review of the act only after having infringed its provisions, by pleading that those provisions are unlawful in proceedings initiated against them before the national court (see judgment of 6 November 2018, *Scuola Elementare Maria Montessori* v *Commission*, *Commission* v *Scuola Elementare Maria Montessori* and *Commission* v *Ferracci*, C-622/16 P to C-624/16 P, EU:C:2018:873, paragraph 58 and the case-law cited).

126 By contrast, where a regulatory act entails implementing measures, judicial review of compliance with the EU legal order is ensured irrespective of whether those measures were adopted by the European Union or the Member States. Natural or legal persons who are unable, because of the conditions of admissibility in the fourth paragraph of Article 263 TFEU, to challenge an EU regulatory act directly before the EU judicature are protected against the application to them of such an act by the ability to challenge the implementing measures which the act entails (see judgment of 6 November 2018, *Scuola Elementare Maria Montessori* v *Commission*, *Commission* v *Scuola Elementare Maria Montessori* and *Commission* v *Ferracci*, C-622/16 P to C-624/16 P, EU:C:2018:873, paragraph 59 and the case-law cited).

127 Where responsibility for the implementation of such acts lies with the institutions, bodies, offices or agencies of the European Union, natural or legal persons are entitled to bring a direct action before the EU judicature against the implementing acts under the conditions stated in the fourth paragraph of Article 263 TFEU, and to plead in support of that action, pursuant to Article 277 TFEU, the unlawfulness of the basic act concerned (see judgment of 6 November 2018, *Scuola Elementare Maria Montessori* v *Commission*, *Commission* v *Scuola Elementare Maria Montessori* and *Commission* v *Ferracci*, C-622/16 P to C-624/16 P, EU:C:2018:873, paragraph 60 and the case-law cited).

128 The Court of Justice has, moreover, repeatedly held that the question whether a regulatory act entails implementing measures should be assessed by reference to the position of the person pleading the right to bring proceedings under the third limb of the fourth paragraph of Article 263 TFEU. It is therefore irrelevant whether the act in question entails implementing measures with regard to other persons (see judgment of 6 November 2018, *Scuola Elementare Maria Montessori* v *Commission*, *Commission* v *Scuola Elementare Maria Montessori* and *Commission* v *Ferracci*, C-622/16 P to C-624/16 P, EU:C:2018:873, paragraph 61 and the case-law cited).

129 In addition, in that assessment, reference should be made exclusively to the subject matter of the action and, where an applicant seeks only the partial annulment of an act, it is solely any implementing measures which that part of the act may entail that must, as the case may be, be taken into consideration (see judgment of 10 December 2015, *Kyocera Mita Europe* v *Commission*, C-553/14 P, not published, EU:C:2015:805, paragraph 45 and the case-law cited; see also, to that

effect, judgment of 6 November 2018, *Scuola Elementare Maria Montessori* v *Commission*, *Commission* v *Scuola Elementare Maria Montessori* and *Commission* v *Ferracci*, C-622/16 P to C-624/16 P, EU:C:2018:873, paragraph 61).

130 Lastly, the wording of the final limb of the fourth paragraph of Article 263 TFEU does not require, for a measure to be classified as an implementing measure of a regulatory act, that that act is the legal base of that measure. The same measure may be an implementing measure both of the act the provisions of which constitute its legal base and of a different act where all or part of the legal effects of the latter act will be produced, vis-à-vis the applicant, only through the intermediary of that measure (judgment of 13 March 2018, *Industrias Químicas del Vallés* v *Commission*, C-244/16 P, EU:C:2018:177, paragraph 72).

131 The question of whether or not the implementing measures are of a mechanical nature is irrelevant (judgment of 13 March 2018, *Industrias Químicas del Vallés* v *Commission*, C-244/16 P, EU:C:2018:177, paragraph 47). In other words, the question of whether or not the contested regulatory act allows a degree of discretion to the authorities responsible for the implementing measures is irrelevant in ascertaining whether it entails implementing measures within the meaning of the fourth paragraph of Article 263 TFEU (judgment of 6 June 2013, *T & L Sugars and Sidul Açúcares* v *Commission*, T-279/11, EU:T:2013:299, paragraph 53; see also, to that effect, order of 14 July 2015, *Forgital Italy* v *Council*, C-84/14 P, not published, EU:C:2015:517, paragraph 44).

132 In that regard, first, it must be noted that the content of recital 3 of the implementing decision of 30 January 2014 is reproduced in the contested decision. Furthermore, it is common ground that the contested decision is based on the implementing decision of 30 January 2014. In its statement in intervention, the Commission stated that the validation refusal in the contested decision was directly linked to the assessments made in the implementing decision of 30 January 2014. In its written responses to the questions put by the Court, the Commission added that the EMA was bound by the content of recital 3 of the implementing decision of 30 January 2014.

133 Second, it should be noted that, during a meeting between the Commission services and Biogen Idec on 16 May 2013, the Commission noted that, in the decisions granting marketing authorisation, no statement was made with regard to data exclusivity, on the ground that data exclusivity was a dynamic concept subject to change in the event of a transfer of assets between companies. In addition, as the Commission explained in its statement in intervention, the EMA checks, in the context of the validation procedure, whether the regulatory data-protection period for the reference medicinal product has expired. In its written responses to the Court's questions, the EMA stated that, in order to determine whether the reference medicinal product had been authorised for less than eight years, it was necessary to ascertain whether the holder of the marketing authorisation for the reference medicinal product also held authorisations for other products containing the same active substance. Lastly, as the EMA and the Commission explained at the hearing, the checks carried out by the EMA in the context of its powers of validation consist, more generally, in assessing whether the dossier of the applicant for marketing authorisation is complete in the light of Article 8(3) and Article 10(1) of Directive 2001/83.

134 Thus, it must be noted that the implementing decision of 30 January 2014, which states that Tecfidera does not belong to the same global marketing authorisation as Fumaderm, had legal effects vis-à-vis the applicant only through the contested decision, which was adopted following the submission of an application for marketing authorisation under an 'abridged' procedure (see paragraph 8 above) and which refused to validate that application.

135 It is true that the Court of Justice has held that it would be artificial to require the competitor of a beneficiary of a national measure that does not constitute State aid to request the national authorities to grant him or her that benefit and to contest the refusal of that request before a national court, in order to cause the national court to make a reference to the Court of Justice on the validity of the

Commission's decision concerning that measure (see judgment of 6 November 2018, *Scuola Elementare Maria Montessori* v *Commission*, *Commission* v *Scuola Elementare Maria Montessori* and *Commission* v *Ferracci*, C-622/16 P to C-624/16 P, EU:C:2018:873, paragraph 66 and the case-law cited).

136 However, in the present case, it was only by submitting an application for marketing authorisation for a generic medicinal product derived from Tecfidera that the applicant was able to demonstrate, in a relevant manner, why the implementing decision of 30 January 2014 was capable of producing direct, concrete and certain effects on its legal situation. Thus, the submission of an application for marketing authorisation for a generic medicinal product derived from Tecfidera cannot be regarded as artificial, since it enabled the applicant to show that it was in a position to manufacture a generic medicinal product derived from Tecfidera and that it had decided to market such a medicinal product. It should be added that, following the submission of that application, the EMA verified whether the reference medicinal product designated by the applicant, namely Tecfidera, benefited from a regulatory data-protection period under Article 14(11) of Regulation No 726/2004.

137 It follows, first, that the implementing decision of 30 January 2014 entails implementing measures, in so far as it finds, in recital 3, that Tecfidera does not belong to the same global marketing authorisation as Fumaderm and, second, that the contested decision, addressed to the applicant, constitutes one of those measures.

138 In any event, there is nothing to prevent an applicant from raising a plea of illegality in respect of an act of general application on the ground that, within the prescribed period for bringing an action for annulment under Article 263 TFEU, it could not prove an interest in bringing proceedings directly against that act (see, by analogy, judgment of 27 March 2019, *Canadian Solar Emea and Others* v *Council*, C-236/17 P, EU:C:2019:258, paragraph 103, and the Opinion of Advocate General Pitruzzella in *Compagnie des pêches de Saint-Malo*, C-212/19, EU:C:2020:179, points 49 and 50).

139 According to settled case-law, an action for annulment brought by a natural or legal person is admissible only in so far as that person has an interest in having the contested act annulled. Such an interest requires that the annulment of that act must be capable, in itself, of having legal consequences and that the action may therefore, through its outcome, procure an advantage to the party which brought it (see judgment of 17 September 2015, *Mory and Others* v *Commission*, C-33/14 P, EU:C:2015:609, paragraph 55 and the case-law cited).

140 By contrast, there is no interest in bringing proceedings when the favourable outcome of an action could not, in any event, give the applicant satisfaction (see judgment of 23 November 2017, *Bionorica and Diapharm* v *Commission*, C-596/15 P and C-597/15 P, EU:C:2017:886, paragraph 85 and the case-law cited).

141 An applicant's interest in bringing proceedings must be vested and current. It may not concern a future and hypothetical situation (see judgment of 17 September 2015, *Mory and Others* v *Commission*, C-33/14 P, EU:C:2015:609, paragraph 56 and the case-law cited).

142 The interest in bringing proceedings is an essential and fundamental prerequisite for any legal proceedings (see judgment of 17 September 2015, *Mory and Others* v *Commission*, C-33/14 P, EU:C:2015:609, paragraph 58 and the case-law cited).

143 In the present case, it is true that, on 27 February 2014, that is to say, the day before a summary of the implementing decision of 30 January 2014 was published in the *Official Journal of the European Union*, the applicant filed a notice of opposition with the European Patent Office to a European patent which had been granted to Biogen Idec in May 2013 and which concerned 'compositions and uses for treating multiple sclerosis' and covered the use of DMF in the treatment of multiple sclerosis using the specific

doses approved for Tecfidera. Furthermore, Biogen has produced a publication by the applicant which, first, relates to the active pharmaceutical ingredients which were at the development stage during the first quarter of 2014 and, second, indicates DMF for the treatment of multiple sclerosis.

144 However, it must be noted that the applicant's publication, produced by Biogen, states that the development of DMF was at an early stage during the first quarter of 2014. Furthermore, it must be noted that the applicant submitted, without being contradicted by the other parties at the hearing, that the process of developing a generic medicinal product involved multiple stages and studies in order to generate the data required by the marketing-authorisation application dossier. It also claimed that the results of some of those studies remained uncertain until their completion. It explained that some of the required studies, such as bioequivalence studies, could not start or be carried out while the reference medicinal product, in the present case Tecfidera, was not on the market.

145 Thus, first, the explanations provided by the applicant show that its interest in directly seeking the annulment of the implementing decision of 30 January 2014 was not vested and current, but future, on the date on which it would have been entitled to bring an action for annulment of that implementing decision, in so far as it was not conceivable that it would submit an application for marketing authorisation for a generic medicinal product derived from Tecfidera on that date, and in so far as the time needed to submit such an application greatly exceeded the time limit for bringing an action for annulment. Second, those explanations also show that the applicant's ability to comply with the requirements for marketing authorisation for a generic medicinal product derived from Tecfidera was uncertain on the date on which it would have been entitled to bring an action for annulment against the implementing decision of 30 January 2014.

146 Therefore, in the light of the applicant's situation between the date on which a summary of the implementing decision of 30 January 2014 was published in the *Official Journal of the European Union* and the expiry of the period available for bringing an action for annulment of that implementing decision, it has not been established that the applicant had a vested and current interest in bringing proceedings directly against that implementing decision.

147 It has also been held that a mere statement of intention to enter into the market, given that it refers to a future and uncertain situation, cannot suffice to establish a current and vested interest in bringing proceedings (see, to that effect, judgment of 23 November 2017, *Bionorica and Diapharm* v *Commission*, C-596/15 P and C-597/15 P, EU:C:2017:886, paragraphs 114 and 115).

148 Consequently, it must be held that it is not apparent from the information in the file that the applicant would have been entitled to bring an action on the basis of Article 263 TFEU for annulment of the implementing decision of 30 January 2014.

149 The plea alleging that the plea of illegality is inadmissible must therefore be rejected.

2. Substance

150 The applicant submits that the Commission applied an incorrect test and made a manifest error of assessment in concluding that Tecfidera and Fumaderm were different and that, consequently, Tecfidera was not covered by the global marketing authorisation for Fumaderm. In the first place, the applicant submits that, in order to establish whether Tecfidera and Fumaderm differed for the purposes of the global marketing authorisation, the Commission applied an incorrect test that did not take into account all the relevant factors. In the second place, the applicant submits that, if the CHMP and the Commission had applied the appropriate test and had taken into account all the relevant factors, they could not have decided that Tecfidera did not fall within the scope of the marketing authorisation for Fumaderm. In the light of the content of the application, the Court considers that those two complaints must be examined together in so far as they both, in fact, seek to argue that the

implementing decision of 30 January 2014 is vitiated by a manifest error of assessment, on the ground that, when adopting that decision, the Commission relied on factors that did not constitute all of the available and relevant data that should have been taken into consideration. More specifically, the applicant claims that, when faced with an application for marketing authorisation for an active substance which was part of a previously authorised combination medicinal product, the assessment as to whether there is a difference between that combination and that isolated active substance depends on whether the individual active substances in the combination provide a documented and relevant therapeutic contribution within that combination.

151 Thus, first of all, the Court will make certain preliminary observations on the effectiveness of the single plea in law and on the scope of judicial review. Next, the Court will assess whether the Commission made a manifest error of assessment when adopting the implementing decision of 30 January 2014, by examining in turn the following four issues: (i) the global marketing authorisation and its objectives; (ii) the applicable EU law and developments in scientific knowledge between 1994 and 2014; (iii) the principle of mutual recognition of decisions adopted by the national authorities; and (iv) the data available, or which could have been available, to the Commission and the EMA regarding the role of MEF in Fumaderm.

(a) Preliminary observations

152 As a preliminary point, it is necessary to ascertain the effectiveness of the single plea in law and to determine the scope of judicial review.

(1) The effectiveness of the single plea in law

153 In its replies to the measures of organisation of procedure referred to in paragraph 63 above, the EMA argued that it was apparent from the wording of the contested decision that it had two separate legal bases, namely Article 14(11) of Regulation No 726/2004, read in conjunction with Article 6(1) of Directive 2001/83, and the Commission's implementing decision of 30 January 2014. The EMA also explained that the contested decision was based on a comparison of the qualitative compositions of Fumaderm and Tecfidera in terms of active substances, on the one hand, and on the implementing decision of 30 January 2014, on the other. According to the EMA, those two legal bases are different because they are based on slightly different lines of reasoning.

154 In the light of the foregoing, the EMA argued, in its written replies to the Court's questions, that the single plea in law was ineffective, given that the applicant had not challenged one of the grounds of the contested decision, namely the comparison of the qualitative compositions of Fumaderm and Tecfidera, carried out by the EMA itself at the validation stage of the application for marketing authorisation for Dimethyl Fumarate Pharmaceutical Works Polpharma.

155 However, first, it should be noted that, in the contested decision, the EMA began by recalling the wording of recital 3 of the implementing decision of 30 January 2014, which itself refers to the assessments carried out by the CHMP. Next, the EMA recalled the provisions of Article 14(11) of Regulation No 726/2004. Lastly, the EMA drew attention to the fact that Tecfidera and Fumaderm differed in their qualitative compositions in terms of active substances. In that regard, it referred to the content of the second subparagraph of Article 6(1) of Directive 2001/83. The EMA added that, as the Commission had indicated in its implementing decision of 30 January 2014, Tecfidera and Fumaderm did not belong to the same global marketing authorisation and that it was clear that Tecfidera benefited from its own independent eight-year data-protection period.

156 The EMA inferred from this that, in the light of the implementing decision of 30 January 2014, which acknowledges that Tecfidera and Fumaderm do not belong to the same global marketing authorisation, and in the light of Article 14(11) of Regulation No 726/2004, it was not in a position to validate the application for marketing authorisation for a generic version of Tecfidera submitted by the applicant.

157 Thus, it is apparent from the contested decision that, in it, the EMA relied exclusively on the conclusion that was already set out in the implementing decision of 30 January 2014, namely: 'MEF and DMF are both active and are not the same active substance since they do not share the same therapeutic moiety, [and therefore] it is considered that Tecfidera containing DMF is different from Fumaderm the other already authorised medicinal product composed of DMF and MEF salts'.

158 The contested decision cannot, therefore, be interpreted as meaning that the EMA itself carried out a comparison of the qualitative compositions of Fumaderm and Tecfidera at the validation stage of the application for marketing authorisation for a generic medicinal product derived from Tecfidera submitted by the applicant.

159 Moreover, since the Commission had already taken a view on the comparison of the qualitative compositions of Fumaderm and Tecfidera, there was no need for the EMA to carry out its own comparison of the qualitative compositions of Fumaderm and Tecfidera.

160 Second, it should be noted that the EMA's interpretation of the contested decision in its written replies to the questions put by the Court is not compatible with the explanations that it provided in the defence and in the rejoinder.

161 It is true that, in the defence, the EMA explained that the finding that there were different global marketing authorisations on the basis of a comparison of the summary of the characteristics of the products at issue ('the SmPC') could be made during the validation of any application for authorisation of a generic version of Tecfidera, whether it was an application made to the EMA or to a competent national authority. In addition, the EMA explained that its decision was based on the fact that Tecfidera was not covered by the global marketing authorisation for Fumaderm, since the qualitative compositions of Tecfidera and Fumaderm differed in terms of active substances.

162 However, in that defence, the EMA argued that the test for comparing the qualitative compositions of the two medicinal products, as authorised, could be satisfied in two ways: either following a comparison of the SmPCs relating to Fumaderm and Tecfidera respectively, as the EMA had indicated in its letter of 3 August 2011 (see paragraph 12 above), or following an assessment leading to the conclusion that DMF and MEF are different active substances (the test that the Commission applied when it granted the marketing authorisation for Tecfidera). Furthermore, it is apparent from the EMA's pleadings that it argued that it could have merely compared the SmPCs relating to the medicinal products at issue and that the mere finding, on the basis of a comparison of those SmPCs, that there was a different qualitative composition in terms of active substances made it possible to draw a conclusion. In other words, the EMA explained that it 'would have been possible' to adopt such an approach in the present case and that it was the approach that would be adopted in the future. By contrast, the EMA never claimed, in the defence or in the rejoinder, that it was the approach that it had actually adopted in the present case, in the contested decision. In that regard, it is telling that, in support of its arguments, the EMA relied, on several occasions, on the approach which it had advocated in its letter of 3 August 2011, and not on the content of the contested decision. Moreover, the contested decision does not contain any reference to the SmPCs relating to Fumaderm and Tecfidera respectively.

163 The EMA's line of argument according to which the single plea in law is ineffective in so far as the applicant did not challenge one of the grounds of the contested decision must therefore be rejected.

(2) The scope of judicial review

164 Where the administrative authority's decision is the result of complex technical assessments, for example, in the medico-pharmacological sphere, those assessments are in principle subject to only limited judicial review, which means that the Courts of the European Union cannot substitute their own assessment of matters of fact for that of the administrative authority (see judgment of 19 November 2008, *Schräder* v *CPVO (SUMCOL 01)*, T-187/06, EU:T:2008:511, paragraph 60 and the case-law cited).

165 Where an EU institution is called upon to make complex assessments, it enjoys a wide measure of discretion, the exercise of which is subject to a judicial review limited to verifying that the measure at issue is not vitiated by a manifest error or a misuse of powers and that the competent authority did not clearly exceed the bounds of its discretion (see judgment of 11 December 2014, *PP Nature-Balance Lizenz* v *Commission*, T-189/13, not published, EU:T:2014:1056, paragraph 34 and the case-law cited).

166 However, while the Courts of the European Union recognise that the administration has a margin of appreciation in economic or technical matters, that does not mean that they must decline to review the administration's interpretation of economic or technical data. Not only must the EU judicature establish, in particular, whether the evidence relied on is factually accurate, reliable and consistent but also whether that evidence contains all the information which must be taken into account in order to assess a complex situation and whether it is capable of substantiating the conclusions drawn from it (see judgment of 19 November 2008, *Schräder* v *CPVO (SUMCOL 01)*, T-187/06, EU:T:2008:511, paragraph 61 and the case-law cited).

167 Even though judicial review is of limited scope, it requires that the EU institutions which have adopted the act in question must be able to show before the EU judicature that in adopting the act they actually exercised their discretion, which presupposes that they took into consideration all the relevant factors and circumstances of the situation the act was intended to regulate (see, to that effect, judgments of 8 July 2010, *Afton Chemical*, C-343/09, EU:C:2010:419, paragraph 34, and of 30 April 2015, *Polynt and Sitre* v *ECHA*, T-134/13, not published, EU:T:2015:254, paragraph 53).

168 In order to establish that an institution committed a manifest error in assessing complex facts such as to justify the annulment of an act, the evidence adduced by the applicant must be sufficient to make the factual assessments used in the act implausible (see, to that effect, judgment of 9 September 2011, *France* v *Commission*, T-257/07, EU:T:2011:444, paragraph 86 and the case-law cited).

169 As regards the CHMP's opinion, the Court cannot substitute its own assessment for that of that committee. It is only the proper functioning of the committee, the internal consistency of the opinion and the statement of reasons contained therein which are subject to judicial review. As regards the last aspect, the Court is empowered only to examine whether the opinion contains a statement of reasons from which it is possible to ascertain the considerations on which the opinion is based, and whether it establishes a comprehensible link between the medical and/or scientific findings and its conclusions. In that respect, in its opinion the CHMP is obliged to refer to the main reports and scientific expert opinions on which it relies and to explain, in the event of a significant discrepancy, the reasons why it has departed from the conclusions of the reports or expert opinions supplied by the undertakings concerned. That obligation is particularly strict in cases of scientific uncertainty. By guaranteeing that the consultation of the committee is *inter partes* and transparent, that obligation ensures that the substance in question has undergone a detailed and objective scientific assessment, based on a comparison of the most representative scientific opinions with the scientific arguments advanced by the pharmaceutical laboratories concerned (see judgment of 11 December 2014, *PP Nature-Balance Lizenz* v *Commission*, T-189/13, not published, EU:T:2014:1056, paragraph 52 and the case-law cited).

170 Lastly, according to settled case-law, in an action for annulment, the legality of the contested measure must be assessed on the basis of the elements of fact and of law existing at the time when the measure was adopted (see judgment of 10 September 2019, *HTTS* v *Council*, C-123/18 P, EU:C:2019:694, paragraph 37 and the case-law cited; judgment of 17 September 2007, *Microsoft* v *Commission*, T-201/04, EU:T:2007:289, paragraph 260) and in the light of the information available to the institution responsible for the measure at the time when it was adopted (judgment of 9 September 2009, *Brink's Security Luxembourg* v *Commission*, T-437/05, EU:T:2009:318, paragraph 96; see also, to that effect, judgment of 12 April 2013, *Du Pont de Nemours (France) and Others* v *Commission*, T-31/07, not published, EU:T:2013:167, paragraph 157).

171 An applicant cannot therefore rely, before the Courts of the European Union, on facts that occurred subsequent to the act the legality of which is contested or if the author of that act could not have been aware of those facts at the time the act was adopted. Arguments based on such facts are ineffective.

172 It is in the light of those considerations that it must be examined whether the Commission made a manifest error of assessment in finding, in the implementing decision of 30 January 2014, that Tecfidera, composed solely of DMF, did not belong to the global marketing authorisation for Fumaderm granted by the BfArM in 1994.

(b) The global marketing authorisation and its objectives

173 The applicant submits that the fact that Tecfidera is authorised under a different procedure, for a different indication, and with a trade name other than Fumaderm, is not a factor that can be relied on as such to argue that Tecfidera does not fall within the scope of the global marketing authorisation for Fumaderm. It submits that the therapeutic activity, or the absence of such activity, of the MEF salts in Fumaderm is the key to establishing whether there is any relevant difference between Tecfidera and Fumaderm for the purposes of the global marketing authorisation. The applicant adds that the therapeutic effect of the MEF salts in Fumaderm must be relevant. In its view, it is inappropriate to regard two products as 'different' merely because one of them contains a particular compound that has some kind of pharmaceutical effect that is not present in the product with which it is being compared. Otherwise, it would be too easy for a marketing-authorisation holder to obtain a long period of additional regulatory data protection by adding or removing, when extending the product to a new therapeutic indication, a substance that is pharmaceutically active but clinically irrelevant. The same applies to a substance that has a relevant activity and that is present in a combination but at a dose too low to have any significant therapeutic effect and that could, also, be removed from the combination without any significant impact on therapeutic activity. The applicant submits that, if such changes were rewarded by the grant of a new regulatory data-protection period solely on the ground that the active substances concerned had been shown, individually, to have (some) therapeutic activity, this would be contrary to the objectives pursued by Directive 2001/83 and would not enable the right balance to be struck between protecting the interests of innovative companies and the need to promote the production of generic medicinal products in the light of the public interest.

174 The EMA disputes the applicant's argument that the legal test that the Commission applied in order to determine whether two medicinal products belong to separate global marketing authorisations could provide undertakings with a way of circumventing the rules on regulatory data protection. According to the EMA, the risk of circumvention raised by the applicant is completely hypothetical.

175 Article 10(1) of Directive 2001/83 (see paragraph 8 above) seeks to reconcile, on the one hand, the provision of adequate protection for the research and development work undertaken by innovative pharmaceutical companies and, on the other, the wish to avoid excessive testing on humans and animals. Thus, according to recital 9 of Directive 2001/83, 'it is advisable to stipulate more precisely the cases in which the results of toxicological and pharmacological tests or clinical trials do not have

to be provided with a view to obtaining authorisation for a medicinal product which is essentially similar to an authorised product, while ensuring that innovative firms are not placed at a disadvantage', whereas recital 10 states that 'there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause' (judgment of 15 September 2015, *Novartis Europharm* v *Commission*, T-472/12, EU:T:2015:637, paragraph 62).

176 The notion of a global marketing authorisation referred to in the second subparagraph of Article 6(1) of Directive 2001/83, as amended (see paragraph 7 above), follows the line of well-established case-law of the Court of Justice, which developed that notion in particular to take account of the objective of the 'abridged' procedure, which is to save the time and expense needed to gather the results of the pharmacological and toxicological tests and clinical trials, and to avoid the repetition of tests on humans or animals. That objective would clearly be jeopardised if the producer of the original medicinal product were able to extend indefinitely the regulatory period of data protection and thus prevent producers of generic medicinal products from using that product as a reference product when the regulatory data-protection period expressly provided for by the legislature in order to reconcile the interests of innovative undertakings and the general interest expired (see judgment of 15 September 2015, *Novartis Europharm* v *Commission*, T-472/12, EU:T:2015:637, paragraph 63 and the case-law cited).

177 It is in the light of the wording of the second subparagraph of Article 6(1) of Directive 2001/83 and of the objective pursued by that provision that the Court has held, first, that the scope of a global marketing authorisation, as defined in the second subparagraph of Article 6(1) of Directive 2001/83, as amended, encompasses developments for which separate marketing authorisations have been granted under the centralised procedure and, second, that the fact that a holder was able to obtain, by means of that procedure, a marketing authorisation for new therapeutic indications with a new name is therefore irrelevant for the purpose of the application of the regulatory data-protection period (judgment of 15 September 2015, *Novartis Europharm* v *Commission*, T-472/12, EU:T:2015:637, paragraph 82). In that regard, the Court of Justice has also held that the concept of a 'global marketing authorisation', within the meaning of the second subparagraph of Article 6(1) of Directive 2001/83, covers all subsequent developments of the original medicinal product, irrespective of their authorisation procedures, namely through the variation of the initial marketing authorisation for that medicinal product or through the grant of a separate marketing authorisation (judgment of 28 June 2017, *Novartis Europharm* v *Commission*, C-629/15 P and C-630/15 P, EU:C:2017:498, paragraph 72).

178 Lastly, it must be added that it is in the light of the objective of '[promoting] research on new therapeutic indications with a significant clinical benefit and bringing an improvement to the quality of life and welfare of the patient' while ensuring 'an appropriate balance between such innovations and the need to favour the production of generic medicines' that the legislature provided, in the fourth subparagraph of Article 10(1) of Directive 2001/83, that the 10-year period of market exclusivity enjoyed by a reference medicinal product was to be increased by a year 'if, during the first eight years of those ten years, the marketing authorisation holder [obtained] an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, [were] held to bring a significant clinical benefit in comparison with existing therapies'. That additional year of market exclusivity therefore constitutes, in the view of the EU legislature, the appropriate advantage to reward the investments in new therapeutic indications (see, to that effect, judgment of 28 June 2017, *Novartis Europharm* v *Commission*, C-629/15 P and C-630/15 P, EU:C:2017:498, paragraphs 77 and 78).

179 Following the same logic, Article 10(5) of Directive 2001/83 provides that, 'in addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication'. Article 10(5) of Directive 2001/83 concerns well-established substances which form part of the composition of medicinal products for which the regulatory data-protection period has expired.

Moreover, data protection lasting one year, as provided for by that provision, applies only to data relating to the new indication and not to all the data relating to the previously authorised medicinal product.

180 It follows that the fact, referred to in recital 3 of the implementing decision of 30 January 2014, that the application for marketing authorisation for Tecfidera was based on Article 8(3) of Directive 2001/83, that is to say, on a 'full' application (see paragraph 5 above), has no effect on the scope of the concept of a global marketing authorisation (see paragraph 177 above). Moreover, it is in the light of the objectives referred to in paragraphs 174 to 179 above that it is necessary to analyse whether, as the applicant in essence claims, there was, in the present case, a risk that Biogen Idec would enjoy a full regulatory data-protection period of eight years on the sole ground that, at the time of applying for a marketing authorisation for an indication other than that covered by Fumaderm, it had removed the MEF, which formed part of the composition of Fumaderm, but which was not clinically relevant or the dose of which was too low to have any significant therapeutic effect in Fumaderm.

(c) The applicable EU law and developments in scientific knowledge from 1994 to 2014

181 The applicant submits that, in the present case, it was not possible to assume that the MEF salts made a relevant therapeutic contribution within Fumaderm, on the ground that Fumaderm had previously been assessed by the BfArM and had been granted a marketing authorisation by that authority. In that regard, the applicant argues that Directive 2001/83 does not require proof of the existence of a therapeutic contribution for all active substances included in fixed combination medicinal products. Moreover, it submits that the content of the guidelines relating to combination medicinal products, and, more specifically, the standard of proof required by those guidelines, has evolved over time. Furthermore, since the guidelines are not legally binding, in the applicant's view, it is possible to depart from them.

182 In the reply, the applicant also criticises the EMA's assertion that the appropriate legal test is the test that the EMA indicated to Biogen Idec in its letter of 3 August 2011 (see paragraph 12 above), according to which the authorisation for a combination medicinal product is not regarded as being covered by the global marketing authorisations for the different active substances which form that combination. First, according to the applicant, that interpretation is not apparent either from the wording of Directive 2001/83 or from the Notice to Applicants. Second, in the applicant's view, the EMA provided a posteriori justification and the simplicity of the test proposed by the EMA was not appropriate to the procedure that was followed in the present case. If the interpretation proposed by the EMA were correct, the discussion as to the possibility of Tecfidera benefiting from a full regulatory data-protection period and the scientific assessment carried out in the present case by the Commission would never have had to take place.

183 The EMA maintains that the conclusion that Fumaderm and Tecfidera are not covered by the same global marketing authorisation is possible, since Fumaderm was authorised as a fixed combination containing the two active substances DMF and MEF, whereas Tecfidera was authorised as a monotherapy containing only the active substance DMF. According to the EMA, that approach reflects the application of two long-standing principles in the legislation. The first principle relates to the notion of a global marketing authorisation and the assessment that two medicinal products are covered by different global marketing authorisations where they differ in their qualitative compositions in terms of active substances. According to that first principle, if a product has been authorised as a fixed combination, this automatically means that its qualitative composition differs in terms of active substances from the qualitative composition of any medicinal product authorised as a monotherapy. The second principle put forward by the EMA relates to the harmonisation of the EU rules on the authorisation of medicinal products for human use, which ensures that, within the European Union, medicinal products are authorised according to the same rules and standards with regard to quality, safety and efficacy.

184 In the first place, it is common ground between the parties that, when Biogen Idec submitted an application for marketing authorisation for Tecfidera, this was the first time that, at EU level, the question arose as to whether or not an authorised combination medicinal product, on the one hand, and a component of that combination, on the other, belonged to the same global marketing authorisation.

185 That finding is confirmed by the amendments made to the part of the Notice to Applicants relating to the concept of a global marketing authorisation.

186 In the version of June 2013, the Notice to Applicants explained only:

'If the medicinal product being assessed contains a modification of an existing substance and belongs to the same applicant/marketing authorisation holder, it should be clarified during the marketing authorisation procedure whether the product contains a new active substance or not. This clarification impacts on the existence or not of a global marketing authorisation. This assessment is to be done in accordance with the criteria of Annex I at the end of this Chapter and the conclusion should be reflected at least in the assessment report. If the assessment report does not indicate that the product contains a new active substance, it will be considered that the product at stake contains the same active substance and belongs to the global marketing authorisation.'

187 It was after the implementing decision of 30 January 2014, namely in July 2015, that the part of the Notice to Applicants relating to the concept of a global marketing authorisation laid down the conditions for the application of that concept to applications relating to a component of a previously authorised combination medicinal product.

188 Point 2.3(3) of the Notice to Applicants, in the version of July 2015, states inter alia:

'If the medicinal product being assessed contains only one active substance which was part of an authorised combination product, the new medicinal product will form a new and unique medicinal product requiring a separate marketing authorisation. Considering that during the assessment procedure of the already authorised combination product, the marketing authorisation holder had demonstrated that each substance of the fixed combination has a documented therapeutic contribution within the combination and therefore all compounds are different active substances, the authorisation for the new medicinal product is not considered to fall within the scope of the global marketing authorisations of the already authorised combination medicinal product as described in Article 6(1) of Directive 2001/83/EC.'

189 In the second place, in the implementing decision of 30 January 2014, the Commission granted a marketing authorisation for Tecfidera and took the view that that medicinal product was not covered by the same global marketing authorisation as Fumaderm. The placing on the market of Fumaderm had been authorised by the BfArM in 1994, that is to say, more than 15 years before the submission of the application for marketing authorisation for Tecfidera.

190 On the date on which the marketing authorisation for Fumaderm was granted, consideration of applications for marketing authorisation relating to combination medicinal products was governed, first, by 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, Series I, Volume 1965-1966, p. 20), amended on several occasions, second, by Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (OJ 1975 L 147, p. 1), amended on several occasions, and, third, by 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), amended on several occasions.

191 Point 8(b) of the second paragraph of Article 4 of Directive 65/65, in the version resulting from Council Directive 87/21/EEC of 22 December 1986 (OJ 1987 L 15, p. 36), provided that, 'in the case of new proprietary medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of pharmacological and toxicological tests and of clinical trials relating to that combination [had to] be provided, but it [was not] necessary to provide references relating to each individual constituent'.

192 Furthermore, as is apparent from the EMA's written replies to the Court's questions, the particulars and documents which were to accompany the application for marketing authorisation pursuant to Article 4 of Directive 65/65 were referred to in Annex I to Directive 75/318, as amended by Commission Directive 91/507/EEC of 19 July 1991 (OJ 1991 L 270, p. 32). That annex comprised four parts relating to, respectively, the summary of the dossier, chemical, pharmaceutical and biological testing of medicinal products, toxicological and pharmacological tests, and clinical documentation.

193 Part 3 of that annex, relating to toxicological and pharmacological tests, included Section II, which concerned the performance of tests. Point F of Section II, relating to pharmacodynamics, namely the study of variations caused by the medicinal product in the functions of organisms, whether normal or experimentally modified, stated:

'Tests on combinations of active substances may be prompted either by pharmacological premisses or by indications of therapeutic effect.

In the first case, the pharmacodynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use.

In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

If a combination includes a novel active substance, the latter must previously have been studied in depth.'

194 In point G of Section II, relating to pharmacokinetics, namely the study of the fate of the product within the organism, which covers the study of absorption, distribution, biotransformation and excretion, it was stated that, 'in the case of new combinations of known substances which [had] been investigated in accordance with the provisions of [that directive,] pharmacokinetic studies [might] not be required, if the toxicity tests and therapeutic experimentation [justified] their omission'.

195 Part 4 of that annex, relating to clinical documentation, included, under Section C entitled 'Presentation of results', Section C.6, worded as follows: 'Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.'

196 First, the documents produced by the parties before the Court do not make it possible to ascertain whether Fumaderm was the result of pharmacological premisses or therapeutic indications. Nor does the material in the file indicate whether the BfArM considered that MEF and DMF were known or new substances. More generally, those elements do not make it possible to ascertain the methodology used by the BfArM to analyse Fumaderm and the various substances of which it is composed.

197 However, the file available to the Court contains the publication by C. Nieboer, D. de Hoop, A.C. van Loenen, P.N.J. Langendijk and E. van Dijk, entitled 'Systemic therapy with fumaric acid derivatives: New possibilities in the treatment of psoriasis' (*J Am Acad Dermatol*, 1989; 20(4):601-608; 'the 1989 Nieboer and Others study'), which was available to the EMA when it examined the application for

marketing authorisation for Tecfidera. In that publication, it is explained that a new therapy called 'fumaric acid therapy' had become popular in the previous 20 years in Western Europe among thousands of patients suffering from psoriasis. That therapy was initiated by a biochemist who himself suffered from psoriasis and who published works in 1959 and 1966. The 1989 Nieboer and Others study then states that that therapy was standardised by a German general practitioner who added a strict diet to it and who published studies in 1982 and 1984. The 1989 Nieboer and Others study also explains that a clinic specialising in that therapy was founded in Switzerland. Furthermore, it is apparent from another publication, dated 1998, which is in the file submitted to the Court and of which the EMA and the Commission could have been aware when examining the application for marketing authorisation for Tecfidera, that fumaric-acid esters were prescribed from 1959 by a small group of doctors in Germany, Switzerland and the Netherlands.

198 Second, it should be noted that the legislative texts referred to in paragraphs 190 to 195 above do not contain any details as to the form which justification for the combination medicinal product may take regarding safety and efficacy.

199 Where Part 3 of Annex I to Directive 75/318 provides that, in the case of medicinal combinations of active substances resulting from pharmacological premisses, the pharmacodynamic study must demonstrate the interactions which might make the combination itself 'of value' in therapeutic use, that annex does not state how those interactions are to be demonstrated. Moreover, that provision refers to the need for the combination as a whole to be 'of value'. Lastly, in the case of combinations of active substances resulting from indications of therapeutic effect, Part 3 of Annex I to Directive 75/318 refers to the expected effects of 'the combination', which may be demonstrated in animals.

200 Third, as the EMA explained in its written replies to the questions put by the Court, the information which, according to the Council of the European Union, had to accompany an application for marketing authorisation for a combination medicinal product in 1994 was in fact set out in Annex V to Council Recommendation 83/571/EEC of 26 October 1983 concerning tests relating to the placing on the market of proprietary medicinal products (OJ 1983 L 332, p. 11). Annex V to that recommendation, entitled 'Fixed-combination products', was a note for guidance concerning the application of point C.2 of Section II of Part 3 of the annex to Directive 75/318 (now Section C.6 of Part 4 of the annex to Directive 75/318 as amended, referred to in paragraph 195 above), for the purposes of the marketing authorisation for a new medicinal product.

201 In that regard, it is true that Annex V to Recommendation 83/571 stated, inter alia:

'Applicants will be required to justify the particular combination of active ingredients proposed. Fixed combination products will only be considered acceptable if the proposed combination is based on valid therapeutic principles.

…

The indications claimed for a fixed-combination product should be such that the presence of each component is justified for each indication. The product should be formulated so that the dose and proportion of each component present is appropriate to all the recommended uses.

…

… It will be necessary to test a new combination clinically against one or more of the components in order to define the role played by each in the total.

…

The possibility of interactions between the components should always be considered. Where a pharmaceutical, pharmacokinetic or pharmacodynamic interaction appears possible, the applicant should submit data either to establish that such interaction does not occur, or that it is clearly recognised and defined.'

202 However, it is not apparent from the wording and content of that document, or from the context in which it was adopted, that it produced binding legal effects for the Member States and, more specifically, for the national authorities.

203 Furthermore, as the applicant observes, the content of the guidelines relating to combination medicinal products and the scope of the information requested from applicants evolved significantly in that regard between the date of the marketing authorisation for Fumaderm (9 August 1994) and the day when the implementing decision of 30 January 2014 was adopted.

204 In other words, an examination of the successive versions of the recommendations or guidelines relating to combination medicinal products shows that they were progressively supplemented and that the purpose of those supplements was to distinguish between different types of combination medicinal products and to recommend to the national authorities that they request an increasing amount of information from applicants.

205 In that regard, the guidelines, in the revised version of April 1996 (Note for Guidance concerning the application of section C.6 [of] Part 4 of the Annex to Directive 75/318/EEC as amended), differ from Recommendation 83/571 as follows:

– they provide that the applicant must clearly indicate whether the claimed indication consists of a first-line therapy (intended for patients who did not receive any of the substances in question) or of a second-line therapy (implemented where monotherapy has not demonstrated a satisfactory risk-benefit ratio), or whether the indication is for other uses. Those guidelines, in the revised version of April 1996, state that clinical developments must be performed accordingly;

– they contain a section relating to pharmacodynamic and pharmacokinetic studies which refer to additional requirements which may be imposed on applicants. Those studies are of particular importance as regards the interactions between the substances of which the combination is composed. Thus, the guidelines, in the revised version of April 1996, explain that the applicant must demonstrate that the various substances do not affect each other's respective pharmacokinetic patterns;

– they contain a section relating to the composition and dosage which recommends that the proposed dosages be justified. It is thus stated that 'the dosage of each substance within the fixed combination must be such [that] the combination is safe and effective for a significant population subgroup and the benefit/risk assessment of the fixed combination is equal [to] or exceeds the one of each of its substances taken alone', that 'the multilevel factorial design may be used, but [that] other confirmatory strategies exist to prove that the combination is superior to its substances', and that 'descriptive tools such as response-surface methods may be useful (see *Dose Response Information to Support Product Authorisation*)';

– they contain a point relating to therapeutic trials which provides that confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the fixed combination is compared to its individual substances. The inclusion of a placebo group is recommended when feasible.

206 It should be added that Annex V to Recommendation 83/571 did not expressly mention the need for each substance of the fixed combination medicinal product to make a documented contribution within the combination. It was the guidelines, in the revised version of April 1996, which mentioned

for the first time that each substance of the fixed combination medicinal product had to make a 'documented contribution' within the combination. Subsequently, the guidelines, in the version adopted in 2009 (Guideline on clinical development of fixed combination medicinal products), referred to a documented 'therapeutic' contribution.

207 More generally, in the guidelines which followed the revised guidelines of 1996, the recommendations were more extensive and the information and particulars expected from applicants increased and were clarified.

208 Thus, on the date on which the decision granting marketing authorisation for Fumaderm was adopted, no legally binding provision laid down, in a precise manner, the conditions governing the grant of a marketing authorisation for a combination medicinal product or the manner in which the combination medicinal product was to be justified. Furthermore, it is true that Recommendation 83/571 already provided that applicants were required to justify the particular combination of active ingredients proposed and that a new combination had to undergo clinical trials in order to determine the role played by each of its components within the combination as a whole. However, those conditions, which were set out in a non-binding text, remained limited and imprecise as to how they would be implemented, in particular as regards the conditions which were subsequently formulated, in order to take into account, inter alia, developments in techniques.

209 In that regard, it must be noted that, in a letter sent to the Commission on 1 May 2013, which was produced before the Court by the Commission, Biogen Idec explained that the BfArM had approved Fumaderm as a combination of four active ingredients. However, Biogen Idec stated that 'according to the BfArM …, the Fumaderm dossier [did] not contain any clinical data on the [active pharmaceutical ingredients (APIs)]; it [contained] only safety and efficacy data on the combination product in total, and the properties of DMF alone [were] unknown'.

210 It is also important to note that, in response to a question put by the Court at the hearing, the EMA's representative explained that, to his knowledge, the concept of 'active substance' had not been defined at EU level before the entry into force of Directive 2001/83. That directive entered into force after the BfArM's decision granting marketing authorisation for Fumaderm.

211 Lastly, in 2013 it was still considered that, as EU law stood, until harmonisation of the measures necessary to ensure the protection of health was more complete, it would be difficult to avoid the existence of differences in the classification of products as between Member States in the context of Directive 2001/83 (see judgment of 3 October 2013, *Laboratoires Lyocentre*, C-109/12, EU:C:2013:626, paragraph 45 and the case-law cited).

212 In the third place, according to recital 7 of Directive 2001/83, 'the concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended'.

213 In that regard, it has already been held that, for the purpose of determining whether a product falls within the definition of a 'medicinal product' for the purposes of Directive 2001/83, the national authorities, acting under the supervision of the courts, must decide on a case-by-case basis, taking account of all the characteristics of the product, in particular its composition, its pharmacological, immunological or metabolic properties, to the extent to which they can be established in the present state of scientific knowledge, the manner in which it is used, the extent of its distribution, its familiarity to consumers and the risks which its use may entail (see judgment of 10 July 2014, *D. and G.*, C-358/13 and C-181/14, EU:C:2014:2060, paragraph 42 and the case-law cited).

214 A marketing authorisation is therefore granted on the basis of the state of scientific knowledge on the date on which the authorisation is granted.

215 In the present case, it must be noted that a period of more than 15 years elapsed between the decision granting marketing authorisation for Fumaderm and the submission of an application for marketing authorisation for Tecfidera. It is apparent from the file submitted to the Court that, during that period, the scientific knowledge of the substances which make up Fumaderm, their respective activities, and the means of studying them, developed considerably.

216 Moreover, it is apparent from the documents in the file that, when examining whether Tecfidera belonged to the same global marketing authorisation as Fumaderm, Biogen Idec submitted evidence after the BfArM's decision and that evidence was taken into account by the CHMP. In its request for Tecfidera to be awarded 'new active substance' status, Biogen Idec referred to several studies published after the BfArM's decision. Furthermore, in support of its request, Biogen Idec produced, inter alia, a letter dated 9 September 2013 entitled 'Comments on the Chemical Structural Differences Between Tecfidera and the combination product Fumaderm'. The scientific literature referred to in that letter, with one exception, post-dated the BfArM's decision. Lastly, in the EPAR, the CHMP took the view that MEF and DMF were both active and that they were not the same active substance, in particular on the basis of data produced by Biogen Idec post-dating the BfArM's decision.

217 In the light of the foregoing, it must be held that, in the present case, the Commission was faced with the new question of whether or not the marketing authorisation for a medicinal product, the only active substance of which was a component of a previously authorised combination medicinal product, belonged to the same global marketing authorisation as that granted to that combination. Moreover, that new question arose in a particular context characterised by the fact that the decision granting marketing authorisation for the combination medicinal product in question had been adopted by a national authority in 1994, that is to say, more than 15 years before the submission of the application for marketing authorisation for a medicinal product composed of a single active substance. In 1994, EU law and scientific knowledge were significantly different.

218 In that particular context, it must be noted, first, that the Commission was right not to adopt the approach set out by the EMA in its letter to Biogen Idec dated 3 August 2011, according to which the authorisation for a combination medicinal product was not regarded as being covered by the global marketing authorisations for the various individual active substances in accordance with Article 6(1) of Directive 2001/83 (see paragraph 12 above), and, second, that the Commission, in its letter of 18 September 2013, was right to request the CHMP to assess whether DMF differed from Fumaderm, which contained DMF and MEF salts (see paragraph 18 above).

(d) The principle of mutual recognition of decisions adopted by the national authorities

219 The applicant submits that it was essential for the Commission to verify whether it was established that the MEF salts had, from a therapeutic point of view, a relevant activity within Fumaderm. However, the applicant claims that the CHMP and the Commission failed to carry out such a verification. In its view, none of the available evidence proves that the documented therapeutic contribution test was actually applied during the initial assessment of Fumaderm in respect of the MEF salts. Furthermore, the applicant argues that there is no evidence that, during the assessment of Tecfidera, the CHMP at any point asked the BfArM to provide it with information in order to ensure that the activity of the MEF salts within Fumaderm had been properly assessed.

220 The EMA relies on the principle of mutual recognition and argues that it is not possible for a regulatory authority, such as the Commission or itself, to revise the assessment of another regulatory authority in the context of the examination of an application for marketing authorisation for a medicinal product. The EMA argues that it is not legally authorised, save in exceptional circumstances (for example, in the case of a referral under Article 31 of Directive 2001/83), to carry out a fresh assessment of the initial scientific assessment of an authorised medicinal product. The EMA adds that

the question of the assessment of the therapeutic efficacy of both DMF and MEF within Fumaderm had already been addressed in the assessment carried out by the BfArM and that, if that had not been the case, Fumaderm could not have been authorised as a combination medicinal product.

221 The EMA disputes the applicant's argument that the assumed therapeutic contribution of MEF within Fumaderm was never verified during the CHMP's assessment or taken into account in the Commission's decision-making procedure. According to the EMA, the verification of the documented therapeutic contribution of MEF in Fumaderm was de facto outside the scope of the assessment that the Commission had requested the CHMP to carry out in relation to DMF. Furthermore, the EMA argues that that verification would be *de lege* outside the scope of the CHMP's assessment, since the CHMP is not authorised, in the context of the marketing authorisation for Tecfidera, to reopen the scientific assessment of Fumaderm that was carried out by the BfArM.

222 Lastly, contrary to the applicant's assertions, the implementing decision of 30 January 2014 contains a clear reference to the BfArM's authorisation of Fumaderm and to the fact that Fumaderm was authorised as a medicinal product containing the active substances MEF and DMF. The EMA argues that such a reference necessarily includes a reference to the scientific assessment of the therapeutic contribution of each substance in the combination that led to the authorisation of Fumaderm as a combination medicinal product.

223 It is true that, as regards the mutual-recognition procedure referred to in Article 28(2) of Directive 2001/83, the Court of Justice has held that it cannot be accepted that the Member State in receipt of an application for mutual recognition is entitled, outside of the situation where there is a risk to public health referred to in Article 29 of that directive, to carry out a fresh assessment of the data on essential similarity which the reference Member State relied on in accepting an abridged application (see, to that effect, judgment of 16 October 2008, *Synthon*, C-452/06, EU:C:2008:565, paragraph 31). The Court of Justice added that such an interpretation would not only run counter to the very wording of Articles 28 and 29 of Directive 2001/83, but also render those provisions redundant. If a Member State which was asked to recognise an authorisation already granted by another Member State could make that recognition subject to a second assessment of all or part of the application for authorisation, that would deprive the mutual-recognition procedure established by the EU legislature of all meaning and seriously compromise the attainment of the objectives of Directive 2001/83, such as, in particular, the free movement of medicinal products in the internal market (judgment of 16 October 2008, *Synthon*, C-452/06, EU:C:2008:565, paragraph 32).

224 It is also true that, with regard to the decentralised procedure, referred to in Article 28(3) of Directive 2001/83, the Court of Justice has held that, once the general agreement of the Member States in which the application for marketing authorisation was submitted is acknowledged, the competent authorities of those Member States may not, when making their decision on the placing on the market of that medicinal product in their territory, call into question the outcome of that procedure. Apart from being contrary to the wording of Article 28(5) of Directive 2001/83, such an interpretation would deprive the decentralised procedure of all meaning and would, inter alia, compromise the attainment of the objective of free movement of medicinal products set out in recital 14 of that directive (judgment of 14 March 2018, *Astellas Pharma*, C-557/16, EU:C:2018:181, paragraph 26).

225 However, first of all, in the judgments referred to in paragraphs 223 and 224 above, the Court of Justice was not called upon to rule on cases in which, as in the present case, an application for marketing authorisation such as that in relation to Tecfidera had been submitted to the EMA under the centralised procedure provided for in Regulation No 726/2004 and in which the Commission was the authority required to adopt a decision on that application.

226 It should be noted that, in the cases which gave rise to the judgments of 16 October 2008, *Synthon* (C-452/06, EU:C:2008:565), and of 14 March 2018, *Astellas Pharma* (C-557/16, EU:C:2018:181), the Court of Justice dealt with questions relating to the powers of the authorities of the Member States in

the context of the mutual-recognition procedure or the decentralised procedure. It is clear from Articles 28 and 29 of Directive 2001/83 that those procedures concern the grant of a marketing authorisation for a medicinal product in more than one Member State, and therefore relations between the Member States.

227 Thus, it cannot be inferred from the judgments of 16 October 2008, *Synthon* (C-452/06, EU:C:2008:565), and of 14 March 2018, *Astellas Pharma* (C-557/16, EU:C:2018:181), relied on by the EMA in the defence, that the Commission was not entitled to request the CHMP to carry out a new scientific assessment of a medicinal product already authorised by a national authority or, at the very least, to ask the BfArM for the information necessary to verify the assessment which had previously been carried out by that national authority.

228 Next, it must be noted that, according to recital 19 of Regulation No 726/2004, the chief task of the EMA should be to provide EU institutions and Member States with the best possible scientific opinions so as to enable them to exercise the powers regarding the authorisation and supervision of medicinal products conferred on them by EU legislation in the field of medicinal products. Also according to recital 19 of Regulation No 726/2004, only after a single scientific evaluation procedure addressing the quality, safety and efficacy of high-technology medicinal products has been conducted by the EMA, applying the highest possible standards, should marketing authorisation be granted by the European Union, and this should be done by means of a rapid procedure ensuring close cooperation between the Commission and Member States.

229 It is apparent from Regulation No 726/2004 that the EMA is responsible for coordinating the existing scientific resources put at its disposal by the Member States for the evaluation, supervision and pharmacovigilance of medicinal products and that it is composed of, inter alia, the CHMP, which is responsible for preparing the EMA's opinion on any question relating to the evaluation of medicinal products for human use. According to the first subparagraph of Article 57(1) of Regulation No 726/2004, the EMA is to provide the Member States and the institutions of the Union with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use which is referred to it in accordance with the provisions of Union legislation relating to medicinal products. According to Article 60 of Regulation No 726/2004, at the request of the Commission, the EMA must, in respect of authorised medicinal products, collect any available information on methods that Member States' competent authorities use to determine the added therapeutic value that any new medicinal product provides.

230 Lastly, it should be noted that, according to recital 12 of Directive 2001/83, in the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken according to an EU standard, leading to a single decision on the area of disagreement binding on the Member States concerned. That decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States. Moreover, according to recital 17 of Regulation No 726/2004, the European Union should have the means to carry out a scientific assessment of the medicinal products presented in accordance with the decentralised authorisation procedures. Moreover, with a view to ensuring the effective harmonisation of administrative decisions taken by Member States with regard to medicinal products presented in accordance with decentralised authorisation procedures, it is necessary to endow the European Union with the means to resolve disagreements between Member States concerning the quality, safety and efficacy of medicinal products.

231 Thus, according to Article 30(1) of Directive 2001/83, if two or more applications submitted in accordance with Articles 8, 10, 10a, 10b, 10c and 11 of that directive have been made for marketing authorisation for a particular medicinal product, and if Member States have adopted divergent decisions concerning the authorisation of the medicinal product or its suspension or revocation, a

Member State, the Commission or the applicant or the marketing-authorisation holder may refer the matter to the CHMP for the application of the procedure laid down in Articles 32, 33 and 34 of that directive.

232 It should also be noted that, according to Article 31(1) of Directive 2001/83, the Member States, the Commission, the applicant or the marketing-authorisation holder must, in specific cases where the interests of the Union are involved, refer the matter to the CHMP for application of the procedure laid down in Articles 32, 33 and 34 of that directive before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary.

233 By the adoption of Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83 (OJ 2004 L 136, p. 34), the EU legislature conferred on the Commission the power to adopt acts having binding effect on the Member States, in particular after amending Article 31 of Directive 2001/83.

234 When particular cases which are relevant to the EU are brought before the CHMP in the context of the procedure set out in Article 31(1) of Directive 2001/83, it is for the CHMP to carry out, at EU level, its own assessment of the relevant medicinal product. The assessment carried out by that committee is independent of that carried out by the national authorities. In that regard, the assessment which a national authority might have had of that information in the past cannot be used to challenge the CHMP's assessment as regards information which it is called upon to analyse for the first time (judgment of 3 December 2015, *PP Nature-Balance Lizenz* v *Commission*, C-82/15 P, not published, EU:C:2015:796, paragraph 37; see also, to that effect, judgment of 19 September 2019, *GE Healthcare* v *Commission*, T-783/17, EU:T:2019:624, paragraph 101).

235 The procedure laid down in Article 31 of Directive 2001/83 may therefore, inter alia on the initiative of the Commission, lead, following an independent assessment carried out by the CHMP, to a Commission decision in which it requires the competent authorities of the Member States concerned themselves to adopt a decision on the basis of Article 116 of Directive 2001/83, namely a decision to suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product concerned is harmful, that it lacks therapeutic efficacy, that the risk-benefit ratio is not favourable or where its qualitative/quantitative composition is not as declared.

236 In view of the foregoing and without it being necessary to rule on the applicability of Article 31 of Directive 2001/83 in the present case, it must be held that, in the context of the marketing-authorisation procedures implemented at EU level or in the Member States, the EMA and the Commission perform a particular function that is not comparable to that of the national authorities. The principle of mutual recognition relied on by the EMA cannot therefore prevent, following the submission of an application for marketing authorisation under the centralised procedure, the CHMP from examining the assessments previously carried out by a national authority or from itself carrying out an independent assessment. That is particularly the case where an application for marketing authorisation is submitted at EU level for a substance which forms part of the composition of a combination medicinal product authorised 15 years previously at national level, and where the data held by the CHMP are such as to render implausible a theory that the substance which has been withdrawn from that combination, in the present case MEF, plays a role within it.

237 That is all the more true in the present case since, following the application for marketing authorisation for Tecfidera submitted under the centralised procedure, the EMA, through the CHMP, and then the Commission, took a decision as to whether Tecfidera belonged to the same global marketing authorisation as Fumaderm. That assessment had, at EU level, an impact on the period of regulatory protection of the data relating to Tecfidera and was liable to impede the grant, by the competent authorities of the Member States or by the Commission, of a marketing authorisation for a generic medicinal product derived from Tecfidera. Thus, the question of whether Tecfidera was

covered by the same global marketing authorisation as Fumaderm, and, in that context, whether MEF played a role within Fumaderm, constituted a particular case of interest to the European Union in the light of the objectives pursued by Directive 2001/83 in general, namely the essential objective of safeguarding public health and the objective of free movement of medicinal products, and in the light of the objectives pursued by the concept of global marketing authorisation referred to in paragraphs 174 to 179 above.

238 The Commission's conduct during the procedure that preceded the adoption of the implementing decision of 30 January 2014, and the analyses carried out by the CHMP at that institution's request in respect of Tecfidera, confirm the particular role played by each of them. They show that the Commission did not consider that it was bound by the decision adopted by the BfArM in 1994. The Commission took the view that the finding that Tecfidera did not belong to the same global authorisation as Fumaderm was subject to an assessment of the status of Tecfidera as a 'new active substance'. In those circumstances, the Commission, by letter of 18 September 2013, requested the CHMP to assess whether DMF differed from Fumaderm (see paragraph 18 above). Following that request, the rapporteurs examined both whether DMF and MEF were different active substances and whether Fumaderm, which contained MEF and DMF, differed from DMF in terms of safety and efficacy. The request made by the Commission on 18 September 2013, as well as the data gathered and the examination carried out by the CHMP following that request, were capable of leading to assessments and to a conclusion which contradicted the BfArM's decision granting marketing authorisation for Fumaderm as a combination medicinal product.

(e) The data available, or which could have been available, to the EMA and the Commission concerning the role of MEF in Fumaderm

239 It is important to note that, in its letter of 18 September 2013 to the Chair of the CHMP, the Commission stated that Biogen Idec had requested that the question of whether the active substance DMF could be classified as a new active substance be analysed. Moreover, the Commission stated that a new active substance was defined as a chemical substance that had not previously been authorised as a medicinal product in the European Union. Furthermore, it noted that DMF had not previously been authorised as a medicinal product in the European Union, but was part of the medicinal product Fumaderm, which had been authorised in Germany in 1994 (see paragraph 18 above).

240 Following that letter, and following the assessments made by the rapporteurs in a joint report of 18 October 2013 (see paragraph 22 above), the CHMP, during a meeting on 24 October 2013, raised two objections to the request for DMF to be awarded 'new active substance' status (see paragraph 23 above). Those objections were aimed, first, at establishing whether DMF and MEF were esters or derivatives of each other and, second, at addressing the relevant clinical differences in terms of safety and/or efficacy between DMF, on the one hand, and DMF combined with MEF, on the other. On 4 November 2013, Biogen Idec provided its responses to the objections raised by the CHMP. In a joint report of 11 November 2013, the rapporteurs analysed Biogen Idec's responses and set out their assessment (see paragraph 25 above).

241 In the EPAR, the CHMP considered that MEF and DMF were both active and were not the same active substance because they did not share the same therapeutic moiety. The CHMP inferred from this that there was no need for further investigation of potential significant differences with regard to the safety/efficacy profile. Moreover, on the basis of the scientific evidence and in line with the clarification provided by the Commission in its letter of 18 September 2013, the CHMP considered that DMF differed from Fumaderm, which contained DMF and MEF salts. That finding, as well as a reminder of the content of the Commission's letter of 18 September 2013, also appear in the CHMP's opinion of 21 November 2013 (see paragraph 26 above).

242 It was in those circumstances that the CHMP collected clinical data relating, inter alia, to MEF's pharmacological activity considered in isolation and to MEF's pharmacological activity within Fumaderm. Those clinical data were produced by the applicant before the Court in support of its arguments.

243 The applicant submits, in essence, that the evidence produced by Biogen Idec and taken into consideration during the procedure preceding the adoption of the implementing decision of 30 January 2014 was neither sufficient nor sufficiently strong to support the conclusion that there was a relevant 'difference' between Tecfidera and Fumaderm. In particular, the applicant submits that the CHMP could not have concluded, on the basis of the available evidence, that the MEF salts had a relevant therapeutic activity within the combination of DMF and MEF salts in Fumaderm. Therefore, according to the applicant, the only relevant active substance in Fumaderm is DMF. In its view, those findings are, moreover, supported by the fact that the available clinical evidence did not demonstrate that MEF, considered in isolation, had therapeutic activity.

244 The EMA contends that the CHMP was correct to conclude that MEF has pharmacological activity on the basis of limited clinical evidence since, first, that evidence was documented by non-clinical data and, second, marketing authorisation had already been granted for Fumaderm and its pharmacological activity had already been established by the competent authority of a Member State. The EMA adds that the arguments put forward by the applicant against the assessment carried out by the CHMP are ineffective. The EMA argues that, in the context of the applicant's challenge to the CHMP's assessment of the clinical and non-clinical data, the applicant has misinterpreted the objective pursued by that assessment and starts from the incorrect premiss that the CHMP was required to carry out an assessment of the therapeutic effect of MEF within Fumaderm. The BfArM had already carried out such an assessment and the fact that Fumaderm had been authorised as a combination medicinal product means that it was shown, during that assessment, that MEF and DMF have a documented therapeutic contribution in the combination. Thus, according to the EMA, the CHMP was not required to carry out another such assessment in the context of the application for marketing authorisation for Tecfidera. The EMA states that the CHMP analysed the clinical data submitted by Biogen Idec, subsequently relied on by the applicant, solely in order to determine the pharmacological activity of MEF. Since the clinical data relating to MEF alone were relatively limited, the activity of MEF was verified indirectly, by comparing the data from patients exposed to MEF combined with DMF with the data from patients exposed to DMF alone. In that regard, the EMA states that the CHMP referred to the publication of C. Nieboer, D. de Hoop, P.N.J. Langendijk, A.C. van Loenen and J. Gubbels, entitled 'Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester' (*Dermatologica*, 1990; 181(1):33-37; 'the 1990 Nieboer and Others study') solely for the purpose of substantiating the conclusion that MEF is pharmacologically active.

245 In the first place, as regards the clinical activity of MEF considered in isolation, the CHMP examined the 1989 Nieboer and Others study (see paragraph 197 above), which describes six therapeutic schemes based on DMF and MEF used in the treatment of psoriasis.

246 In the defence, the EMA states that the research carried out in the context of that study revealed that 'the itching score [had shown] a greater drop in the [MEF] group than in the placebo group' and that 'significant differences ($p < 0.05$) [had been] noted between the final scores of scaling and itching of both groups' of patients who had received different doses of MEF.

247 According to the EMA, it is clear from the foregoing that administering MEF provided results that differ from those obtained by administering the placebo as regards the itching test, and that different doses of MEF produced very different results as regards the scaling and itching test.

248 However, first, in the rapporteurs' joint assessment report of 18 October 2013, they state that the 1989 Nieboer and Others study relates to formulations of products which are not fully described and to a population for whom the criteria for inclusion and severity of symptoms are also not indicated. Furthermore, the rapporteurs' joint assessment report of 11 November 2013 states that '… DMF and the MEF salts do not exert clinically relevant differences in terms of safety[, that it] is not possible to conclude to clinically relevant differences in terms of efficacy as the only available data comes from [the 1989 Nieboer and Others study, and that] only 10 psoriasis patients took MEF alone in a study, which methodology cannot be reliably assessed'.

249 Second, in the EPAR, the CHMP explains that the available clinical data on MEF alone are derived from published literature and are limited.

250 Thus, the documents in the file show that the 1989 Nieboer and Others study does not provide relevant and sufficient data concerning the clinical activity of MEF considered in isolation.

251 In any event, it should be noted that the 1989 Nieboer and Others study compared MEF sodium salt (MEFAE-Na) with a placebo. MEFAE-Na is not part of the composition of Fumaderm (see paragraph 2 above). Moreover, as regards the comparison between the group that received a daily 240 mg dose of MEF sodium salt (MEFAE-Na) and the group that received the placebo, it is stated that there was no difference between the numbers of improved, unimproved, or deteriorated cases in both groups. In the same study, it is explained that the average final score was the same in both groups and that only the itching score showed a significant reduction in the group that received MEFAE-Na. The authors of the study also explain that a comparative study between taking 720 mg of MEFAE-Na daily and 240 mg of MEFAE-Na daily was performed because the daily 240 mg dose of MEFAE-Na had proved ineffective. Again in the 1989 Nieboer and Others study, the authors state that no difference was seen between taking 720 mg of MEFAE-Na and 240 mg of MEFAE-Na in terms of the number of improved patients.

252 In the second place, as regards the comparison between DMF alone and the combination of DMF and MEF salts, first, the EMA states, with regard to the 1989 Nieboer and Others study, that the CHMP, in the EPAR, also 'noted that treatment effects [had been] seen earlier with DMF/MEF combination than with DMF alone'. According to the EMA, only the pharmacological activity of MEF can explain why administering DMF in combination with MEF leads to effects more quickly than administering DMF alone.

253 However, first of all, it should be noted that the 1989 Nieboer and Others study methodology could not be reliably assessed (see paragraph 248 above). Thus, the information in the file shows that that study does not provide relevant data regarding the role of MEF within Fumaderm.

254 Next, it is apparent from the rapporteurs' joint assessment report of 18 October 2013 that the 1989 Nieboer and Others study did not enable an assessment to be made as regards the extent of the pharmacological activity of DMF and MEF in Fumaderm. Thus, the rapporteurs took the view, in essence, that the respective activities of DMF and MEF had to be described in greater depth by Biogen Idec in order to help establish the role played by MEF in Fumaderm.

255 Furthermore, in the 1989 Nieboer and Others study, the authors noted that, in the context of the combination of DMF and MEF, the DMF dose was considerably higher than the dose used for tests relating to DMF alone. Thus, in view of the doses which had been used, the results of the 1989 Nieboer and Others study were not sufficient to conclude that the effects of the treatment had been noted more quickly with a combination of DMF and MEF than with DMF alone.

256 Lastly, in the 1989 Nieboer and Others study, the authors stated that the question of whether the addition of MEF salts to DMF had an additional effect or even a potential effect would be a matter of investigation.

257 Second, it should be noted that, when examining whether Tecfidera was covered by the same global marketing authorisation as Fumaderm, the CHMP also examined the 1990 Nieboer and Others study (see paragraph 244 above), which concerns a double-blind trial comparing the effects of DMF as a single agent with the combination of DMF and MEF.

258 In that regard, the EMA states that, following the 1990 Nieboer and Others study, the CHMP concluded that '… [the] improvement percentage (i.e. psoriasis severity score more than halved) was 55% in the DMF group and 80% in the DMF/MEF salt combination group' and that 'the course of the total score and of the separate parameters during the four months of the study showed a tendency towards a more rapid result with the DMF/MEF salt combination group than with the DMF single treatment'. The EMA infers from this that administering DMF in combination with MEF produces effects that differ from those obtained by administering only DMF.

259 However, in the 1990 Nieboer and Others study, the authors explain, by way of introduction, that DMF and MEF salts form the active ingredients of gastro-resistant tablets that are usually prescribed as part of fumaric-acid therapy. According to the authors, that combination appears to be based on historical factors rather than on a rational therapeutic approach.

260 Furthermore, as the applicant submits, the summary carried out by the CHMP does not adequately reflect the authors' main findings and conclusions, which were that:

– 'the observed differences between the two groups appeared to be not significant';

– the course of the total average score in both groups that received treatment with DMF alone, on the one hand, and with DMF and MEF, on the other, 'was not significantly different at any time point', 'subsequently the separate parameters too did not show a significant difference in time course' and 'the results after four months were not statistically different';

– 'the course of the total score and of the separate parameters during the four months of the study showed a tendency towards a more rapid result with [the DMF and MEF combination] than with [DMF] monotherapy [alone]'; 'however, this difference was not significant and the final score in both groups was the same';

– in summary, 'one could state that treatment of psoriasis with [the DMF and MEF combination] [did] not result in a better therapeutic result compared to [DMF] monotherapy [alone]'.

261 Furthermore, in the publication by M. Rostami-Yazdi, B. Clement and U. Mrowietz, entitled 'Pharmacokinetics of anti-psoriatic fumaric acid esters in psoriasis patients' (*Arch Dermatol Res*., 2010; 302(7):531-538), which was available to the CHMP when it assessed Tecfidera, the authors interpreted the results of the 1990 Nieboer and Others study as meaning that it showed 'that the essential compound of Fumaderm is DMF, since treatment of psoriasis with a mixture of DMF and MEF in comparison to a monotherapy with DMF was not superior'.

262 Third, in their joint assessment report of 18 October 2013, the rapporteurs explained that there was a special interest in the contribution of MEF salts to the pharmacological activity in Fumaderm. Although Fumaderm was authorised and placed on the market in Germany for the treatment of psoriasis in 1994, the rapporteurs observed that Biogen Idec had not performed a clinical study with Fumaderm on patients suffering from multiple sclerosis, which complicated the assessment.

263 Furthermore, it is important to note that, despite the fact that the results of the 1989 Nieboer and Others study and the 1990 Nieboer and Others study were available to the rapporteurs, in their joint assessment report of 18 October 2013 they stated that Biogen Idec had to describe in greater detail the extent to which DMF and MEF respectively exerted their pharmacological activities as components of Fumaderm, in order to establish the role played by MEF within Fumaderm. Thus, they

took the view, in essence, that very few clinical data had been presented by Biogen Idec and that it had to describe in greater detail the respective activities of DMF and MEF in order to help establish the role played by MEF in Fumaderm.

264 Fourth, and above all, it is important to note that, in their joint report of 11 November 2013, the rapporteurs analysed Biogen Idec's responses and considered that the active substance DMF contained in the medicinal product Tecfidera could not be classified as a 'new active substance', on the ground that it was not clear from the data submitted that the properties of DMF differed significantly, in terms of safety and/or efficacy, from the product Fumaderm, which was authorised at that time and which contained a mixture of DMF and MEF salts.

265 It follows from the foregoing that the clinical studies examined by the CHMP did not support the conclusion that the effects of administering DMF in combination with MEF differed from those obtained by administering only DMF. The information available to the EMA and to the Commission was, on the contrary, such as to render implausible the theory that MEF played a therapeutic role within Fumaderm.

266 As an annex to the defence, the EMA produced the decision granting marketing authorisation for Fumaderm and the annexes thereto dated 1994, namely, inter alia, the SmPC for that medicinal product and the conditions to which its being placed on the market was subject.

267 As a preliminary point, it should be noted that, in response to a written question put by the Court, the EMA and the Commission explained that they were not in possession of those documents when the implementing decision of 30 January 2014 was adopted.

268 In any event, it should be noted that, in the SmPC for Fumaderm, it is explained that 'the mechanism of action of fumaric acid esters in the treatment of vulgaris psoriasis has not yet been clarified' and that 'no pre-clinical study is available due to the absence of appropriate animal models'.

269 Moreover, certain explanations in the documents produced call into question the role of MEF in Fumaderm.

270 It should be noted that the BfArM granted two marketing authorisations, the first for Fumaderm prae or Fumaderm initial, and the second for Fumaderm. The quantity of DMF contained in a Fumaderm prae tablet is four times lower than the quantity of DMF contained in a Fumaderm tablet (see paragraph 2 above).

271 In the annex relating to the conditions for placing Fumaderm prae and Fumaderm on the market, the BfArM explains that Fumaderm prae cannot be a therapy for psoriasis because its clinical effectiveness has not been demonstrated. In that regard, the BfArM states that it is possible to accept that three-week pre-treatment with Fumaderm prae improves the tolerance of treatment with Fumaderm. However, the BfArM states that it is still impossible to understand why the percentage of the mixture of three fumaric-acid compounds in Fumaderm prae must be completely different to the mixture present in Fumaderm. The BfArM adds that a more detailed examination is required.

272 It is true that, in the SmPC for Fumaderm, it is stated that, as regards acute toxicity, the components of Fumaderm gastro-resistant tablets proved to be less toxic in combination than individually. However, as the EMA noted in the defence, the joint assessment report of 11 November 2013 states that '[DMF and MEF] appear to have a similar nephrotoxic potential, which coincides with the adverse events observed after treatment with fumarate esters in psoriasis patients'. In that report, it is also stated that 'as … mentioned in the section on renal toxicity, a certain threshold dose of fumarate esters (regardless of the content of DMF and MEF) is apparently sufficient to induce gastrointestinal (and also renal) [adverse events]'. Furthermore, it is important to note that, in their joint report of 11 November 2013, the rapporteurs analysed Biogen Idec's responses and considered that the active

substance DMF contained in the medicinal product Tecfidera could not be classified as a 'new active substance', on the ground that it was not clear from the data submitted that the properties of DMF differed significantly, in terms of safety and/or efficacy, from the product Fumaderm, which was authorised at that time and which contained a mixture of DMF and MEF salts. Moreover, the EPAR relating to Tecfidera contains a number of references to experience acquired with regard to safety following the marketing of Fumaderm.

273 It follows that, when the implementing decision of 30 January 2014 was adopted, the EMA and the Commission had, or could have had, data capable of rendering implausible the theory that MEF played a role within Fumaderm.

274 There was therefore a risk that Biogen Idec would obtain a full and additional period of regulatory data protection, lasting eight years, on the sole ground that, at the time of applying for a marketing authorisation for an indication different to that covered by Fumaderm, it had removed the MEF which formed part of the composition of Fumaderm, but which was not clinically relevant or the dose of which was too low to produce any significant therapeutic effect within Fumaderm.

275 In such particular circumstances, the grant to Biogen Idec of a new regulatory data-protection period, lasting eight years, in respect of a medicinal product which covers a new therapeutic indication combined with a change in the strength of the medicinal product would run counter to the objectives pursued by Articles 6 and 10 of Directive 2001/83 (see paragraphs 174 to 179 above). Such a regulatory data-protection period would not ensure a fair balance between the protection of the interests of innovative companies and the need to promote the production of generic medicinal products. Furthermore, that protection would run counter to the objective of the 'abridged' procedure, which is to save the time and expense needed to gather the results of the pharmacological and toxicological tests and clinical trials and to avoid the repetition of tests on humans or animals.

276 That conclusion is not called into question by the fact, noted by the EMA, that, in the EPAR, the CHMP also took into account Article 10(2)(b) of Directive 2001/83 and the provisions of point 3 of Part II of Annex I to that directive (see paragraph 29 above).

277 First, it must be noted that those provisions were applied solely in order to examine whether MEF and DMF, considered individually and not within a combination medicinal product, constituted different active substances. Thus, in the EPAR, the CHMP found that MEF and DMF were both active and were not the same active substance because they did not share the same therapeutic moiety. As it noted in its revised opinion of 21 November 2013 (see paragraph 26 above), the CHMP, in the EPAR, considered that DMF differed from Fumaderm, which contained DMF and MEF, 'on the basis of an examination of the scientific evidence and in line with the clarification provided by the Commission in its letter of 18 September 2013'. The information provided by the Commission included the fact that DMF was part of the medicinal product Fumaderm, which had been authorised in Germany in 1994.

278 Second, the provisions of point 3 of Part II of Annex I to Directive 2001/83 apply to the assessment of the relationship between an essentially similar medicinal product and an already authorised product where the active substance of the essentially similar medicinal product contains the same therapeutic moiety associated with a salt/ester complex/derivative. Those provisions therefore concern the relationship between a potential generic medicinal product and a reference medicinal product. Those provisions do not concern the examination, as in the present case, of the relationship between two reference medicinal products in order to determine whether they are covered by the same global marketing authorisation. In reality, the purpose of point 3 of Part II of Annex I to Directive 2001/83 is to assess whether or not the relevant active substance constitutes a 'new active substance'. As follows from paragraphs 26 to 39 above, the CHMP had, in its revised opinion and in the EPAR, initially concluded that DMF was a new active substance. The Commission had adopted that conclusion in the draft implementing decision that it had submitted to the Standing Committee on

Medicinal Products for Human Use established by Article 121(1) of that directive. However, following objections raised on that point within that committee, the reference to 'new active substance' status as regards DMF was removed from recital 3 of that implementing decision, as adopted by the Commission. Consequently, the EPAR was amended by the addition of a note stating that the final declaration of the CHMP's opinion on the award of that status to DMF was obsolete.

279 In addition, it must be noted that Article 10(2)(b) of Directive 2001/83 sets out the definition of a generic medicinal product. In that regard, it should be noted that it is true that any medicinal product which may, under Article 10(2)(b) of Directive 2001/83, claim to be a generic medicinal product of a previously authorised reference medicinal product is necessarily covered by the same global authorisation as that medicinal product. However, the fact that a medicinal product falls outside classification as a generic medicinal product within the meaning of Article 10(2)(b) of Directive 2001/83 does not necessarily preclude that medicinal product from being covered by the same global authorisation as a previously authorised medicinal product. The concept of a global marketing authorisation referred to in Article 6(1) of Directive 2001/83 is thus broader than the definition of a generic medicinal product referred to in Article 10(2)(b) of Directive 2001/83.

280 As regards the relationship between a combination medicinal product and the substances of which it is composed, it is common ground that the documented therapeutic contribution of each of those substances within that combination is a condition for authorisation of that combination as being composed of different active substances. In its written replies to the Court's questions, the Commission also stated that 'there [was] a clear correlation between establishing the therapeutic contribution of each of the two or more active substances in a fixed combination medicinal product, and the answer to the question of whether or not a single active substance used in a different medicinal product [qualified] as the same active substance as the active substances included in the fixed combination'. Thus, the assessment of a difference between a combination medicinal product and the substances of which it is composed depends on the existence of a documented therapeutic contribution of each of those substances within that combination. It follows that the finding that MEF and DMF are two different active substances, when they are analysed individually in the light of Article 10(2)(b) of Directive 2001/83, does not support the conclusion that DMF on its own differs, and is therefore covered by a different global marketing authorisation, from a combination medicinal product composed of MEF and DMF. In order to draw such a conclusion, it is necessary to establish that MEF and DMF each make a therapeutic contribution within that combination.

281 Third, it is clear from recital 3 of the implementing decision of 30 January 2014 that the assessment that Tecfidera differs from Fumaderm and is not covered by the same global marketing authorisation as that combination medicinal product is based on two findings: the CHMP's finding that MEF and DMF are both active and are not the same active substance, and the finding that a marketing authorisation had already been granted for Fumaderm as a combination medicinal product composed of DMF and MEF.

282 In the present case, those findings were not sufficient to conclude that Tecfidera was covered by a different global marketing authorisation than Fumaderm. In view of the objectives of global marketing authorisations, the EU law applicable to combination medicinal products in 1994 and the development of scientific knowledge between 1994 and 2014, the particular function performed by the EMA and the Commission, and the data available, or which could have been available, to them which rendered implausible the theory that MEF played a role within Fumaderm (see paragraphs 175 to 275 above), it must be held that the Commission was not entitled to conclude that Tecfidera was covered by a different global marketing authorisation than Fumaderm, which had previously been authorised, without verifying or requesting the CHMP to verify whether and, if necessary, how, the BfArM had assessed the role of MEF within Fumaderm, or without requesting the CHMP to verify the role played by MEF within Fumaderm.

283 First, it must be noted that, as is apparent from the written replies to the questions put by the Court, neither the EMA nor the Commission had, prior to the adoption of the implementing decision of 30 January 2014, the file which led to the marketing authorisation for Fumaderm. It should also be noted that, on the date that implementing decision was adopted, the EMA was not in possession of the documents annexed to the defence, namely the decisions in German granting marketing authorisation for Fumaderm prae and Fumaderm, and the annexes to those decisions (see paragraph 266 above). By way of comparison, it is possible to point out that, under Article 28 of Directive 2001/83, which concerns the mutual-recognition procedure and the decentralised procedure, all the Member States are to receive the dossiers in respect of an application for marketing authorisation, together with the assessments carried out by the reference Member State (see also Article 60 of Regulation No 726/2004, referred to in paragraph 229 above).

284 It must also be noted that, in response to a question put by the Court, the applicant produced the decision by which the BfArM refused its application for access to the documents relating to the marketing authorisation for Fumaderm (see paragraph 51 above). In that decision, the BfArM explained that, for medicinal products for which authorisation had been sought before 6 September 2005, there was no obligation to draw up or publish a public assessment report and that, consequently, the information to which the applicant had requested access did not fall within the public domain.

285 Nor has it been established that, during the assessment of Tecfidera, Biogen Idec provided the EMA or the Commission with the data that had been produced with a view to obtaining a marketing authorisation for Fumaderm. In that regard, it should be noted that, in its written replies to the questions put by the Court, the EMA explained that it was not possible to identify with certainty the document(s) and scientific literature in its possession during the assessment of Tecfidera which had also been analysed by the BfArM in the context of the application for marketing authorisation for Fumaderm.

286 Furthermore, it is apparent from the information in the file, in particular from the written replies to the questions put by the Court, that, during the procedure which preceded the adoption of the implementing decision of 30 January 2014, the EMA and the Commission did not request information from the BfArM; nor did they verify whether the BfArM had assessed the role of MEF within Fumaderm or examine how the BfArM had carried out its analysis.

287 Second, it is apparent from the information in the file that the CHMP, and then the Commission in its implementing decision of 30 January 2014, merely explained that DMF was part of an already authorised combination medicinal product, namely Fumaderm, and that it had never been authorised as a medicinal product in the European Union.

288 Third, it is common ground that, despite the particular circumstances of the present case, the EMA, and, more specifically, the CHMP, limited itself, in the EPAR relating to Tecfidera, to assessing whether the MEF salts, considered in isolation, were active from a pharmacological point of view (see paragraph 242 above). However, the examination carried out was not intended to assess the role of MEF within Fumaderm or to request information from the BfArM in that regard.

289 In the light of all of the foregoing, it must be held that, prior to the adoption of the implementing decision of 30 January 2014, the Commission did not analyse all the relevant data which had to be taken into consideration in order to conclude that Tecfidera and Fumaderm were covered by separate global marketing authorisations.

290 That conclusion is not called into question by the Opinion of Advocate General Bobek in Joined Cases *Novartis Europharm* v *Commission* (C-629/15 P and C-630/15 P, EU:C:2016:1003) relied on by the EMA.

291 It is true that, in point 43 of his Opinion in Joined Cases *Novartis Europharm* v *Commission* (C-629/15 P and C-630/15 P, EU:C:2016:1003), Advocate General Bobek stated that the most important element of a medicinal product is its active substance. He added that a marketing authorisation granted for a medicinal product that is based on a different active substance to the initial medicinal product can hardly be seen to be a development considering the wording of the second subparagraph of Article 6(1) of Directive 2001/83. He stated that if a difference in active substance did not lead to a different global marketing authorisation, it was difficult to perceive what kind of innovation would provide the applicant with a different regulatory data-protection period. Furthermore, in point 45 of that Opinion, Advocate General Bobek explained that the examples which the Commission had provided regarding changes to the initial medicinal product that were not covered by the same global marketing authorisation all concerned scenarios under which there was a change to the active substance (or combination of active substances) in the initial medicinal products and that that was the case for, first, fixed combination products pursuant to Article 10b of Directive 2001/83, second, the separation of the substance from a previous combination of active substances or, third, a modification of an existing active substance that amounted to a new active substance. He inferred from this, in point 46 of his Opinion, that the notion of global marketing authorisation was based on identity of the marketing-authorisation holder and of the active substance(s) and that if the marketing-authorisation holder or the active substance changed, the same global marketing authorisation no longer applied.

292 However, it should be noted that, in the judgment of 28 June 2017, *Novartis Europharm* v *Commission* (C-629/15 P and C-630/15 P, EU:C:2017:498), the Court of Justice gave no indication to the effect proposed by Advocate General Bobek. Furthermore, in the case which gave rise to that Opinion, the Court of Justice was not asked to rule on whether a marketing authorisation granted at EU level for a component of a combination medicinal product previously authorised by a national authority was covered by the same global authorisation as the combination at issue. Furthermore, it must be pointed out that, as is apparent from paragraphs 150 to 282 above, an approach based solely on a difference in active substances presented the risk, in the present case, of regulatory data protection being granted contrary to the objectives pursued by the concept of a global marketing authorisation.

293 In the light of all of the foregoing, and, more specifically, in so far as, despite the particular circumstances of the case, neither the CHMP nor the Commission assessed the role played by MEF within Fumaderm or requested information from the BfArM in that regard, the single plea in law relied on by the applicant must be upheld on the ground that the implementing decision of 30 January 2014 is vitiated by a manifest error of assessment inasmuch as the Commission concluded in that implementing decision that Tecfidera did not belong to the same global marketing authorisation as Fumaderm.

294 In so far as that conclusion is not based on a complaint alleging infringement of the principle of sound administration, on the content of Annexes C.1 and C.2 to the applicant's observations on the statements in intervention, or on the content of Annex R.8 to the applicant's written replies to the Court's questions, it is not necessary to rule on the admissibility of that complaint, which is disputed by the EMA, or on the admissibility of those annexes.

295 It is therefore necessary to uphold the plea of illegality raised by the applicant and to declare that the implementing decision of 30 January 2014 is inapplicable in so far as, in that implementing decision, the Commission found that Tecfidera did not belong to the same global marketing authorisation as Fumaderm.

296 Consequently, the contested decision, which is based on the implementing decision of 30 January 2014, is unfounded and must be annulled.

IV. Costs

297 Under Article 134(1) of the Rules of Procedure, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings. Since the EMA has been largely unsuccessful, it must be ordered to bear its own costs and to pay those incurred by the applicant, in accordance with the form of order sought by the applicant.

298 In accordance with Article 138(1) of the Rules of Procedure, the Commission must bear its own costs.

299 Lastly, in accordance with Article 138(3) of the Rules of Procedure, Biogen must bear its own costs.

On those grounds,

THE GENERAL COURT (Seventh Chamber, Extended Composition)

hereby:

1. **Annuls the decision of the European Medicines Agency (EMA) of 30 July 2018 not to validate the application submitted by Pharmaceutical Works Polpharma S.A. with a view to obtaining a marketing authorisation for a generic version of the medicinal product Tecfidera;**

2. **Dismisses the action as to the remainder;**

3. **Orders the EMA to bear its own costs and to pay those incurred by Pharmaceutical Works Polpharma;**

4. **Orders Biogen Netherlands BV and the European Commission to bear their own costs.**

Da Silva Passos Valančius Reine

Truchot Sampol Pucurull

Delivered in open court in Luxembourg on 5 May 2021.

E. Coulon
Registrar

S. Papasavvas
President

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