This document contains a translation of the main content of the ruling of the Administrative Jurisdiction Division of the Dutch Council of State of 10 October 2018 (ECLI:NL:RVS:2018:3298). Recitals on Dutch procedural law have not been translated. The Division cannot be held responsible for any inaccuracies.

ENGLISH TRANSLATION OF THE DECISION BY THE ADMINISTRATIVE JURISDICTION DIVISION OF THE COUNCIL OF STATE OF 10 OCTOBER 2018 IN CASE NO. 201801209/1/A3 (ECLI:NL:RVS:2018:3298)

INTRODUCTION
The Medicines Evaluation Board (referred to hereafter as: the MEB) issued, in respect of decisions on 19 May 2016, marketing authorisations to Synthon B.V. and Mylan B.V. for the medicine 'Brabio 20 mg/ml, solution for injection in a pre-filled syringe, RVG 115980', 'Sclerthon 20 mg/ml, solution for injection in a pre-filled syringe, RVG 115987' and 'glatiramer acetate Mylan 20mg/ml, solution for injection in a pre-filled syringe, RVG 115993' (referred to hereafter as: the authorised medicines). Teva raised an objection to this, an objection that the MEB declared unfounded. Teva subsequently lodged an appeal. The court declared this appeal unfounded. In response, Teva lodged an appeal with the Council of State's Administrative Jurisdiction Division.

Raad van State

201801209/1/A3.
Date of decision: 10 October 2018

ADMINISTRATIVE
JURISDICTION DIVISION

Decision on the higher appeal by:

[...]

INTRODUCTION

1. Teva GmbH is the holder of the Dutch marketing authorisation for Copaxone, and Teva Nederland B.V. is the distributor. Copaxone is a medicine used to treat multiple sclerosis. The active substance in Copaxone is glatiramer acetate. The authorised medicines are used to treat multiple sclerosis as well, and also contain glatiramer acetate as the active substance. Copaxone and the authorised medicines are chemical medicines.

Synthon and Mylan have applied for marketing authorisations for the authorised medicines in the Netherlands and 27 other European countries. The decentralised procedure was followed in this case and the Netherlands acted as the Reference Member State. The MEB applied the abridged hybrid procedure (referred to hereafter as: hybrid procedure) as referred to in Article 42 (6) of the Netherlands Medicines Act (referred to hereafter as the Gmw) and issued the marketing authorisations. Teva's medicine Copaxone was used as the reference medicine for the applications submitted by Synthon and Mylan. This means that in their applications, Synthon and Mylan referred to the studies conducted by Teva to demonstrate the

safety and efficacy of Copaxone.

RELEVANT REGULATION

2. The relevant provisions in the Charter of Fundamental Rights of the European Union (referred to hereafter as: the Charter), the Treaty on the Functioning of the European Union (referred to hereafter as: TFEU), Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use - as amended, for example, by Directive 2004/27/EC, Regulation 1901/2006/EC, Regulation 1394/2007/EC and Directive 2011/62/EU - the Gmw (Netherlands Medicines Act), the General Administrative Law Act (Awb) and the Wet op de rechterlijke indeling (Structure of the Judiciary Act) are included in the appendix to this decision and thus form a part thereof.

TERMS USED IN THE PROCEEDINGS

3. In the proceedings the terms 'medicines', 'active substance', 'therapeutic moiety', 'bioequivalence' and 'therapeutic equivalence' are key. A number of these terms are defined in Directive 2001/83/EC and the Gmw. For the sake of this decision's legibility the Division deems it useful to explain below what it understands by these terms, following the example of the parties.

A medicine (Article 1, (b) of the Gmw) consists of one or more active substances and one or more excipients.

An active substance (Article 1, 3a, of Directive 2001/83/EC and Article 1, x.1, of the Gmw) consists of a therapeutic moiety and a non-active component. After being administered the therapeutic moiety brings about the therapeutic effect in the patient's body. Non-active substances, such as salt, facilitate the absorption of the medicine in the patient's body and promote this process but do not have an effect on the treatment of the condition for which the medicine has been registered.

Bioequivalence means the biological availability of medicines, the degree and speed at which the active substances are released from the pharmaceutical form, absorbed into the blood and available at the place where their main effect is targeted, are the same.

Therapeutic equivalence means the effect and safety of the medicines are similar.

THE SUPREME COURT

[...]

The Division's ruling

11. Therefore, the Division shall first and foremost assess whether the appellant is an interested party in contesting the decision based on Article 1:2 of the Awb. The Division shall subsequently assess whether the relativity requirement as included in Article 8:69a of the Awb precludes the annulment of the contested decision.

[...]

The interests of Teva

13. The court has rightly ruled, albeit on different grounds, that Teva is an interested party in the decisions to issue marketing authorisations to Synthon and Mylan.

14. [...] The court rightly ruled that Teva Pharmaceuticals Ltd. (now: Teva GmbH) as holder of the Dutch marketing authorisation for Copaxone and Teva Nederland B.V. as distributor of Copaxone on the Dutch market, as a competitor of Synthon and Mylan, work in the same market segment and in the same catchment area. This means that Teva is an interested party in the sense of Article 1:2, first paragraph, of the Awb in the decisions to grant marketing authorisations.

15. The Olainfarm-ruling is not relevant in this context. In this ruling the Court answered the question of whether, pursuant to Article 10 of Directive 2001/83/EC, in conjunction with Article 47 of the Charter, the marketing authorisation holder of a reference medicine has the right to lodge an appeal against a marketing authorisation for a generic medicine being granted. However, this article and this interpretation by the Court do not affect the legal protection available under national law. [...]

[...]

The relativity requirement in this case

16. In the Division's opinion, the court wrongly ruled that Article 42 (6) of the Gmw is clearly not intended to protect the interests of Teva and that therefore the relativity requirement precludes the annulment of the decision. [...]

[...]

Conclusion concerning the higher appeal

22. The appeal is founded. The disputed ruling must be annulled.

[...]

24. In accordance with that which is required of the court, the Division will handle Teva's appeal against the decision of 3 November 2016 in light of the grounds of the appeal lodged against it.

THE APPEAL

[...]

Teva's standpoint

26. Teva argues that in this case the full procedure should have been applied. The hybrid procedure can only be applied if the reference medicine and the hybrid medicine contain the same active substance, at least the same therapeutic moiety thereof. This therefore concerns a preliminary question before it can be assessed whether Article 42 (6) of the Gmw is satisfied. In this case it cannot be demonstrated that Copaxone and the authorised medicines contain the same therapeutic moiety.

The MEB's standpoint

27. The MEB has taken the position that Synthon and Mylan have chosen to make an application pursuant to Article 42 (6) of the Gmw. The MEB subsequently assessed, in accordance with this paragraph, whether the difference with the reference medicine Copaxone was bridged with pre-clinical and clinical trials. The MEB established that this is the case. This means the hybrid procedure could be applied and that the requested authorisations could be granted. In this context, the MEB pointed out that the generic procedure could not be applied because bioequivalence between the reference medicine and the hybrid medicine could not be demonstrated. Furthermore, the MEB takes the view that, contrary to Teva's submission, for the application of the hybrid procedure a preliminary question of whether the two medicines contain the same active substance, at least the same therapeutic moiety, does not apply. The MEB points out that, in accordance with the literal wording of Article 42 (6) of the Gmw, the hybrid procedure can be applied in the event of a change in the active substance.

The standpoint adopted by Synthon and Mylan

28. Synthon and Mylan argue that it could not be demonstrated that both medicines are bioequivalent nor that they contain the same active substance. Therefore, the hybrid procedure and not the generic procedure is applied. Synthon and Mylan also point out that Copaxone and the authorised medicines both contain glatiramer acetate as the active substance. Glatiramer acetate is a polypeptide mixture and the concentration of individual molecules in this mixture cannot be properly measured, so it cannot be demonstrated that the active substance is the same. Furthermore, bioequivalence cannot be demonstrated in view of the rapid degradation of the active substance after injection and the fact that it is not possible to measure the concentrations of the degradation products in the blood plasma. Synthon and Mylan indicate that this also means it is not possible to demonstrate that two batches of Copaxone contain the same active substance and that they are bioequivalent.

The opinion of the Division

Introduction

29. The parties are divided with regard to the procedure that Synthon and Mylan should have followed in order to obtain a marketing authorisation. According to Teva, the full procedure under Article 8 of Directive 2001/83/EC should have been followed, which includes providing the results of pre-clinical and clinical trials. Such a procedure requires a significant investment. The MEB, and Synthon and Mylan, are of the opinion that an abridged procedure could be followed, with reference to the studies carried out to obtain the marketing authorisation for Teva's reference medicine Copaxone. This abridged procedure obviously requires a more modest investment than the full procedure. Both the generic procedure and the hybrid procedure are abridged procedures. According to the MEB, and Synthon and Mylan, the generic procedure could not be applied in this case. After all, this procedure can only be applied if bioequivalence can be demonstrated. Since it was not possible to demonstrate this, it was assessed whether the hybrid procedure of Article 10 (3) of Directive 2001/83/EC could be followed, in which therapeutic equivalence must be demonstrated. For this purpose, additional preclinical and clinical trials must be conducted to assess whether the medicines are therapeutically equivalent and whether it is therefore justified to refer

to the case of the reference medicine. In other words, when using the hybrid procedure, it is assessed whether the differences between the reference medicine and the hybrid medicine have been bridged. This is the case according to the MEB and Synthon and Mylan. That is why, in their opinion, the marketing authorisations were rightly granted under the hybrid procedure.

30. The appeal, therefore, only disputes the procedure that should have been followed by Synthon and Mylan. It is not in dispute whether the data submitted by Synthon and Mylan substantively met the requirements that apply to the application of the hybrid procedure.

Explanation of Article 42 (6) of the Gmw

General

31. It is not disputed between the parties that Copaxone and the authorised medicines cannot be shown to contain the same active substance, at least the same therapeutic moiety. The dispute concerns whether the hybrid procedure can be applied if the active substance is changed or it cannot be demonstrated that the same active substance is present.

32. The hybrid procedure is stated in Article 42 (6) of the Gmw. In the legislative history, the following has been included with regard to Article 42 (6) of the Gmw: 'Sections a, b, c and d of the sixth paragraph all relate to an application for a marketing authorisation for a medicine referring to a reference medicine, and to which application there are shortcomings with regard to the demonstration of the equivalence with the reference medicine. This inequality can be eliminated by providing results from preclinical and/or clinical trials that can bridge the difference with the reference medicine.' (Parliamentary Papers II, 2004/05, 29 359, no. 8, page 50).

33. Article 42 (6) of the Gmw relates to an implementation of Article 10 (3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC, and must therefore be explained in light of that Article.

Article 10 (3) of Directive 2001/83/EC states: 'In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.'

34. The interpretation of provisions of European Union law must take place in accordance with the method described by the Court in its case law. According to this method, the interpretation of the wording of Article 10 (3) of Directive 2001/83/EC requires, in the first instance, a comparison of the different language versions (see paragraph 18 of the judgment of the Court of 6 October 1982, 283/81, Cilfit, ECLI:EU:C: 1982:335). Furthermore, with regard to the need for a uniform interpretation of those versions, where there are differences between them, the provision in question must be interpreted in light of the general design and purpose of the regulation of which it is part (see paragraph 28 of the judgment of the Court of 24 October 1996, C-72/95, Kraaijeveld, ECLI:EU:C:1996:404). Even if the language versions are fully consistent, one must bear in mind that European Union law applies its

own terminology. Secondly, when determining the meaning and scope of those terms, according to the Court's established case law, account is taken of both the wording of the relevant provisions of European Union law and its context, as well as the objectives of the regulation of which they are part and the history of that regulation (see paragraph 58 of the judgment of the Court of 24 June 2015, 2015, C-373/13, H.T., ECLI:EU:C:2015:413). Thirdly, the preamble to Directive 2001/83/EC may specify the content of the provision (see paragraph 42 of the judgment of the Court of 11 June 2015)., C-554/13, Z. Zh. and I.O., ECLI:EU:C:2015:377).

Text, purpose and history

35. The Dutch version of article 10 (3) of Directive 2001/83/EC states that 'de werkzame stof(fen) [...] wordt of worden gewijzigd'('the active substance (s) [...] is or are changed'). The English version of the article states 'changes in the active substance (s)' and the French version states 'changements de la ou des substances actives'. The literal text of the paragraph confirms the view of the MEB that the hybrid procedure can be applied to a change of the active substance. It does not otherwise follow from Article 10 that the condition for applying the hybrid procedure would be whether the same active substance, at least the same therapeutic moiety, is concerned. This condition does apply in view of the literal text of Article 10 (2) of Directive 2001/83/EC when applying the generic procedure, where there is a medicine with the same qualitative and quantitative composition of active substances.

36. The conditions for applying the hybrid procedure are partly formulated in a negative way. After all, this procedure can be applied if certain circumstances do not occur or if there are certain changes. It is not determined how far these changes may go. In the first instance, it therefore seems unclear where the dividing line lies between the application of the hybrid procedure and the application of the full procedure of Article 8 of Directive 2001/83/EC. In this context, the way the Dutch version of Article 10 (3) of Directive 2001/83/EC, in particular the phrase "moeten de resultaten van de desbetreffende preklinische of klinische proeven worden verstrekt" ("the results of the relevant preclinical or clinical tests must be provided"), is stated in other languages is relevant. The English version of this paragraph states that 'the appropriate pre-clinical tests or clinical trials shall be provided'. In the French version it says that 'les résultats des essais précliniques ou cliniques appropriés sont fournis'. 'Appropriate' and 'appropriés' both mean 'appropriate'. The term 'appropriate' implies that it is up to the evaluation authority to assess whether the submitted preclinical and clinical trials are appropriate. In the opinion of the MEB, this means that if the submitted preclinical and clinical trials are appropriate in its view, in other words if the relevant differences with the reference medicine have been bridged, it appears that the hybrid procedure may be applied.

37. The Division finds support for this view in the preamble of Directive 2001/83/EC, which states that the essential aim must be to safeguard public health. According to the preamble, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products . Furthermore, the preamble states that there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause. Furthermore, the preamble to Directive 2004/27/EC, point 10, states that since generic medicines account for a major part of the market in medicinal products, their access to the Community market should be facilitated in the light of the experience acquired. This recital concerns not only the generic but also the hybrid procedure, since the term

generic medicines is used in this recital as the umbrella term for these two categories of medicines.

38. Teva's viewpoint means that with regard to complex chemical medicines - in which it is assumed that the active substance is the same or virtually the same, but the latter cannot be demonstrated - the abridged procedure will never be followed, and the full procedure must always be followed. This means that Teva's competitors will only be able to market glatiramer acetate through the use of the very time-consuming and costly full procedure for years to come. Teva thus retains market exclusivity, unless competitors are prepared to follow this very costly procedure without having a period of ten years' market exclusivity to recoup these costs in practice. This is not in line with the above-mentioned important recitals in the preamble that the development of the pharmaceutical industry or trade in medicinal products will not be hindered, that there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause, and that access for generic medicines to the Community market should be facilitated.

39. As far as the history is concerned, the Division considers that the current hybrid procedure in Article 10 (3) of Directive 2001/83/EC, according to the wording, has a broader scope of application than the old hybrid procedure. This broader scope of application is in line with the aforementioned goals in the preamble. In this respect, it is important that the old generic procedure and the old hybrid procedure were included in Article 4 (3) under 8, sub a (iii) of Directive 65/65/EC. This part of the article has subsequently been incorporated in Article 10 (1), under a, sub iii, of Directive 2001/83/EC. The old hybrid procedure was mentioned in the second paragraph of this article. This paragraph read as follows: However, where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate toxicological and pharmacological tests and/or of appropriate clinical trials must be provided.' It follows from this paragraph that the old hybrid procedure, unlike the current hybrid procedure, could only be applied in three specific, cited situations. A change in the active substance was not included here.

40. On the basis of the text, the purpose and the history, the Division concludes that with regard to the question of whether Article 10 (3) of Directive 2001/83/EC can be applied, it is not important whether Copaxone and the authorised medicines contain the same active substance, at least the same therapeutic moiety, but whether the relevant differences between reference medicine Copaxone and the authorised medicines have been bridged. It is therefore a matter of demonstrating therapeutic equivalence between Copaxone and the authorised medicines.

41. Teva has put forward a number of arguments which, in its view, give rise to a different conclusion. The Division does not deem these arguments to be convincing. The reasons for this are provided in recitals 42 through 49.

Discussion of the other arguments

42. Teva argues that Annex I, Part II, point 3, of Directive 2001/83/EC specifies the additional information required if a medicine contains the same therapeutic moiety as the reference medicine in combination with, for example, another salt. It does not specify which additional information is required if a medicine contains a modified therapeutic moiety. Teva infers from this that such a change is not permitted and that

the full procedure under Article 8 of Directive 2001/83/EC must then be applied. The Division does not agree with this conclusion. Indeed, Annex I, Part II, point 3, was already part of Directive 2001/83/EC before the current hybrid procedure was included in it and as discussed above under 39, the scope of application of the old hybrid procedure was more limited than that of the current hybrid procedure.

43. Teva also relies on the Notice to Applicants, which contains a non-binding guideline from the European Commission for the application and interpretation of Directive 2001/83/EC. Section 5.3.2 contains an explanation of the abridged procedures from article 10 of this directive. The Division does not find support for Teva's viewpoint in this section. Section 5.3.2.1 contains an explanation of the generic procedure as contained in Article 10, first and second paragraphs. This section states that the different salts, etc. of an active substance must be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. Within the generic procedure, additional information can be provided as evidence of the safety and/or efficacy of the different salts etc. If this evidence cannot be provided with additional information, then it would be necessary to submit the results of appropriate pre-clinical tests and clinical trials in accordance with the requirements of Article 10 (3) of Directive 2001/83/EC. In this case, the hybrid procedure is therefore applied because preclinical and clinical trials are necessary to demonstrate the safety and/or efficacy of the different salts, etc. Teva rightly pointed this out. Teva, however, fails to recognise that in section 5.3.2.2 of the Notice to Applicants, which refers to the hybrid procedure, three other circumstances are mentioned in which the hybrid procedure may be applied. This section states: 'Article 10 (3) considers three circumstances where such additional data will be necessary: [...] where there are changes in the active substance(s)'. This section therefore points out that in accordance with Article 10 (3) of Directive 2001/83/EC, the hybrid procedure may be applied, inter alia, if the active substance is changed.

The concluding sentence of this section states: 'Some guidance on the appropriate additional studies required is indicated in the table given in Annex II at the end of this Chapter.' As Teva rightly points out, this table does not provide any indication for the situation in which the active substance is changed. However, from the words 'Some guidance', the Division concludes that the table is not intended to be exhaustive with regard to the circumstances in which the hybrid procedure can be applied. The Division finds support for this decision in the following. This table was virtually the same before the current hybrid procedure was incorporated in Directive 2001/83/EC. After the entry into force of the current hybrid procedure, only three categories have been deleted from the table. While, with this entry into force, the possibilities for applying the hybrid procedure have been broadened compared with the old hybrid procedure. This confirms that the table is not intended to provide an exhaustive list of circumstances under which the hybrid procedure can be applied.

44. Furthermore, Teva refers to section 2 of the 'Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances'. This reflection paper of 17 December 2015 consists of non-binding guidelines prepared by the Committee for Medicinal Products for Human Use (referred to hereafter as: CHMP) of the European Medicines Agency (referred to hereafter as: EMA) (referred to hereafter as: EMA Guidelines). Herein, the Division does not find support for Teva's standpoint. Section 2 states the following: 'A chemical active substance that is not previously authorised in a medicinal product for human use in the European Union and that is from a chemical structure

point of view not related to any other authorised substances should be considered as an NAS. Such substance is considered to be new in itself when the administration of the applied active substance would not expose patients to the same therapeutic moiety as already authorised active substance(s) in the European Union.' In contrast to Teva, the Division does not read that an active substance is considered as a new active substance if it does not contain the same therapeutic moiety as previously authorised active substances. In the first sentence of this quotation there are two more conditions that must be met in order to be classified as a new active substance, namely, in short, that the chemical active substance has not been authorised in the European Union before, and that the chemical active substance is unrelated to other authorised substances from the point of view of its chemical structure.

45. Teva also referred to the position of the European Commission as expressed in the decision of the Division of 25 April 2018 (ECLI:NL:RVS:2018:1354). According to recital 10.3, the European Commission referred to the opinion of the Committee for Medicinal Products for Human Use that monoethyl fumarate and dimethyl fumarate (the substances in question) are both active but do not consist of the same active substance, since the therapeutic moiety differs. Teva infers from this that it must be demonstrated that the therapeutic moiety is the same in the reference medicine and in the generic medicine. The Division does not agree with this standpoint. In this decision by the Division a bibliographic application had been made in accordance with Article 42 (5), preamble and under b, of the Gmw. The conditions under which this procedure can be applied differ from the circumstances under which the hybrid procedure can be applied.

46. Nor does the Division find in the Smithkline Beecham judgment (ECLI:EU:C:2004:541) an argument for Teva's viewpoint that the hybrid procedure can only be applied if the active substance, at least the therapeutic moiety, is the same. In this context it is important that Directive 65/65 was applicable in that case and the question was whether the procedure for medicinal products which are essentially similar, now the generic procedure, could be applied. The decision of the Court that an exact moleculair match is not required between the active ingredients to satisfy the criterion of essential similarity (now: generic) is relevant to the question of in which cases the generic procedure of Article 10, first and second paragraphs of Directive 2001/83/EC, may be applied. This decision is irrelevant to the scope of application of the current hybrid procedure, in which the requirement of essential similarity (now: generic) does not apply. Moreover, in recital 35 of the Smithkline Beecham judgment, the Court ruled as follows: 'Moreover, the parties in the main proceedings, the Governments which have submitted observations and the Commission seem to agree that, where an examination is made as to whether two products are essentially similar, it is more realistic to base one's enquiry on therapeutic action than on the precise molecular structure of the active ingredients.' This quote may also refer to 'medicinal products which are essentially similar', currently generic medicines, but if it applies to generic medicines that the therapeutic action is deemed more important than the precise molecular structure of the active ingredients, this applies all the more to hybrid medicines.

47. Point 25 of the Conclusion of Advocate General Wahl in the Olainfarm ruling (ECLI:EU:C:2014:342) is, contrary to Teva's submission, currently not relevant in the Division's opinion. This point relates to the procedure under Article 10 (1) and (2) of Directive 2001/83/EC and the procedure under Article 10 (bis) of that directive. For the

application of these procedures, unlike with the application of the hybrid procedure, it must concern the same active substance.

48. Teva further relies on Commission Regulation 1234/2008/EC of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ 2008, L334). In particular, Teva relies on Annex I, which specifies the cases in which a change in the active substance falls under an extension of the marketing authorisation. A change in the therapeutic moiety is not mentioned therein. Teva argues that if the marketing authorisation holder does not have the possibility to change the therapeutic moiety of its medicine within the same marketing authorisation, a competitor should not be able to do so by applying the abridged procedures in Article 10 of Directive 2001/83/EC. This argument already fails because the change to an existing marketing authorisation is logically possible under different circumstances than granting a new marketing authorisation, with or without the application of the abridged procedures.

49. Teva further points out that Article 10 (4) of Directive 2001/83/EC lays down a separate procedure for similar biological medicines for which it cannot normally be established that they contain the same active substance as the reference medicine. If Article 10 (3) of Directive 2001/83/EC also permits the granting of medicines for which it cannot be established that they contain the same active substance, it is not possible to explain why the legislature considered it necessary to include a separate provision for biological medicines in Directive 2001/83/EC. The Division does not agree with Teva's standpoint. It follows from the legislative history that a proposal of the European Parliament aimed to explicitly establish in Article 10 (1) of Directive 2001/83/EC that biosimilar medicines - similar biological medicines - always require preclinical and clinical tests. The justification for this amendment was that the biological steps in the creation of biosimilar medicines are much more complicated than with generic chemical products. This is due to the fact that the side effects of the by-products of biosimilar medicines are unknown. In the amended proposal of 3 April 2003 (COD 2001/0253 and 2001/0254) in amendments 167 and 168, the European Commission then considered that biologically similar medicines are not always generic medicines within the meaning of Article 10 (2) of Directive 2001/83/EC, but are nonetheles not required to provide a full dossier. The dossiers must include relevant studies which take the place of bioavailability studies. According to the European Commission, the amendment needs to be reworded so that it reflects the specific conditions for these medicines, in particular by adding a specific paragraph on them to Article 10. This view demonstrates that Article 10 (4) is specifically included because biological medicines form a special category of medicines and therefore not, as Teva argues, because the hybrid procedure should not be applied if medicines are similar but not generic.

Conclusion

50. It follows from recitals 42 through 49 that, in the opinion of the Division, Teva's arguments cannot detract from the conclusion reached by the Division in recital 40 on the basis of the wording, objective and historical development of Article 10 (3) of Directive 2001/83/EC. This means the Division draws the final conclusion that in the question of whether Article 10 (3) of Directive 2001/83/EC can be applied, it is not important whether Copaxone and the authorised medicines contain the same active substance, at least the same therapeutic moiety, but whether the relevant differences between the reference medicine Copaxone and the authorised medicines have been bridged. It is therefore a matter of demonstrating therapeutic equivalence between

Copaxone and the authorised medicines. The Division therefore does not agree with Teva's argument that, from the point of view of safety and efficacy, it is only justified to refer to research data from the reference medicine file if the active substance, at least the therapeutic moiety, is the same. In particular, the Division does not agree with Teva's view that changes to the active substance are only permitted if the changes concern salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives and not the therapeutic moiety. This condition only applies, in accordance with the wording of Article 10 of Directive 2001/83/EC, to the generic procedure and not the hybrid procedure. In this context it is important that in a change to the active substance, the aforementioned safety and efficacy are ensured by the fact that in the hybrid procedure with preclinical and clinical studies, the difference with the reference medicinal product must be bridged.

51. The other evaluation authorities, who agreed with the MEB's assessment, as well as the High Court of Justice of England and Wales (decisions of 17 October 2016 in case no. CO/3516/2016 and of 29 November 2016 in case no. CO/3516/2016) and the Court of Appeal of England and Wales (decision of 8 September 2017 in case no. C1/2016/4510) arrive at the same conclusion as the Division. The public assessment reports, on which agreement has been reached in the decentralised procedure, as referred to in Article 28 (1) of Directive 2001/83/EC, state in this respect that Article 10 (3) of this Directive forms a suitable legal basis for the application and that the 28 Member States have therefore granted marketing authorisations. This conclusion also involved the advice of the EMA, the debate conducted within the Coordination group for Mutual recognition and Decentralised procedure for human medicinal products (referred to hereafter as CMDh) in February 2016 as well as the Notice to Applicants. In connection with the above, it is important that Teva presented its view, in particular with regard to the legal basis for granting marketing authorisations, to the CMDh, but the CMDh has not found any reason to recommend that the full procedure must be followed. Several of the arguments raised by Teva are also involved in the aforementioned statements of the High Court of Justice of England and Wales and the Court of Appeal of England and Wales.

Preliminary questions

52. Teva has submitted four questions for a preliminary ruling. The Division sees no reason for this in view of the Cilfit judgment (see points 10 and 16). The answer to the first question of whether Article 10 of Directive 2001/83/EC, read in conjunction with Article 47 of the Charter, gives rise to the right for Teva to appeal against the granted authorisations, cannot affect the solution of the dispute. The Division has ruled that Teva already has this right under national law. The answer to the second question as to the extent to which judges in other Member States are competent to substantively review the decision of the national evaluation authorities to grant authorisations to Synthon and Mylan, cannot influence the outcome of the present dispute either. After all, it has been established that the Division is in any case competent to substantively assess the MEB's decision in detail, now that the Netherlands, in the capacity of the MEB, has acted as the Reference Member State. As regards the third question, the Division takes the view that it follows from what has been considered with regard to Teva's appeal that, in contrast to Teva's argument, the correct application of EU law is so evident in this case that there is no reasonable doubt about the way in which the question of the applicability of Article 10 (3) of Directive 2001/83/EC must be resolved in this case. The answer to the fourth question of where exactly the dividing line lies

between the application of Article 10 (3), and the application of Article 8 (3) and Article 10 (4) of Directive 2001/83/EC, can therefore not impact the outcome of this dispute either.

Application of Article 42 (6) of the Gmw in this case

53. As the Division considered in its decision of 25 April 2018 (ECLI:NL:RVS:2018:1354), the evaluation authority, in this case the MEB, has to perform complex assessments when carrying out its tasks and in doing so has a margin of appreciation. The administrative court cannot substitute its assessment of the facts for that of the evaluation authority. The assessment of the correctness of the opinion set out in the decision on the objection that the relevant differences with the reference medicine have been bridged, is therefore also limited to an examination of the factual basis and the qualification based thereon applied by the MEB, and in particular the question of whether the MEB has manifestly erred or misused its authority, or has manifestly exceeded the limits of its discretionary scope for assessment. The fact that, with regard to the question of whether the hybrid procedure may be applied, the MEB also has a margin of appreciation, follows from what has been considered under 36.

54. In the appeal, Teva has not argued that the data submitted by Synthon and Mylan display inaccuracies or are incomplete in concluding that the relevant differences with Copaxone have been bridged. Therefore, in Teva's appeal no grounds are found for the opinion that the MEB has unjustly granted marketing authorisations under the hybrid procedure.

Conclusion related to the appeal

55. The appeal is unfounded.

56. There exists no reason to issue an order in respect of legal costs.

[...]

APPENDIX

Charter of Fundamental Rights of the European Union

Article 47 (Right to an effective remedy and to a fair trial)
Everyone whose rights and freedoms guaranteed by the law of the Union are violated has the right to an effective remedy before a tribunal in compliance with the conditions laid down in this Article. [...]

Treaty on the Functioning of the European Union

Article 26
1. The Union shall adopt measures with the aim of establishing or ensuring the functioning of the internal market, in accordance with the relevant provisions of the Treaties.
2. The internal market shall comprise an area without internal frontiers in which the free movement of goods, persons, services and capital is ensured in accordance with the provisions of the Treaties.
3. The Council, on a proposal from the Commission, shall determine the guidelines and conditions necessary to ensure balanced progress in all the sectors concerned.

Article 114
1. Save where otherwise provided in the Treaties, the following provisions shall apply for the achievement of the objectives set out in Article 26. The European Parliament and the Council shall, acting in accordance with the ordinary legislative procedure and after consulting the Economic and Social Committee, adopt the measures for the approximation of the provisions laid down by law, regulation or administrative action in Member States which have as their object the establishment and functioning of the internal market.

Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use - as amended by Directive 2004/27/EC, Regulation 1901/2006/EC, Regulation 1394/2007/EC and Directive 2011/62/EU

Preamble
(2) The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.
(3) However, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community.
(4) Trade in medicinal products within the Community is hindered by disparities between certain national provisions, in particular between provisions relating to medicinal products (excluding substances or combinations of substances which are foods, animal feeding-stuffs or toilet preparations), and such disparities directly affect the functioning of the internal market.
(5) Such hindrances must accordingly be removed; whereas this entails approximation of the relevant provisions.
(6) In order to reduce the disparities which remain, rules should be laid down on the control of medicinal products and the duties incumbent upon the Member States' competent authorities should be specified with a view to ensuring compliance with legal requirements.

(7) 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. The particulars and documents which must accompany an application for marketing authorization for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.
(10) However, there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause.
(14) Since generic medicines account for a major part of the market in medicinal products, their access to the Community market should be facilitated in the light of the experience acquired. Furthermore, the period for protection of data relating to pre-clinical tests and clinical trials should be harmonised.
(15) Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product mainly due to manufacturing process characteristics, raw materials used, molecular characteristics and therapeutic modes of action. When a biological medicinal product does not meet all the conditions to be considered as a generic medicinal product, the results of appropriate tests should be provided in order to fulfil the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both.

Article 1
3a. Active substance:
Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.
3b. Excipient:
Any constituent of a medicinal product other than the active substance and the packaging material.

Article 6
No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use. […]

Article 8
1. In order to obtain an authorization to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned.
2. A marketing authorization may only be granted to an applicant established in the Community.
3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:
[…]
(i) Results of:
— pharmaceutical (physico-chemical, biological or microbiological) tests,
— pre-clinical (toxicological and pharmacological) tests,

— clinical trials.
[...]

Article 10

1. By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community. A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.
[...]
2. For the purposes of this Article:
(a) 'reference medicinal product' shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;
(b) 'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. 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. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.
3. In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.
4. Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

Article 26

1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that:
(a) the risk-benefit balance is not considered to be favourable; or
(b) its therapeutic efficacy is insufficiently substantiated by the applicant; or

(c) its qualitative and quantitative composition is not as declared.
2. Authorisation shall likewise be refused if any particulars or documents submitted in support of the application do not comply with Articles 8, 10, 10a, 10b and 10c.

Article 28
1. With a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States. The dossier shall contain the information and documents referred to in Articles 8, 10, 10a, 10b, 10c and 11. The documents submitted shall include a list of Member States concerned by the application.

Directive 2001/83/EC as it read until the entry into force of Directive 2004/27/EU

Article 10
1. In derogation of Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property:

(a) The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he can demonstrate:
(i) either that the medicinal product is essentially similar to a medicinal product authorized in the Member State concerned by the application and that the holder of the marketing authorization for the original medicinal product has consented to the toxicological, pharmacological and/or clinical references contained in the file on the original medicinal product being used for the purpose of examining the application in question;
(ii) or that the constituent or constituents of the medicinal product have a well established medicinal use, with recognized efficacy and an acceptable level of safety, by means of a detailed scientific bibliography;
(iii) or that the medicinal product is essentially similar to a medicinal product which has been authorized within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made. This period shall be extended to 10 years in the case of high-technology medicinal products having been authorised according to the procedure laid down in Article 2(5) of Council Directive 87/22/EEC (1). Furthermore, a Member State may also extend this period to 10 years by a single Decision covering all the medicinal products marketed on its territory where it considers this necessary in the interest of public health. Member States are at liberty not to apply the six-year period beyond the date of expiry of a patent protecting the original medicinal product.

However, where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate toxicological and pharmacological tests and/or of appropriate clinical trials must be provided.

(b) In the case of new medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of toxicological and pharmacological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide references relating to each individual constituent.

Geneesmiddelenwet (Netherlands Medicines Act)

[…]

Article 42
[…]
6. If the application concerns a medicinal product:
a. that does not satisfy the definition of generic medicine,
b. whose bioequivalence cannot be demonstrated by scientific studies on bioavailability,
c. whose concentration, pharmaceutical form or mode of administration is changed in relation to the reference medicinal product, or
d. whose active substances or therapeutic indications are changed in relation to the reference medicine,
it may suffice for the applicant of the marketing authorisation with regard to preclinical and clinical data and records, to submit the results of preclinical or clinical trials with which the difference with those submitted for the relevant reference medicinal product is bridged.

[…]