Neutral Citation Number: [2018] EWHC 228 (Admin)

Case No: CO/1643/2017

IN THE HIGH COURT OF JUSTICE
QUEEN'S BENCH DIVISION
ADMINISTRATIVE COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 13/02/2018

Before:

MR JUSTICE JAY

- -

Between:

THE QUEEN (oao TEVA B.V.)	**Claimant**
- and –	
THE SECRETARY OF STATE FOR HEALTH acting as THE LICENSING AUTHORITY	**Defendant**
- and –	
BIOGEN IDEC LTD	**Interested Party**

- -
- -

Kelyn Bacon QC and Emily MacKenzie (instructed by **CMS Cameron McKenna Nabarro Olswang LLP**) for the **Claimant**
Anneli Howard and Anneliese Blackwood (instructed by **Government Legal Department**) for the **Defendant**
Jemima Stratford QC and Charlotte Thomas (instructed by **Arnold & Porter Kaye Scholer LLP**) for the **Interested Party**

Hearing dates: 29th – 31st January 2018

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Approved Judgment

MR JUSTICE JAY:

A. Introduction

1. The Claimant ("Teva") is a pharmaceutical company established in the EU which manufactures and supplies both innovative and generic medicines. The Defendant is the UK Licensing Authority under the Human Medicines Regulations 2012 (S.I. 2012 No. 1916) and acts through the Medicines and Healthcare Products Regulatory Agency ("The MHRA"). The Interested Party ("Biogen") holds the marketing authorisation ("MA") for a drug whose brand name is Tecfidera. Biogen's MA was granted by the European Commission ("the Commission") pursuant to the centralised procedure on 30th January 2014.

2. Tecfidera is used to treat relapsing remitting multiple sclerosis, and has established efficacy for that condition. Tecfidera's active substance is dimethyl fumurate ("DMF"). DMF is also an active substance within a different medicinal product, Fumaderm, which was granted an MA by the German competent authority in 1994. Fumaderm, used to treat a different auto-immune condition, psoriasis, contains in addition to DMF three monoethyl fumurate esters ("MEF"). The precise basis on which Fumaderm was authorised is not altogether clear given the lapse of time and loss of relevant documents. What is clear is that the Commission concluded in 2014 that DMF and MEF are different active substances.

3. On 22nd December 2016 Teva applied to the MHRA under the decentralised procedure for an MA for a generic medicinal product it proposed to manufacture and sell in the UK and Luxembourg, namely "DMF 120 mg and 240 mg gastro-resistant capsules". This product's active substance is DMF. The legal basis for the application was described in the form as "Article 10(1) generic application". Teva nominated the "reference medicinal product" as Tecfidera. The MHRA's refusal to validate Teva's application has given rise to these judicial review proceedings.

4. The MHRA refused to validate the application because, in its view, Teva was not entitled to apply for an MA within the data exclusivity period for Tecfidera, which is not due to expire until 4th February 2024. Teva's case, which it had laid out carefully in its application for an MA, is that MEF has no clinically relevant therapeutic effect in Fumaderm. It follows, on this line of argument, that the sole active substance within Fumaderm is DMF because MEF should be disregarded. It follows that Tecfidera and Fumaderm contain the same active substance, and it also follows that the former falls within the "global marketing authorisation" ("GMA") of Fumaderm. Consequently, and this is the final stage in Teva's logic, Tecfidera does not have a data exclusivity period which commenced in February 2014: the only relevant period relates to Fumaderm, and it has expired. In the result, there is no impediment to Teva's application for an MA for its generic product.

5. Teva recognises that its free-flowing logic faces at least this barrier: that the Commission concluded in 2014 that Tecfidera and Fumaderm do not belong to the same GMA (I deploy the verb "concluded" without any diffidence because it appears in Teva's application for an MA). In these proceedings Teva stresses that this

conclusion appears in a recital to the Commission's decision: it submits that it was not a necessary or essential part of that decision, and was not binding on the MHRA.

6. A mass of evidence and submission has been brought to bear in these proceedings. Not all of that evidence is admissible (I am referring in particular to parts of Doctor Feldschreiber's witness statement) but I have considered it all carefully. The standard of written and oral argument has been uniformly excellent. I tend to agree with one of the opening observations of Ms Kelyn Bacon QC for Teva that the legal issues are quite narrow in scope. One consequence of this is that the arguments which are critical or central to the resolution of the two essential legal questions which arise for my determination are also quite narrow; or, put another way, that some of the arguments are of peripheral relevance and cannot be determinative. However, I recognise the commercial importance of this litigation to Teva and Biogen, and I also recognise the extent of MHRA's concern as to the legal integrity of its practice and policy in relation to decision-making in this domain. I am genuinely grateful to the industry and intellectual rigour which has consistently been applied to the issues.

7. Reduced to their essentials, the two issues are:

> (1) is MHRA bound by recital (3) to the Commission's decision granting Biogen an MA for Tecfidera?
>
> if not
>
> (2) did MHRA apply the correct test in concluding that DMF and MEF are different active substances?

Under this second rubric Teva contends that the test the MHRA in fact applied was whether MEF is an active substance at some high level of abstraction: it should have considered whether MEF exerted a clinically relevant therapeutic effect in Fumaderm. Teva accepts that it must succeed on both these issues in order to win this application for judicial review.

8. It is convenient at this stage to set out the shape and direction of this judgment. In Chapter B I will address the fundamentals of the scheme or code for EU pharmaceutical regulation. In Chapter C I will set out key provisions of EU legislation. In Chapter D I will set out certain non-legislative provisions and review what I consider to be the essential jurisprudence on the topic. In Chapter E I will provide an essential factual narrative. In Chapter F I will address Teva's first ground and in Chapter G its second ground.

B. The Fundamentals of the Scheme for EU Pharmaceutical Regulation

9. Medicinal products cannot be marketed in Member States of the EU (or the EEA) without an MA. The system for granting such authorisations has been fully harmonised under the legislative code and is referred to here as the "common regulatory framework". The relevant parts of that code for present purposes are contained in Directive 2001/83/EC on the Community Code relating to Medicinal Products for Human Use ("the Directive") and Regulation 726/2004 laying down

Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary use and establishing a European Medicines Agency ("the Regulation"). My attention was drawn to a number of recitals in the Directive. To my mind the following are particularly relevant:

> "(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.
>
> …
>
> (8) Standards and protocols for the performance of tests and trials on medicinal products are an effective means of control of these products and hence of protecting public health and can facilitate the movement of these products by laying down uniform rules applicable to tests and trials, the compilation of dossiers and the examination of applications.
>
> …
>
> (11) The adoption of the same standards and protocols by all the Member States will enable the competent authorities to arrive at their decisions on the basis of uniform tests and by reference to uniform criteria and will therefore help to avoid differences in evaluation."

10. Thus, as Mr Keith McDonald, Deputy Director of the Licensing Division of the MRHA, has clearly explained, the common regulatory framework provides for institutional structures to be put in place to implement these common rules, which are designed to: (a) safeguard public health and public confidence in medicinal products, (b) remove disparities between national provisions that might otherwise hinder the internal market, (c) prevent the application of different scientific standards and protocols for awarding an MA in different Member States which would act as a barrier to free trade, (d) create "uniform rules" so that national competent authorities arrive at their decisions via applying uniform tests and criteria to avoid differences in evaluation, and (e) avoid parallel and duplicative assessments by the relevant authorities in different Member States.

11. The common regulatory framework provides four different procedures for applications for, and concomitantly the bases for the subsequent grant of, MAs. These are:

    (1) on a single national basis ("the national procedure") by the competent authority of an individual Member State: see Article 8 of the Directive. As regards applications for generics of a reference medicinal product, Article 10 provides for an abridged or streamlined procedure as a derogation from Article 8.

(2) on a centralised or pan-EU basis ("the centralised procedure"), as set out in the Regulation. For medicinal products listed in the Annex to the Regulation, the applicant must apply to the Commission under the centralised procedure (see Article 3(1)). For unlisted medicinal products the application may be made under the centralised procedure if, insofar as is material for present purposes, the applicant can demonstrate a significant therapeutic, scientific or technical innovation (see Article 3(2)(b)).

(3) under the mutual recognition procedure set out in Article 28(2) of the Directive. It is not directly relevant to this case.

(4) under the decentralised procedure, whereby the applicant requests that the reference Member State takes the lead in assessing the merits of the application, and then any concerned Member States (as nominated by the applicant) participate in agreeing that assessment: each concerned Member State will then grant its own MA for the product: see Article 28 sub-articles 3-5.

12. In the present case Biogen's application for an MA relating to Tecfidera was made under the centralised procedure and Article 3(2)(b) of the Regulation. Teva's application for an MA relating to its generic product was made under the decentralised procedure, with the UK nominated as the reference Member State and Luxembourg the concerned Member State. I should add that Article 28(1) of the Directive is concerned generally with applications made in more than one Member State, and specifically refers to Articles 8 and 10. Consequently, the Article 10 abridged procedure is capable of applying to applications under the decentralised procedure.

13. The workings of the centralised procedure have been explained in some detail in Mr McDonald's evidence. Apart from the Commission, which is at the heart of the process, the key entities at EU level are the European Medicines Agency ("the EMA"), the Committee for Medicinal Products for Human Use ("the CHMP"), and the Standing Committee on Medicinal Products for Human Use ("the Standing Committee").

14. Mr McDonald has provided a valuable epitome of the centralised procedure:

> "24. The sequence of steps for an application under the centralised procedure are as follows. At phase one, full copies of the application file ("the dossier") are sent to the rapporteur and a co-rapporteur designated by the competent EMA scientific committee. They co-ordinate the EMA's assessment of the medicinal product and prepare draft assessment reports. Once the draft reports are prepared they are sent to the CHMP, whose comments or objections are communicated to the applicant through the EMA. The rapporteur and co-rapporteur then assess the applicant's replies and submit them for discussion to the CHMP. Taking into account the conclusions of this debate the rapporteur and co-rapporteur prepare a final assessment report. Once the final assessment report is completed, the CHMP gives a favourable or unfavourable opinion as to whether to grant the authorisation based on its

> assessment of the risk-benefit balance. When the opinion is favourable, it shall include the draft summary of the product's characteristics ("SmPC"), the package leaflet and the texts proposed for the various packaging materials. The time limit for the evaluation procedure is 210 days.
>
> 25. The second phase of the procedure, the decision-making process, starts with the EMA forwarding copies of the CHMP opinion and the final assessment report to the Commission within fifteen days. During the decision-making process, the Commission services verify that the grant of the MA would comply with EU law, including the common regulatory framework. The Commission has fifteen days to prepare a draft decision.
>
> 26. The draft decision is then sent to the Standing Committee for its opinion. Member States have fifteen days to return their linguistic comments and 22 days for scientific and technical objections. This procedure is conducted in writing but if a duly justified objection is raised by one or more Member States, the Standing Committee will convene a plenary meeting to discuss it.
>
> 27. If the opinion of the Standing Committee is favourable, the draft decision is adopted by the Commission. The applicant is then notified of the decision."

15. I should add that the decision at any plenary meeting is taken by majority vote. Thus, the centralised procedure involves the participation of all Member States although the decision itself is formally taken by the Commission. In that way the decision becomes a binding instrument throughout the EU.

16. Ms Bacon does not disagree with the simplicity or generality of this final proposition, but observes that in the complex circumstances of the present case it has a tendency to beg the question: what is, or was, the *decision* made by the Commission in January 2014, being a decision with salient legal effects?

17. It is unnecessary for me to deal in similar detail with the other three procedures I have summarised under paragraph 11 above. It is common ground that decisions made by individual Member States are directly applicable only in those Member States. The extent to which, under this harmonised regime, other Member States are duty-bound to recognise national decisions when subsequent applications are made under the mutual recognition procedure, and the extent to which decisions made under the decentralised procedure have direct or indirect precedential effect in other Member States, is not agreed by Counsel. Although I can see that these questions bear to some degree on the first central question I am required to resolve, I do not propose to suggest definitive answers of general application.

C. Key Provisions of EU Legislation

18. The relevant provisions of the Directive are as follows:

> "DEFINITIONS
>
> *Article 1*
>
> 2. Medicinal Product
>
> (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
>
> (b) Any substances or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a diagnosis.
>
> …
>
> 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 diagnosis.
>
> 3b. Excipient
>
> Any constituent of a medicinal product other than the active substance and the packaging material.
>
> [Articles 3a and 3b inserted by the Falsified Medicines Directive, 2012/26/EU]
>
> …
>
> MARKETING AUTHORISATION
>
> *Article 6*
>
> 1. No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with [the Regulation] …
>
> When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administrative

routes, presentation, 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. [This subparagraph inserted by Directive 2004/27/EC]

…

Article 8

1. In order to obtain an authorisation to place a medicinal product in the market …, an application shall be made to the competent authority of the Member State concerned.

…

3. The application shall be accompanied by [the dossier] …

…

Article 10

1. By way of derogation from Article 8.3(i) [the requirement to file a dossier], the applicant shall not be required to provide the results if pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community

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

…

The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies. [This is the fourth subparagraph of Article 10(1)]

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 …. The different salts, esters, 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.
…

…

Article 10b

In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8.3(i), but it shall not be necessary to provide scientific researches relating to each individual active substance.

Article 10c

Following the grant of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, pre-clinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

[Articles 29ff set out a procedure for dealing with situations where a Member State cannot approve an application because in its view there would be a serious risk to public health.]

ANNEX 1

Standard Marketing Authorisation Dossier Requirements

…

> 1.2 Application Form
>
> The Medicinal product, which is the subject of the application, shall be identified by name and name of the active substance(s), together with the pharmaceutical form, the route of administration, the strength and the final presentation, including packaging.
>
> …
>
> Specific Marketing Authorisation Dossiers and Requirements
>
> …
>
> 3. Additional Data Required in Specific Situations
>
> 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 pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered a new active substance."

D. Non-Legislative Provisions and Essential Jurisprudence

19. The concept of the GMA was, as has already been noted, introduced into the Directive in 2004. It had emerged in the jurisprudence of the CJEU as well as its first instance tribunal, the General Court, and the inference must be that a decision was by the EU Legislature formally to recognise it. However, the concept has not been defined in the Directive and the location of the GMA in the second paragraph of Article 6(1) appears, at least to this reader, somewhat adventitious. Part of the present difficulty flows from these prefatory observations.

20. The Commission has sought to assist applicants and Member States with the concept of the GMA in non-binding guidance given over recent years. Ms Bacon submitted that the Commission has on at least three occasions expressly disavowed any intention to decide the issue of data exclusivity. My response is on two levels. First, it is necessary to point out that the correct and accurate understanding of the concept of active substance segues into a similar understanding of the concept of GMA, with yet similar knock-on consequences for the issue of data exclusivity. These concepts may be partitioned in formalistic or linguistic terms but, in terms of their substance, data exclusivity should be envisaged as an attribute or concomitant of the GMA. Secondly, my attention was not drawn to section 6 of the Commission's Notice to Applicants (see paragraph 23 below) which does provide express guidance on the topic of data exclusivity. Decision-making flows from the application of this guidance.

21. In March 2009 the Pharmaceutical Committee – Human of the Commission's Enterprise and Industry Directorate-General advised as follows:

> "The Commission representatives called the Committee attention to the fact that in cases where a marketing authorisation application relates to a product which contains a change of an existing substance, the issue whether it is a new active substance in accordance with Notice to Applicants, should be addressed and clarified during the marketing authorisation procedure, and lead subsequently to a harmonised approach across the Community."

22. On 23rd March 2017 the EMA issued a Guideline on Clinical Development of Fixed Combination Medicinal Products. This was after the decision under challenge in these proceedings but Ms Bacon relies on the following sentence:

> "Clinical Development should correspond to the intended claim … Particular attention should be given to the doses of each active substance in the fixed combination medicinal product, with each dose combination being scientifically justified and clinically relevant. The proposed combination should always be based on valid therapeutic principles. Also, the combined safety (and efficacy) profile of all active substances in the fixed combination medicinal product should be considered."

Ms Bacon recruited this passage in support of her submission, primarily under the rubric of the second ground, that the test for new or different active substance is clinical relevance. However, this Guideline is not directed to the antecedent issue of defining or ascertaining active substance(s) in combinations, whether by addition or subtraction, but to the wider and logically subsequent question of whether a combination product should be authorised on proper clinical grounds.

23. The Commission's Notice to Applicants applicable at the time the MHRA's impugned decision was made was the December 2016 edition, revision 6. In December 2017 revision 7 was published. There are no significant differences between these revisions and I therefore intend to refer to the most recent. The salient parts of this Notice are as follows:

> "**2.3 Notion of 'global marketing authorisation'**
>
> Article 6(1) second subparagraph of Directive 2001/83/EC provides that when a medicinal product has been granted an initial marketing authorisation, any additional strengths, pharmaceutical forms, administration routes, presentations as well as any variations and extensions must also be granted an authorisation or be included in the initial marketing authorisation. All these marketing authorisations are considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10 of the directive, which lays down rules on data exclusivity and market protection and on the so-called European Reference Product.

Thus, the global marketing authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes or presentations authorised through separate procedures, including in different Member States within the EU, and under a different name, granted to the marketing authorisation holder of the initial authorisation. Where a product is initially authorised nationally and, subsequently, an additional strength, pharmaceutical form, administration route or presentation is authorised through the centralised procedure, this is also part of the same global marketing authorisation. To determine the notion of same marketing authorisation holder or applicant in this context, see section 2.8.

1. If the medicinal product being assessed contains a modification of an existing active substance, 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 if the medicinal products belong to the same marketing authorisation holder. Request for a new active substance claim should be submitted within the initial marketing authorisation application for medicinal product containing the modified substance and will not be considered retroactively. This assessment is to be done in accordance with the definition of a new active substance provided in 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 of the already authorised medicinal product(s) as described in Article 6(1) of Directive 2001/83/EC.

Example: Active substance A in MP 1 → active substance A' in MP 2

2. If the medicinal product being assessed contains within the same pharmaceutical form a combination of active substances, it will form a new and unique medicinal product requiring a separate marketing authorisation, regardless whether all of the active substances contained therein were already authorised in a medicinal product or not. In its application for the new combination, the applicant must demonstrate that each active substance has a documented therapeutic contribution within the combination and therefore all compounds are different active substance. The authorisation for this new combination medicinal product is not considered to fall within the scope of the global marketing authorisations of the already authorised

medicinal product(s) as described in Article 6(1) of Directive 2001/83/EC.

Examples:

Active substance A in MP1, active substance B in MP2 → Active substances A+B in MP3

Active substances A+B in MP1, Active substances C+D in MP2 → Active substances A+C in MP3

Active substances A+B in MP1, Active substance C in MP2 → Active substances A+C in MP3

Active substances A+B in MP1 → Active substance A+C in MP2

3. 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.

Example: Active substances A+B in MP1 → Active substance A in MP2

The implications of the notion of global marketing authorisation for the purpose of the application of rules on data exclusivity and market protection are referred to in section 6 below. Multiple applications of the same marketing authorisation holder are covered by the notion of 'global marketing authorisation'.

[My comment: section 2.8 deals with the concept of "applicant" and "marketing authorisation holder". Essentially, there may be situations in which changes in the identity of the latter breaks the chain of continuity requisite for the continuation of the GMA. In this respect, it may be seen that the GMA is not immutable, in the sense of being a fixed and certain attribute of the MA *ab initio*, but I do not draw any principle of general application from this feature of the regime.]

…

3.2 Decentralised procedure and mutual recognition procedure

Both the decentralised and the mutual recognition procedures are based on the recognition by national competent authorities of an assessment performed by the authorities of one Member State. According to the European Court of Justice [in Synthon], "[…] Article 28 of Directive 2001/83/EC […] confers a Member State in receipt of an application for mutual recognition only a very limited discretion in relation to the reasons for which that Member State is entitled to refuse to recognise the marketing authorisation in question. In particular, as regards any assessment going beyond the verification of the validity of the application with regard to the conditions laid down in Article 28, the Member State concerned, except where there is a risk to public health, must rely on the assessments and scientific evaluations carried out by the reference Member State". Although the facts of the case relate to a MRP, the ECJ is interpreting Article 28(4) which applies both to MRP and DCP.

To allow operation of the system, applicants for marketing authorisation are obliged to include in their applications copies of any authorisation previously obtained in other Member States as well as a list of those Member States in which an application for authorisation is under examination (article 8(3)(l) of Directive 2001/83/EC). In addition, the dossier on which the marketing authorisation is based must be regularly updated (see section 5.1.1 below).

3.2.1 Decentralised procedure

For medicinal products not falling within the mandatory scope of the centralised procedure, the applicant may request one or more concerned Member State(s) to approve a draft assessment report, summary of product characteristics (SmPC), labelling and package leaflet as proposed by the chosen reference Member State. An application is submitted to the competent authorities of the reference Member State and the concerned Member State(s), together with the information and particulars referred to in Articles 8, 10, 10a, 10b, 10c, and 11 of Directive 2001/83/EC. The applicant must give an assurance that the dossier, including the proposed SmPC, labelling and package leaflet, is identical as submitted in all Member States concerned (reference Member State and concerned Member State). Differences in proposed prescription status and names of the medicinal product are acceptable, in line with national rules in force.

At the end of the decentralised procedure with a positive agreement, a national marketing authorisation will be issued in the reference Member State and the concerned Member State. The harmonisation is maintained through the procedures of Regulation (EC) No 1234/2008 for the examination of variations and the use of the decentralised and mutual recognition procedures for extensions.

[My comment: the same general principles apply to the mutual recognition procedure]

…

6.1 Data exclusivity and market protection period for reference medicinal products

6.1.1 Principles on data exclusivity and market protection of 'reference medicinal product'

The medicinal product, once authorised on the basis of Article 10, can however only be placed on the market 10 or 11 years after the authorisation of the reference medicinal product, depending on the protection period applicable for the reference medicinal product. The protection period in the concerned Member State must also be taken into consideration before placing the medicinal product on its market. It should be noted, however, that these periods of protection will only apply to applications for reference medicinal products submitted once the provisions of Directive 2004/27/EC and Regulation (EC) No 726/2004 start to apply; see section 6.1.2.

6.1.2 Data exclusivity and market protection for applications submitted after the implementation of the amended legislation

Directive 2004/27/EC, amending Directive 2001/83/EC, and Regulation (EC) No 726/2004 have introduced new rules concerning the periods, from the initial marketing authorisation of the reference product, during which generic product applicants cannot rely on the dossier of the reference product for the purposes of submitting an application, obtaining marketing authorisation or placing the product on the market.

For products authorised by the national competent authorities, according to the first subparagraph of Article 10(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC, the applicant is not 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 Union.

According to the second subparagraph of Article 10(1), generic products authorised in this way must not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. (This ten-year period may be extended to eleven if the conditions of the fourth subparagraph of Article 10(1) are fulfilled, see section 6.2 below).

The period of eight years from initial authorisation of the reference product provides a period of so-called "data exclusivity", after which valid applications for generic products can be submitted and lead to the granting of a marketing authorisation. The period of ten years from initial authorisation of the reference product provides a period of so-called "market protection" after which generic products authorised in this way can be placed on the market.

The same periods of protection apply in the case of centrally authorised products pursuant to Article 14(11) of Regulation (EC) No 726/2004.

…

The new harmonised data exclusivity and market protection periods in Article 10(1) of Directive 2001/83/EC do not apply retroactively. It follows that:

– An application in accordance with Article 10 of Directive 2001/83/EC can only be processed via the centralised procedure after expiry of the period of protection of the Member State where the reference medicinal product was authorised (e.g. if the reference product is authorised in a Member State where a ten-year period of protection applies, the application under the centralised procedure may only be submitted after the 10 year period);

– An application in accordance with Article 10 of Directive 2001/83/EC can only be submitted under the decentralised/mutual recognition procedure after expiry of the period of protection of the reference medicinal product in the Reference Member State and the Concerned Member States. It follows that, if the period of protection in the Reference Member State and in three Concerned Member States is six years, a decentralised procedure to obtain a marketing authorisation in accordance with Article 10 of Directive 2001/83/EC is only possible regarding these four Member States. A mutual recognition procedure can be triggered *a posteriori* to cover other Concerned Member States once the protection period therein expires also.

…

> **6.1.5. Protection periods and global marketing authorisation**
>
> For the notion of global marketing authorisation, see section 2.3. The global marketing authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes or presentations authorised through separate procedures and under a different name, granted to the marketing authorisation holder of the initial authorisation. In accordance with Article 6(1) of Directive 2001/83/EC, all these presentations of a given product are considered to be part of the same marketing authorisation for the purposes of applying the rules on data exclusivity and marketing protection. This means that for a reference medicinal product, the start of the data exclusivity and market protection periods is the date when the first marketing authorisation was granted in the Union in accordance with the pharmaceutical acquis. New additional strengths, pharmaceutical form, administration routes, presentations as well as any variation and extensions do not restart or prolong this period. All additional strengths, pharmaceutical form, administration routes, presentations as well as any variation and extensions have the same end point of the data exclusivity and market protection periods, namely 8 and 10 years after the first marketing authorisation was granted, respectively. This will apply even if the new presentation has been authorised to the same marketing authorisation holder through a separate procedure, national or centralised procedure (see section 2.3), irrespective of the legal basis and under a different name. This ten-year period can only be prolonged in the case of certain new indications, as described in section 6.2"

24. I will be returning to this non-binding guidance in Chapters F and G.

25. It is convenient at this stage to review a limited quantity of the very considerable European jurisprudence bearing on these issues. At this point I will address those cases which seem to me to set out helpful principles of general application. I will be obliged to mention other cases when I grapple with the detail of the first and second grounds.

26. In Case C-74/03, SmithKline Beecham v Lægemiddelstyrelsen, a case decided before the amendments to the Directive, the central issue was whether two products which shared the same active substance should be regarded as "essentially similar" for the purposes of enabling reliance on the then applicable abridged procedure. In a number of places in his Opinion, Advocate General Jacobs referred to the "therapeutically active part" of the ingredient as being its active substance, and also relevant to the question of therapeutic moiety. In its judgment, the Court stated that the concept of "active principle", which was not defined either in the then current Directive or relevant jurisprudence, "designate[d] both the therapeutically active part of an active substance and the active substance itself" [32]. This fell to be assessed in the context

of the two medicinal products to be compared [28]. Further, "it is more realistic to base one's enquiry on therapeutic action than on the precise molecular structure of the active ingredients" [35]. To the extent that replacing one salt with another created a risk that the safety and efficacy of the product might be affected, the solution was to take that matter into account on an exceptional basis in the light of further evidence: if such evidence revealed a material risk, then the two substances would not be regarded as "essentially similar" [36-38].

27. I consider that this authority is helpful in two respects, recognising always its early location in the chronological line of cases. First, the key to understanding "active substance" is to grasp the notion of "therapeutic action". Secondly, in situations where the therapeutically active portion remains the same, the two substances should be treated as dissimilar if evidence emerges as to differences in safety or efficacy.

28. Ms Bacon did not rely on SmithKline Beecham for the purposes of her submissions in the second ground. At this stage I should say that this authority supports the proposition that "active substance" must be assessed in the context of a medicinal product as must its therapeutic action. This authority does not directly support the proposition that the therapeutic action must be "clinically relevant", but much may depend on what that phrase means.

29. At paragraph 23 above I referenced Case C-452/06, Synthon BV v MHRA. The issue in that case was the mutual recognition procedure and duties on national authorities to respect authorisations granted by other Member States. Paragraphs 32 and 33 of the Court's judgment are relevant:

> "32. As the Advocate General stated in points 100 and 101 of his Opinion, not only would such an interpretation run counter to the very wording of Articles 28 and 29 of Directive 2001/83, but it would 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 Community 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, referred to in paragraph 25 above.
>
> 33. The reply to the first question must therefore be that Article 28 of Directive 2001/83 precludes a Member State to which an application is made for mutual recognition of a marketing authorisation of a medicinal product for human use granted by another Member State under the abridged procedure provided for in Article 10(1)(a)(iii) of that directive from refusing that application on the ground that the medicinal product in question is not essentially similar to the reference product."

30. This authority carries with it the following slight health warning. I have noted that it was referred to by the Commission in the latest revision of its Notice to Applicants. In

Case C-557/16, Astellas Pharma GmbH and others Advocate General Bobek pointed out that Synthon was decided under an antecedent regime and that the approach needed to be "nuanced" to reflect that [50]. Astellas came too late for the latest revision of the Commission's Notice to Applicants (the Opinion was delivered on 7th December 2017) and the judgment of the Court is not yet available.

31. In Case T-275/09, Sepracor Pharmaceuticals (Ireland) Ltd v Commission, the applicant sought an MA under the centralised procedure for Lunivia, the active substance of which was eszopiclone. The CHMP recommended that an MA be granted but it took the view that eszopiclone could not be regarded as a new active substance. Ms Bacon informed me that this was because it possessed the same therapeutic moiety as zopiclone, which is correct, but the Court's judgment did not in my view turn on that. Sepracor stated its intention to withdraw its application because for its understandable commercial purposes it did not welcome a grant of an MA which did not treat eszoplicone as a new active substance. However, before it did so the Commission issued a letter to the effect that it had no reason to depart from CHMP's opinion. The ruling of the Court was that Sepracor's challenge to the Commission's letter was inadmissible because it did not alter its legal position. However, both the MHRA and Biogen rely on paragraphs 29-32 of the Court's judgment:

> "29. Firstly, the applicant submits that a decision to grant or refuse marketing authorisation would not have contained a decision about whether eszopiclone is or is not a new active substance. That implies that the Commission's position as regards the notion of new active substance and the legal test applied by the Committee to determine whether an active substance may be regarded as new could not be subject to review by the Court.
>
> 30. In that regard, the Commission does not dispute that, if the decision to grant marketing authorisation had been adopted in favour of the applicant, the operative part of that decision would have been limited to the grant of that authorisation and would not have dealt with the question whether eszopiclone is or is not a new active substance. According to the Commission, the operative part of the decision would have contained a simple reference to the Committee's opinion.
>
> 31. However, that does not mean that that question cannot be subject to review by the Court. The Committee's opinion that eszopiclone cannot be regarded as a new active substance must be regarded as a preparatory act to the decision to grant the marketing authorisation which the Commission is to adopt under Regulation No 726/2004. In accordance with the case-law, whilst measures of a purely preparatory character may not themselves be the subject of an action for annulment, any legal defects therein may be relied upon in an action directed against the definitive act for which they represent a preparatory step (*IBM* v *Commission*, paragraph 15 above, paragraph 12).

> 32. Accordingly, if the applicant had not withdrawn its application for marketing authorisation, it would have been able to challenge, by an action against the Commission's decision granting marketing authorisation, both the Committee's refusal to recognise eszopiclone as a new active substance and the legal test applied by that Committee to reach that conclusion. Accordingly, it cannot rightfully be claimed that the refusal to recognise eszopiclone as a new active substance, as decided upon by the Committee and confirmed by the Commission, could not be subject to any review in the event of an action against the decision to grant the marketing authorisation, adopted by virtue of Regulation No 726/2004."

32. In my view, these paragraphs are deeply unhelpful to Teva's case on its first ground. Had an MA been granted, the Commission's opinion that eszopiclone was not a new active substance would (a) have been *intra vires* its powers (had it been otherwise the Court would have said so), (b) have been regarded as at the very least preparatory to a definitive act and could therefore be challenged on standard EU judicial review principles as, in effect, part of it (*a fortiori* if the Commission's opinion is incorporated in a recital), and (c) imports legal effects. Sepracor is not, however, decisively in the MHRA's favour, and I did not understand Ms Anneli Howard so to submit.

33. In Case C-104/13, AS "Olainfarm" v Latvia, the Court held that the holder of an MA for a reference medicinal product had the right to challenge the MA for a generic which used that product as the reference product during the ten-year data exclusivity period to which the holder is entitled under the Directive. Paragraph 37 of the Court's judgment is material:

> "It should be observed that Article 10 of the Directive lays down the conditions under which the holder of a MA for a medicinal product is required to accept that the manufacturer of another medicinal product is entitled to refer to the results of pre-clinical tests and clinical trials contained in the dossier relating to the application for the MA for the former product, rather than perform those tests or trials himself, for the purpose of obtaining a MA for the other medicinal product. It is apparent that that provision confers a concomitant right on the holder of the MA for the former medicinal product to demand that the rights attaching to him by virtue of those conditions are observed."

"That provision" at the start of the second sentence of paragraph 37 clearly refers to Article 10. The "concomitant right" in the holder of a MA for the reference medicinal product also flows from Article 10 in the sense that this provision lays down a precondition for the exercise of any generic manufacturer's rights: the expiry of eight years after the first MA was granted. But, the "rights attaching to the [holder of a MA for the reference medicinal product] by virtue of those conditions", which lie at the centre of the present case, are the rights which flow from the grant of his MA. In practice, these rights will not require invocation unless and until someone else applies for a MA relying on his reference medicinal product. Yet, that does not mean that the

locus of the underlying right is to be found in Article 10, or that this is the sole provision which governs its recognition or adjudication. The better analysis, and I will need to return to this, is that during the currency of the data exclusivity period any generic applicant has no right (in Hohfeldian terms – the concept is that of a "no right") to rely on the data that relate to the protected product. This is because the rights which inhere in the reference medicinal product under the scheme of the Directive stem from its GMA, which is the platform for the bundle of rights enuring to the benefit of the MA holder in recognition of the innovative development that had been undertaken in relation to the active substance of that product.

34. In Cases C-629/15 P and C-630/15 P, Novartis Europharm Ltd v Commission the issue was whether two drugs with the same active substances but with separate market authorisations for different therapeutic indications should enjoy separate data exclusivity periods. This issue turned on whether the second drug for the different indication fell within the same GMA as the first.

35. Advocate General Bobek held that there were two constitutive elements of the GMA: first, it was linked to the identity of the MA holder [39-42]; secondly, it was anchored to constancy of the active substance. On the other hand, if two drugs with the same active substance [72] differed in terms of their dose strengths or therapeutic indications, that did not affect the GMA or lead to a new data exclusivity period [70].

36. The following paragraphs of Advocate General Bobek's Opinion are germane to the present case:

> "30. All four medicinal products concerned in the present case have been authorised through the centralised procedure, provided for initially in Regulation No 2309/93 and subsequently in Regulation No 726/2004.
>
> 31. It is undisputed that the GMA concept applies to nationally authorised products under Directive 2001/83 in the same way as products authorised in the centralised procedure under Regulation No 726/2004 and, previously, Regulation No 2309/93.
>
> 32. Pursuant to the second subparagraph of Article 6(1) of Directive 2001/83, the initial marketing authorisation as well as those pertaining to the developments of the initial medicinal product shall be considered as belonging to the same GMA, in particular for the purpose of using the abridged procedure upon the expiration of the applicable regulatory data protection period, as specified in Article 10(1) of Directive 2001/83 and, in the present case, in Article 13(4) of Regulation 2309/93.
>
> 33. In the light of the connection established in Article 6(1) of Directive 2001/83 between the regulatory data protection period and the GMA, the latter notion is instrumental in the determination of the conditions under which applicants in the abridged procedure may rely on the data contained in the file of the reference medicinal product. Pursuant to Article 10(2)(a) of

Directive 2001/83, a reference medicinal product is defined as 'a medicinal product authorised under Article 6, in accordance with the provisions of Article 8'.

34. It follows from the second subparagraph of Article 6(1) of Directive 2001/83 that only one regulatory data protection period is associated with the GMA. That regulatory data protection period applies to the data related to the initial medicinal product as well as to the data submitted in respect of developments based on it.

35. The second subparagraph of Article 6(1) of Directive 2001/83 lists the developments of the initial medicinal product that constitute variables that would fall, if developed, under the GMA concept. These variables are: additional strengths, pharmaceutical forms, administration routes, presentations, and any variations and extensions.

36. By contrast, the second subparagraph of Article 6(1) of Directive 2001/83 does not specify the constitutive elements by which a GMA can be identified, and by which a specific GMA can be distinguished from another GMA.

…

43. Secondly, the most important element of a medicinal product is its active substance. 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 language of second subparagraph of Article 6(1) of Directive 2001/83. Further, if a difference in active substance does not lead to a different GMA, it would be difficult to perceive what kind of innovation would provide the applicant with a different regulatory data protection period.

44. The conclusion that the active substance (or a combination of active substances) is a constitutive element of the GMA is also confirmed in the Commission's Notice to Applicants: 'If the medicinal product being assessed contains a modification of an existing active substance, it should be clarified … whether the product contains a new active substance or not. This clarification impacts on the existence or not of a global marketing authorisation if the medicinal products belong to the same marketing authorisation holder.

45. The examples provided by the Commission on changes to the initial medicinal product that do not fall within the same GMA all concern scenarios under which there is a change to the active substance (or combination of active substances) in the initial medicinal products. This is 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 amounts to a new active substance.
>
> 46. It thus follows that the notion of GMA is based on identity of the marketing authorisation holder and of the active substance(s). If the marketing authorisation holder or the active substance changes, the same GMA no longer applies.
>
> …
>
> 59. By contrast, Directive 2001/83 provides for rather broad possibilities as to data that may be referred to in the abridged procedure. Article 10(1) of Directive 2001/83 expressly connects the regulatory data protection period with the GMA notion, irrespective of the fact that that notion covers various developments of the initial product, in relation to which separate data have to be supplied at different points over the course of time. The starting point of the 10-year data protection period is thus determined by the granting of the marketing authorisation for the initial medicinal product. There is no rule on the protection of separate subsequent studies, as acknowledged in the Generics case."

37. I will return to this analysis under the rubric of the first ground.

38. Finally, I should return briefly to the Opinion of Advocate General Bobek in Astellas which was relied on by all Counsel before me, albeit in different ways. The crux of the case was an intricate procedural issue which arose in the context of the decentralised procedure. At paragraph 49 of his Opinion, Mr Bobek provided a homely metaphor in the context of that procedure of Member States "cooking with friends", i.e. participating in the elaboration of their decision at the same time. Ms Bacon rightly said that he was referring to a number of chefs, whereas in the context of the centralised procedure we have only one. However, that in my opinion would be an even stronger reason for respecting MA decisions made under the common regulatory framework.

39. The parties also analysed [78-80] of Mr Bobek's Opinion:

> "78. There is, however, a deeper layer to the assessment of 'a potential serious risk to public health'. Since what is being requested is the authorisation of a generic product, that process relies on the extant data of the reference product. Now if the data protection period has not yet lapsed, then there is no data to be relied on. If the relevant data cannot yet be consulted, it is logically impossible to conduct any scientific assessment of the generic medicinal product at issue.

> 79. I therefore agree in substance with arguments advanced by the Governments of Belgium and the United Kingdom in their submissions. The impossibility of referring to the data of a reference medicinal product logically hampers, in my view, the evaluation of a public health risk of the generic product. In this manner, the agreement as to the expiration of the data exclusivity period is, in a way, a preliminary, but indispensable, part of the approval process.
>
> 80. In the light of the abovementioned, I consider, in response to the first preliminary question posed, that Article 28(5) and Article 29(1) of Directive 2001/83 should be interpreted as meaning that the competent authority of the concerned Member State, acting in the decentralised procedure for marketing authorisation for a generic medicinal product, is not competent, when issuing the national marketing authorisation pursuant to Article 28(5) of Directive 2001/83, to determine unilaterally the time from which the data exclusivity period for the reference medicinal product begins to run. However, that authority takes part in that assessment at an earlier stage in the decentralised procedure pursuant to Article 28(3) and (4) of Directive 2001/83. The participation of the competent authority of the concerned Member State in the approval process thus makes that authority co-responsible for the documents approved in that procedure."

I draw the following from these paragraphs. First, that during the currency of the data exclusivity period, it is not possible for the generic applicant to rely on the data that relate to the reference medicinal product. Put another way, that applicant has no relevant right, or entitlement, during the currency of that period. Secondly, the last sentence of [79] is looking at the process whereby the data exclusivity period is being agreed by relevant Member States as part and parcel of the approval process within the decentralised procedure (see, for example [70] and [80]); it is not concerned with any subsequent decisions made under Article 10. In my judgment, it is not difficult to extrapolate from Advocate General Bobek's reasoning the proposition that, in a case involving the centralised procedure, any decision regarding the GMA (with which the data exclusivity period is inextricably linked) should be regarded as a "preliminary, but indispensable, part of the approval process", namely the approval process carried out within the context of that procedure.

E. The Facts

40. Here, I draw heavily from the helpful agreed Chronology and the evidence of Mr Robert Hemmings, who is a scientist employed by the MHRA and is also a co-opted member of the CHMP.

41. In the spring of 1988 Fumapharm AG submitted to the German competent authority, later renamed Bundesinstitut fur Arzneimittel und Medizinprodukte (the Federal Institute for Drugs and Medicinal Devices ("BfArM"), an initial full dossier

application for a national MA under Directive 65/65 for two strengths of its drug Fumaderm, containing DMF and MEF. In December 1990 following a request by BfArM (I will use this acronym throughout although the date it changed its name is unclear) to withdraw its application and resubmit with a justification for the combination of DMF and MEF, Fumapharm did withdraw its initial application.

42. In October and November 1991 Fumapharm resubmitted its applications and filed in support an expert report from Professor Altmeyer dated 14th October 1991. It is clear from the application forms that both DMF and MEF were listed as active substances. Mr Hemmings explains that under guidance applicable at around this time, applicants were required to "justify the particular combination of active ingredients proposed". Professor Altmeyer's report did not, on my understanding of it, directly address the issue of whether DMF and MEF were active substances in their own right; he made a different point about toxicity, which was relevant to the need to justify the particular combination.

43. On 9th August 1994 Fumapharm received its national MA from BfArM for Fumaderm, indicated for the treatment of psoriasis, in two strengths. On my understanding of paragraph 16(a) of Mr Hemmings' first witness statement, DMF was present in larger concentrations in the "forte" than in the "mite" dose. Fumaderm's period of data exclusivity expired in August 2004.

44. Owing to the lapse of time, certain of BfArM's approval documents and scientific appraisals are no longer available. Ms Howard asked me to infer that BfArM must have concluded at some stage that DMF and MEF were independent active substances in Fumaderm, in the sense that each had a discrete pharmacological activity. Ms Bacon strongly submitted that there was no evidence enabling me to draw that inference. For the reasons appearing under paragraph 151 below, it is unnecessary to decide this point.

45. In October 2003 Biogen was granted exclusive licence by Fumapharm of the rights to develop and market products containing DMF, and in 2006 Biogen acquired Fumapharm.

46. Mr Trevor Mill, Biogen's senior Vice-President, Regulatory Affairs, draws my attention to the fact that in correspondence with Biogen in 2006 the Commission agreed in principle that an active substance which has not previously been assessed individually would be entitled to its own data exclusivity period.

47. In 2011 Biogen submitted its application for eligibility for the centralised procedure on the basis that DMF in a mono-product is a new active substance. The EMA found that Tecfidera was eligible for the centralised procedure despite concluding that DMF was not a new active substance, and indicated that in principle it would be entitled to data exclusivity.

48. On 28th February 2012 Biogen applied for a centralised MA for Tecfidera under Article 8(3) of the Directive on the basis that DMF is a known active substance. The application stated that the product was indicated for multiple sclerosis. The Tecfidera assessment period commenced on 21st March 2012.

49. In January 2013 Teva applied to the Dutch Medicines Evaluation Board for an MA for its DMF product indicated for psoriasis, under Article 10a of the Directive – well established use.

50. On 21st March 2013 the CHMP gave a positive opinion recommending the grant of an MA for Tecfidera.

51. Following concerns expressed to the Commission, the details of which remain confidential, in September 2013 Biogen requested that the MA process be put on hold. It wrote to the Commission requesting an assessment of Tecfidera's new active substance status. Accordingly, on 19th September 2013 the Commission asked the CHMP to consider Tecfidera's new active substance status.

52. On 11th November 2013 Teva submitted an anonymous written intervention requesting that the CHMP consider whether DMF was in well established use. Coincidentally, on the same day the joint rapporteurs (the co-rapporteur being Mr Hemmings) issued a draft assessment report "on the claim of new active substance status of DMF contained in Tecfidera". The overall conclusion of the report was as follows:

> "Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the rapporteurs consider that DMF contained in Tecfidera is not to be qualified as a new active substance as from the submitted data it does not appear to differ significantly in properties with regard to safety and/or efficacy from the currently authorised product Fumaderm …"

53. Teva obtained this draft report only very recently following a disclosure request made to the Commission. It was neither disclosed by the MHRA nor referred to by Mr Hemmings at paragraph 34 of his first witness statement – being, in terms of the chronology, the natural habitat for such a reference. However, I take his point that this was one of a series of drafts and does not represent the concluded opinion of the CHMP. I do not accept that this draft report was addressing the wrong test, namely "new" as opposed to "different" active substance, because that did not impact on the scientific analysis (see the "Post-Opinion Note", paragraph 68 below). I would add that the overall conclusion in the draft report did not directly address the issue of whether MEF was an active substance in Fumaderm. The closest that the draft report got to this issue is in relation to "Major Objection 2", where the point was made that "the extent by which DMF and MEF exert their pharmacological activity as part of the Fumaderm product must be further described by the applicant in order to help establish the role MEF plays in Fumaderm". It should also be noted that at least at this stage of this iterative process those conducting the scientific analysis were not of the opinion that the Commission was somehow bound by any determination made by BfArM back in 1994.

54. On 21st November 2013 the CHMP met and concluded that DMF is a new active substance. That conclusion was included in its final report dated 26th November 2013 published on the following day. It follows, of course, that the full Committee did not agree with the joint rapporteurs.

55. Close attention was given by Counsel to the CHMP final report. Ms Howard had had the benefit no doubt of much help behind the scenes from Mr Hemmings, but I was impressed by the clear and effective way in which she could explain it to me. Ms Bacon, in her consistently acute and penetrating manner, also made effective submissions on this report. They have assisted me in interpreting it to the extent necessary for present purposes.

56. The assessment that the CHMP was asked to conduct was whether DMF was different from MEF. This was with a view to deciding whether DMF in Tecfidera should be given active substance status. Ms Bacon submitted that it was clear that the CHMP were not therefore asked to consider whether MEF was an active substance in its own right in Fumaderm because the premise of the question posed was that both DMF and MEF *were* active substances. At more than one stage in her submissions Ms Howard appeared unwilling to submit that the CHMP considered the independent contribution of MEF to Fumaderm. Reading between the lines, I believe that the MHRA was concerned about subparagraph 3 of paragraph 2.3 of the Commission's Notice to Applicants. However, I think that it is fair to say that she eventually did agree that the CHMP carried out that assessment: see Transcript, pages 353 and 354.

57. Following the hearing I have given careful consideration to this issue because I recognise that it is not easy, and that in the cockpit of oral argument Counsel may in the end find themselves accepting olive branches from the Court which end up being Greek gifts. In my judgment, and putting aside the question of new active substances (as distinct from different active substances, insofar as truly separate questions are raised), it seems to me that DMF and MEF could be regarded as different active substances on any one of the following bases:

    (1) MEF has an independent therapeutic activity in Fumaderm; or

    (2) DMF and MEF do not share the same therapeutic moiety; or

    (3) DMF and MEF share the same therapeutic moiety but differ in terms of their safety and/or efficacy profile.

58. Some additional explanation is required. If MEF has no independent therapeutic activity in Fumaderm, it would naturally follow that DMF in Tecfidera and DMF in Fumaderm were the same active substance (DMF plus zero = DMF). Thus, in logical terms the first of my three bases falls to be addressed unless it could be said that issue had already been conclusively determined, i.e. by BfArM in 1994. However, a close examination of the CHMP report discloses that no reference was made to any conclusive or binding BfArM determination.

59. If two molecules share the same therapeutic moiety, that means that the functional part of the molecules under comparison are the same, or cannot be regarded as materially dissimilar. Other non-functionally relevant parts of the molecules may differ, but given that they do nothing they may be disregarded. Thus, if DMF and MEF share the same therapeutic moiety, they could not be regarded as different active substances.

60. Identity of therapeutic moiety but differences in terms of safety and efficacy profiles will turn cases which are *prima facie* the same into different cases. This principle has

been clearly explained by Advocate General Jacobs and the Court in the SmithKline Beecham case: see paragraph 26 above.

61. There are two additional considerations which flow from the basic science. First, if the evidence demonstrated that DMF and MEF became the same substance in the human body, they would in practical and functional terms be the same active substance. The CHMP considered this issue and concluded that the two substances did not interconvert. Secondly, I raised the possibility in argument that one substance in a combination might neutralise or nullify the therapeutic effect of the other. I was not intending to suggest that this could be a live possibility in relation to DMF and MEF. Their respective pharmacological properties are not such as to lead to this inference, and MEF would never have been included in Fumaderm if the scientists knew that it would be somehow nullified by DMF.

62. Returning to the CHMP report, I have noted the following conclusions:

(1) "in non-clinical investigations, DMF and MEF independently demonstrated pharmacological activity by the regulation of Nrf-2 dependent gene expression".

(2) "the available clinical data on MEF alone were derived from published literature and are limited. These confirmed the pharmacological activity seen preclinically and the most relevant data are summarised" (I should add that the summary included the two Nieboer studies in 1989 and 1990, and covered the therapeutic effect of MEF administered without DMF in psoriasis patients. They do not include, on my understanding, MEF taken in combination with DMF).

(3) "MEF is well absorbed and comprises a significant active fumarate exposure following administration of Fumaderm".

(4) "The evidence provided, although limited and based on literature precluding full assessment, support the non-clinical data and suggests that both DMF and MEF have pharmacological activities, with MEF showing activity alone in psoriasis both from an efficacy and safety/tolerability point of view …".

63. There were three stages to the CHMP's final conclusion that DMF and MEF are different active substances. The first stage is that they are molecularly different and are esters of an inert substance (fumaric acid). The second stage is that non-clinical and clinical data clearly show that DMF is pharmacologically active. The position is less clear in relation to MEF but "in vitro and in vivo non-clinical data including Nrf2-dependent gene expression together with published clinical data suggesting the pharmacological activity of MEF in psoriasis lead to the conclusion that DMF and MEF are both active". The third stage is that, given that DMF and MEF do not share the same therapeutic moiety, they are different active substances; and it is unnecessary to investigate whether their safety and efficacy profiles differ.

64. Mr Hemmings has provided me with further assistance on the topic of Nrf2-dependent gene expression. As paragraph 37 of his first witness statement explains:

> "In laymen's terms, they do this [sc. demonstrate pharmacological activity] by activating a particular pathway (called the "Nrf2" transcriptional pathway), which activates the

> immune system promoting cellular defence to potentially toxic stimuli. Once the pathway is activated, genes will be expressed (switched on) and proteins synthesised (produced) which are protective in relation to certain kinds of harm such as inflammatory and oxidative stress."

65. On 19th December 2013 the draft Tecfidera decision based on the CHMP assessment report was submitted to the Standing Committee.

66. On 10th January 2014 the UK member of the Standing Committee, who I believe must have been Mr McDonald, requested that the draft Tecfidera decision be discussed at the plenary meeting of that Committee. Paragraph 35 of Mr Hemmings' witness statement gives a clue as to why this occurred:

> "The CHMP's assessment of NAS status represented an exceptional and novel case, where a medicinal product containing active substance A and active substance B had already been authorised, and authorisation was subsequently sought for a different medicinal product containing solely active substance A. The assessment of NAS in that precise situation had not arisen before, to my knowledge."

67. Mr Hemmings has provided helpful evidence as to what happened at the Standing Committee plenary meeting on 28th January 2014. In short, the Commission strongly took the line that Tecfidera should be regarded as a new active substance; many Member States, led it seems by the UK, took the view that it could not be, because it had already been included in a previously authorised product – but it could and should be regarded as a different active substance, with its own GMA; and ultimately the latter view prevailed.

68. The Standing Committee also resolved to amend the Commission's draft of recital (3) to its implementing decision. This decision was promulgated on 30th January 2014 and published in the Official Journal on 28th February. It was addressed to Biogen. An MA was granted for "Tecdifera – DMF" for five years. Article 1 provided that the characteristics of the product were summarised in Annex I to the decision. This has been provided to me but it is unnecessary to examine the detail. Recital (3) provides:

> "Dimethyl fumarate (DMF), the active substance of "Tecfidera - Dimethyl fumarate", is part of the composition of the authorised medicinal product Fumaderm which consist [sic] 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." (italics mine)

The sentence I have italicised is a somewhat compressed summary of what the CHMP decided in full. Insofar as there may be any doubt, recital (3) should be read and understood in the light of the CHMP report. In any event, I do not read recital (3) as stating that the sole issue determined by the CHMP was that of therapeutic moiety: the Commission stated, entirely correctly, that it had been concluded by the CHMP "that MEF and DMF are both active …". The meaning would be even clearer if the italicised sentence had read: "The [CHMP] concluded that MEF and DMF are both active, *and that* they are not the same active substance since they do not share the same therapeutic moiety." (Here, my italics denote the additions, including the addition of a comma after "both active"). I should add that following this decision the CHMP added a "Post-Opinion Note" to its report. It remarked on "this evolution of the regulatory considerations", recorded that its conclusion on new active substance was "obsolete", but stated that in all other respects its scientific conclusions and assessments remained valid.

69. On 2nd July 2014 the Dutch Medicines Evaluation Board refused Teva's application for an MA for its DMF generic product. This decision, which related to well established use rather than Article 10(1), is under appeal.

70. On 22nd December 2016 Teva applied under Article 10(1) of the Directive, and the decentralised procedure, for an MA for its generic product indicated for multiple sclerosis. The UK was the reference Member State and Luxembourg the sole concerned Member State.

71. Teva submitted three papers or assessment reports in conjunction with its application. First, reliance was placed on the 1990 Nieboer paper which had already been considered by the CHMP in November 2013. Secondly, there was a paper by Mrowietz et al, known as the BRIDGE paper, published in the British Journal of Dermatology in 2016. Thirdly, there was an unpublished report ("the Fumurate Report") authored by Dr John Warren, which appears to be undated. Dr Warren describes himself as "an independent consultant in the pharmaceutical industry" who had been "retained by the Teva group of companies to review and summarise scientific literature relating to the pharmacologically active substance DMF".

72. I did not receive oral submissions on these reports. However, it is obvious to me that the BRIDGE study was a well-designed and rigorous study intended to measure the efficacy and safety of a new formulation of DMF compared with placebo and Fumaderm. The authors concluded that DMF is effective in the treatment of adults with moderate-to-severe chronic plaque psoriasis. It is true that the authors noted in passing that "the MEF salts alone have not been shown [by other studies] to have significant clinical efficacy". However, the study was not designed to supplement existing learning on that topic, still less examine the question whether MEF was or is an active substance in Fumaderm.

73. Dr Warren's unpublished report contains no original research and has not been peer-reviewed. However, it is not for me to assess its quality. To be fair to Teva, I have noted the following conclusions:

> "The evidence for the three salts of MEF, of which the calcium salt comprises 89% of the MEF content of Fumaderm mite and 92% of the MEF content of Fumaderm [I believe that he has omitted "forte"], is that they do not have convincing evidence of relevant pharmacological activity when tested in vitro at concentrations that are relevant in vivo
>
> …
>
> Both MEF and DMF have similar pharmacological activity in vitro, though DMF is generally more active. There is no evidence from clinical trials for sufficient efficacy of MEF as oral monotherapy to justify its inclusion at the doses used in Fumaderm. There is an absence of data to show that MEF makes a significant additional contribution to the DMF component of Fumaderm. DMF is rapidly hydrolysed in the wall of the small intestine and may act through its metabolite MMF and possibly other yet unidentified metabolites, perhaps adducts with GSH. The better physico-chemical properties of DMF compared to MEF, in terms of lipid solubility, may account for the greater potency of DMF with oral dosing in humans."

I think that the point that Dr Warren was making was that, although MEF has pharmacological action in principle, it shows no clinically relevant pharmacological activity in human beings at the doses in which it is used in Fumaderm.

74. On 16th January 2017 MHRA sought two opinions from scientific assessors within its licensing division on Teva's application. The email requesting that advice reminded the scientific team that the Commission's 2014 decision in relation to Tecfidera "was based on the conclusion that the MEF salts contribute to the therapeutic effects of Fumaderm, in addition to DMF". Ms Bacon submitted that this completely mischaracterised what the Commission decided, but I disagree. However, the email does assist her in a different respect in identifying what the relevant legal test might be for the purposes of Teva's second ground.

75. The scientists did not take long to respond to the material submitted with Teva's application. Ms Bacon took a forensic point about this but in my view it has no merit. An experienced scientist could readily provide a quick and accurate response to material of this nature, together with brief reasons. Dr Sue Morgan said this:

> "I have had a look. I think Teva has presented data to demonstrate the esters are less active than DMT [her acronym for DMF] but not that they have no activity. The non-inferiority study (Mrowietz) shows that DMT alone is not >15% worse than the DMT + esters. The point estimates in the main favour Fumaderm. Speed of onset data not presented. The other study

> is v small but again point estimates appear to favour FAC-EC (combination tablet). So some additional activity possible – whether clinically important is another matter."

Dr Sabine Lenton pointed out that the 1990 Nieboer study had been addressed in the CHMP's report. Her position on the Mrowietz study did not materially differ from her colleague's. As for Dr Warren's report:

> "… although doubts are being raised with regards to the activity of MEF in Fumaderm, a number of elements had been given in the EPAR for Tecfidera that remain.
>
> Conclusion: differences are noted between DMF on its own and associated with fumurate salts hence the conclusion for Tecfidera remains, although as Sue mentions the importance of these differences could be questioned."

76. Meanwhile, the MHRA was seeking confirmation from the EMA as to the data exclusivity period applicable to Tecfidera. On 17th January 2017 the EMA confirmed that Tecfidera could not be used as a reference medicinal product for eight years from 3rd February 2014. On the following day the MHRA notified Teva that in its view "the procedure is invalid in the UK". This was because Teva had not submitted the ASMF for DMF (i.e. any dossier under Article 8(3)), and "we consider that Tecfidera was awarded data exclusivity as a new GMA at time of approval".

77. On 19th January 2017 Teva invited the MHRA to consider its decision, contending that recital (3) of the Commission's decision was not binding.

78. Teva's contention was raised at a meeting of the Co-Ordination Group for Mutual Recognition and Decentralised Procedures (human) ("the CMDh") which took place between 23rd and 25th January 2017. Representatives from the Commission and the EMA were present. Mr McDonald presented a paper to the meeting which outlined the MHRA's position. His evidence is that there was unanimous support for it. The CMDh therefore noted:

> "… that the EC decision on Tecfidera clearly states that MEF and DMF are not the same active substance and Tecfidera does not belong to the same GMA as Fumaderm. Generic applications relating to Tecfidera are therefore not yet possible."

79. On 15th February 2017 the MHRA notified Teva that:

> "[t]he position on the data exclusivity enjoyed by Tecfidera, as set out in the EPAR and the recital to the Commission Decision granting the MA, remains the current position."

It is this decision that Teva formally challenges in these proceedings for judicial review.

F. Teva's First Ground of Challenge

Teva's Case

80. Ms Bacon's able, clear and well-crafted submissions on her first ground may be reduced to three essential elements, although the first two appear to me to be more essential than the third. Following the oral hearing, I have re-read her skeleton argument, the various notes she supplied to assist me, and the whole transcript of the proceedings. In the circumstances it is unnecessary for me to summarise everything that she said.

81. Ms Bacon submitted that recital (3) to the Commission's decision on Tecfidera was not binding on the MHRA although account could properly be taken of it. This is because (element 1) data exclusivity is determined under the statutory scheme not at the time the MA is issued for the reference medicinal product but at the time the matter falls to be considered under Article 10(1). It follows, or it is in any event the case, that recital (3) is not the operative part of the Commission's decision (element 2). It carries no legal effects at all; and, in particular, no legal effects *vis-à-vis* Teva. Consequently, the issue of whether Tecfidera is within the GMA of Fumaderm, because the active substance in Tecfidera is the same as the active substance in Fumaderm, must be addressed by the MHRA.

82. The third essential element of Ms Bacon's argument has a number of related facets, but its gravamen is that there are sound policy reasons for favouring Teva's approach. Teva could not challenge the Commission's decision on Tecfidera and the common regulatory framework should be predicated on effective judicial scrutiny.

83. In elaboration of the first essential element, Ms Bacon focused on the language of the second paragraph of Article 6(1) of the Directive: the consideration of whether an MA falls within the "same GMA" falls to be carried out "in particular for the purpose of the application of Article 10(1)". Thus, the true focus is Article 10(1), not the first paragraph of Article 6(1) or Article 8(1). Ms Bacon further submitted that the weight of authority supports her approach; and, in particular, that Advocate General Bobek's Opinions in Novartis Europharm and Astellas do not cut across it. Specifically, at no stage was Mr Bobek opining on the central question which taxes this Court: whether the decision on GMA was to be taken at the time of issuing the MA for the reference medicinal product.

84. Ms Bacon recognised that subparagraph 3 under paragraph 2.3 of the Commission's Notice to Applicants (see paragraph 23 above) was inconsistent with her case, or at least unclear. However, Ms Bacon did place some reliance on the Commission's formulation of "documented therapeutic contribution", but that was in the context of her second ground.

85. In elaboration of her second essential element, Ms Bacon drew my attention to additional EU case law in support of the proposition that recital (3) should not be regarded as the operative part of the Commission's decision. At paragraph 8(b) of her Note in Reply, Ms Bacon properly grasped the nettle and submitted that it was *ultra vires* for the Commission to adopt a binding decision on GMA, given the absence of any power in the Directive to do so.

86. I will cover the different aspects of Ms Bacon's third essential element in the section which follows.

Analysis and Conclusions on Ground 1

87. I intend no discourtesy to Ms Howard and Ms Jemima Stratford QC for Biogen by not summarising their submissions in my judgment. They may rest assured that I have taken them into account.

88. I observed more than once during the hearing that the present difficulty arises because of the way in which the important concept of GMA has been woven into the Directive by amendment in 2004. It is located at the end of the second paragraph of Article 6(1) when it might better have been inserted earlier, and given some sort of definition. Furthermore, the second paragraph of Article 6(1) deals with situations ("additional strengths etc.") where it seems clear that subsequent MAs must be encompassed within the same GMA as the initial MA for the product. In the absence of a proper working definition or a more explicit setting out of the decision-making process, courts are left to their own devices in giving substantive and procedural content to this concept.

89. The constitutive elements of the GMA have been expounded by Advocate General Bobek, which means that what he calls its "notion" may be properly conceptualised. At its core lies continuity of active substance; or, put conversely, a different active substance breaks the chain of continuity and leads, at least conceptually, to a different GMA.

90. Article 6(1) of the Directive uses the verb "issued" in relation to an MA: no medicinal product may be marketed in a Member State unless an MA is *issued* by the competent authorities of that Member State. This requires a formal decision whereby the date and circumstances of the issuance can be ascertained, so that the rights of the holder and of the public may properly be respected. To my mind, it cannot be said that a GMA is "issued" in the same way. Indeed, the second paragraph of Article 6(2) uses different wording: "shall be considered as belonging". This means, or at the very least suggests, that no formal act is required.

91. The rights which flow from the initial MA to the advantage of the MA holder (assuming that such rights are not lost because its identity changes) are not limited to the right to market the medicinal product in the Member State or, in a centralised procedure case, the EU as a whole. This is because the initial MA is always the starting-point for the GMA, which in turn is the wellspring for a further bundle of rights which protect the innovative development of the active substance and impinge on the ability of competitors to rely on Article 10(1). I said during oral argument that the GMA inheres in the initial MA. On reflection, that was imprecise. A more accurate formulation is that the concept of the GMA flows out of the innovative active substance in the initial MA, and the GMA inheres in that active substance. As the descriptor "global" suggests, the GMA incorporates or envelops the initial MA; it is not the other way round. It is, therefore, the bundle of rights I have been referring to which inhere in or flow out of the GMA.

92. This analysis is reinforced by paying attention to the verbal phrase "belonging to" in the second subparagraph to Article 6(1). The initial MA referred to in that subparagraph has, as its core constitutive element, an active substance which can be identified and described. Subsequent MAs containing the same active substance will be considered to belong to the same GMA as the initial MA. In my judgment, it is clear that the GMA is the source of the right, or bundle of rights, which flow by operation of the scheme of the Directive. Or, as the Commission has stated at paragraph 6.1.5 of its Notice to Applicants, "the GMA contains the initial authorisation and all variations and extensions thereof … granted to the MA holder of the initial authorisation".

93. On Ms Bacon's analysis the locus of the relevant right is Article 10(1), and this is triggered only as and when an application for a generic product is made. She used the adjective "inchoate" to underscore that submission. It is for that reason, she further submitted, that the second paragraph of Article 6(1) looks forward to Article 10(1).

94. I disagree. Articles 6 and 10 of the Directive must be read together as part of a unitary statutory code. Whereas it is true that the issue may not arise in practical terms unless and until an application is made for a generic medicinal product under Article 10(1), that application falls to be determined with regard to the MA of the reference medicinal product specified in the application itself. It is this product which is treated as the "initial MA" being the starting or reference point for (i) the GMA and (ii) the rights which ensue by operation of the Directive. This is the point which I made at paragraph 33 above in the context of the Olainfarm case and which I repeat. In my view, the relevant right is not generated afresh and/or for the first time when an Article 10 application is made.

95. Furthermore, this analysis is supported by paragraph 59 of Advocate General Bobek's Opinion in Novartis Europharm (see paragraph 36 above) although I take Ms Bacon's point that the verb "determined" in the penultimate sentence of that paragraph does not mean that a determination has formally been made at the time the initial MA was issued. My preference would be to substitute "governed" for "determined".

96. In short, the locus of the relevant right, or package of rights, is not Article 10(1) but, insofar as it is necessary to specify it, Article 6(1) of the Directive. The GMA, and the rights which ensue, stem from the initial MA of the innovative product. Equally, the GMA of the reference medicinal product stems from that product by virtue of the operation of the general principles to be found in Article 6(1).

97. The late Professor Hart explained the distinction between what he called "primary rules" of obligation (and correlative rights) and "secondary rules" of adjudication and recognition. Thus far, the focus has been on the former. It was also clearly part of Ms Bacon's case, although she eschewed Professor Hart's terminology, that the relevant secondary rule is located in Article 10(1) and nowhere else.

98. I must address Ms Bacon's submission under that sub-rubric in two different ways. In the first, I shall endeavour to explain how I consider the Directive is intended to operate. In the second, I shall recognise that the parties, in particular the MHRA, are not inviting me to decide this application for judicial review on the basis that appealed to Lavender J when he refused permission (see the second paragraph of his ruling),

and I shall therefore hew more closely to the submissions advanced by Ms Howard and Ms Stratford.

99. The way I think that the Directive is supposed to operate may be illustrated by examining what the position would have been had the Commission said nothing about active substances and GMA in its 2014 decision. On these hypothetical facts it would have been much easier for Teva to say that the MHRA should determine the issue of whether or not Tecfidera was encompassed by the GMA of Fumaderm because there would have been no antecedent determination by anyone to that effect. Ms Stratford expressly conceded that in the foregoing counterfactual, which I posited to her during oral argument, the MHRA would indeed be required to rule on the issue under the rubric of Article 10(1). There was no judicial come-back at the time, but I am far from convinced that Ms Stratford is correct.

100. This is because the manner in which Article 10(1) operates, or is supposed to operate, is that the generic applicant has an unqualified right to apply for an MA on an abridged basis if the data exclusivity period for the reference medicinal product has expired. It has no right to apply on this abridged basis during the currency of that period. The premise of Article 10(1) is that the reference medicinal product will always possess its "own" GMA since it is this which is the bar to an early application being made. In my judgment, the generic applicant is deemed to accept that this is the case by the very nature of its application, referencing as it must do a particular medicinal product. Furthermore, the wording of Article 10(1) supports this austere approach because it does not refer to any determination being made as to the scope of the GMA of the reference medicinal product: the consequences in terms of the rights of the relevant entities are entirely mechanistic if not pre-determined.

101. There is no obvious unfairness in this approach. Generic applicants are being required to take it or leave it. If they take it, they must also take what necessarily flows. If they leave it, they are free to apply under Article 8(1) and submit a full dossier.

102. The counter argument would be that the second subparagraph of Article 6(1) provides that the relevant determination is being made under Article 10(1). Although Ms Bacon was not being required to meet the argument I am putting forward, because it was not advanced, she did expressly submit that the only relevant determination as to the scope of the GMA can be made under Article 10(1) (this was part of what I have been calling the first element of her case on the first ground). On my understanding of her submissions, Ms Stratford accepted that relevant decisions may be made under Article 10(1); she did not of course accept that they had to be made thereunder.

103. In my view, the correct analysis requires an accurate reading of the second subparagraph of Article 6(1). In a case expressly catered for by this subparagraph, any additional strengths etc. may either be treated as included in the initial MA, or be granted or issued a separate MA. In the second instance, the separate MA shall be considered, i.e. treated, as being within the same GMA as the initial MA. The point of the subparagraph is to help identify, at least conceptually, to which GMA a particular MA belongs. Further, the subordinate clause, "for the purpose of the application of Article 10(1)", should not be interpreted as meaning that GMA decisions are made under Article 10(1). The clause is designed to make clear that the main purpose of the GMA, as well as the treatment of the MA(s) which belong to it, is to govern the operation or application of Article 10(1). For the purpose of that provision, the

reference medicinal product is, as I have said, to be treated as being the subject of the initial MA mentioned in the second subparagraph of Article 6(1). This does not mean that a decision to that effect is being made under Article 10(1) – or, I might add, at all.

104. The upshot is – at least in my eyes - that the competent authority seized of an application under Article 10(1) determines it simply by ascertaining whether the data exclusivity period relating to the reference medicinal product has expired. To that extent only, the competent authority is giving consideration to the GMA of the reference medicinal product.

105. Tempting as it might be to decide this application for judicial review on this narrow and some would say adamantine basis, I decline to do so for at least three reasons. First, on my understanding of the MHRA's submissions, and I sought clarification from Ms Howard by email after the hearing with reference to the second paragraph of Lavender J's decision refusing permission, I am not being invited to conclude that that Teva would be bound to accept Tecdifera's GMA even had there been no recital (3) to the Commission's decision. I am far from convinced that Ms Howard properly understood the point I was endeavouring to make in my email to the parties (the fault could be mine), but Ms Bacon certainly did and she objected to the MHRA expanding its case in any way. Ms Howard has not sought to do so, and I may leave it there. Secondly, it is clear that the reasoning which I personally find compelling is not supported by two institutions of the EU – either in the Commission's Notice to Applicants, or in the approach taken in January 2017 when advice was sought from the CMDh. Thirdly, I can see the force of the argument that, in the novel situation which has risen, being one uncovenanted by the welding of the concept of the GMA onto the second subparagraph of Article 6(1), the possibility of a genuine *casus omissus* or legislative gap has been generated. It follows that, regardless of the manner in which the parties' submissions were presented to me, it would be wrong to follow my own path without making a reference to Luxembourg.

106. In the circumstances, I am both able and content to plot a safer and less controversial pathway through these provisions. This requires me to examine whether decisions as to active substance and GMA may properly be made under Article 6(1).

107. It is not in dispute that the Commission in its 2014 decision could have said nothing explicit about identity of active substances and GMA. However, the Commission considered and analysed the issue very carefully indeed, and one is left wondering – certainly on Ms Bacon's submissions – whether this was a complete waste of time. According to recital (3), the legal basis for the Commission's ruling on GMA was Article 6(1). Ms Bacon has to say that this is wrong.

108. I am sure that it was to obviate difficulties created by a potential *casus omissus* that the Commission's representatives issued guidance in March 2009 (see paragraph 22 above) advising competent authorities to address and clarify whether a change in an active substance amounts to a new active substance. In its Notice to Applicants, paragraph 2.3, it is clear that the Commission's thinking is along the lines that decisions on active substances and GMAs may properly be made under Article 6(1). Although no detailed reasoning is provided, and the Notice to Applicants is non-binding, Ms Bacon is inevitably placed onto the back foot.

109. If I am proceeding along this less controversial pathway, I must recognise that what all parties are submitting to me is that decisions as to GMA are capable of being made under Article 10(1). The fault line between Ms Bacon and her opponents relates to Article 6(1): Ms Bacon submits, relying on the statutory scheme, its purposes and the wording "in particular", that the decision cannot be made under Article 6(1). Her opponents submit that it can.

110. In my judgment, the highest that Ms Bacon is entitled to put her case in relation to "in particular" is that the second subparagraph of Article 6(1) recognises that as a general rule the relevant consideration, and therefore decision, will be made under Article 10(1). This of course does not take Ms Bacon high, or perhaps far, enough. The general rule is that Article 8 applications based on active substances which are undoubtedly innovative will not require any explicit decisions to be made by the competent authorities on the issue of GMA: this will be implicit in the issuance of the MA itself. However, on my reading of the statutory scheme, adopting a purposive approach which pays due obeisance to the underlying notions of comity, harmony and consistency of decision-making within the common regulatory framework, there was nothing to prevent the Commission proceeding as it did in 2014 and making a decision on GMA, and there were many sound policy reasons for doing so. The wording of the second paragraph of Article 6(1) is wide enough to permit the relevant consideration to take place at the application stage under any one of the four procedures I have mentioned, although for present purposes I may confine myself to the centralised procedure where decisions are intended to apply across the EU.

111. In my judgment, Article 6(1) is apt to permit a decision to be made in relation to an application for a medicinal product containing a new or different active substance that the MA as granted shall or shall not be treated as belonging to the GMA of an already authorised medicinal product. I agree with Ms Stratford that the adverbial phrase "in particular" does not confine the exercise of the power to being under Article 10(1). Even if, contrary to my strongly preferred approach, "in particular for the purposes of the application of Article 10(1)" means something along the lines of "in particular for the purposes of determining the scope of the GMA of a reference medicinal product in the context of an application made under Article 10(1)", this does not preclude any consideration, and determination, being given or made under Article 6(1).

112. Submissions were also advanced under the rubrics of the fourth paragraph of Article 10(1) and Article 10(2)(b). As for the former provision, enabling the ten-year data exclusivity period to be extended by a further year in cases of new therapeutic indications and significant clinical benefit, it needs to be understood that the extension is achieved by operation of law once the subsequent MA is granted. In other words, the extended data exclusivity period is a right which flows from the GMA of the innovative product in exactly the same way as does the ten-year period. The way I see Article 10(2)(b) operating in an abridged procedure case is as follows: if the generic medicinal product is a different salt, ester etc. of the reference medicinal product, the presumption will be that the active substance has not changed; and so the reference medical product may be relied on for the purpose of Article 10(1). However, in such cases it is incumbent on the applicant to file additional information proving the safety and efficacy of the derivative or related product. It follows that these provisions do not avail Teva's argument.

113. Summarising the position in relation to the first element of Ms Bacon's case on ground 1, I would hold that decisions as to GMA may be made under Article 6(1) and are not limited to Article 10(1).

114. Turning to the second element of Ms Bacon's case on the first ground, her headline submission was that recital (3) of the Commission's decision did not form any of its operative part. She drew my attention to a number of authorities.

115. In Case T-387/04, EnBW Energie Baden-Württemberg v Commission, the Court stated:

> "127. However, as may be seen from the settled case-law, only the enacting terms of a decision are capable of producing legal effects and, consequently, of adversely affecting a person's legal interests, regardless of the grounds on which the decision is based. By contrast, the assessments made in the recitals in the preamble to a decision are not in themselves capable of forming the subject of an application for annulment and can be subject to review by the Community judicature only to the extent that, as grounds for an act adversely affecting a person's interests, they constitute the essential basis for the enacting terms of that act … It should also be pointed out that, in principle, the enacting terms of an act are inextricably linked to the statement of reasons for them in the recitals, so that, if they had to be interpreted, account must be taken of the reasons which led to the adoption.
>
> …
>
> 129. Although the Commission none the less comments, *obiter*, in the recitals in the preamble to the contested decision on aspects of the NAP to which it does not object, those recitals cannot produce binding legal effects or constitute the necessary basis for the enacting terms of the decision, given that Article 9(3) of Directive 2003/87 does not give the Commission the power to determine, in a legally binding manner, the lawfulness of a rule contained in a NAP. Moreover, in those circumstances, the recitals also cannot provide useful information for the interpretation of the enacting terms of the contested decision within the meaning of the case-law cited in paragraph 127 …"

116. The decision of the Court in Case C-164/02, Netherlands v Commission [21], is to identical effect. Case T-452/14, Laboratoires CTRS v Commission [51, 56 and 57] does not materially advance the discussion, although Ms Howard strongly relied on [60 and 61] as indicating that where a recital refers to a CHMP report in circumstances where it is an integral part of the statement of reasons for the decision, it should be regarded as indissociably linked with that decision.

117. In my judgment, the critical question is whether the Commission's decision of 30th January 2014 produced legal effects in relation to Tecfidera's GMA. That question is

not answered by focusing on the location of that decision, namely within a recital, because to address it in that manner would tend to beg it. I consider that the right approach may be drawn from [129] of the Court's judgment in EnBW Energie Baden-Württemberg, with the focus being on whether the Commission had power to determine, in a legally binding manner, the question at issue. This is why Ms Bacon eventually had to submit (see paragraph 8(b) of her Reply Note), that there was no power in the present case for the Commission to determine the issue of GMA under Article 6(1). In my judgment, and for the reasons I have already given, the Commission *did* have power to act as it did. Furthermore, I am far from convinced that it would be open to me to hold otherwise because Ms Bacon's arguments amount to an invitation to set aside, not merely to interpret, the Commission's reasoning and conclusion.

118. It naturally follows from this conclusion that the assertion that recital (3) does not have legal effects elevates form over substance and cannot be reconciled with [129] of EnBW Energie Baden-Württemberg. It is also not readily reconcilable with [29-32] of Sepracor although it should be observed that the present case is *a fortiori*. In Sepracor the Committee's opinion was a preparatory act of a decision which could be challenged, but it was not part of the recital to it.

119. Ms Howard and Ms Stratford advanced a number of submissions directed to the proposition that the Commission's decision should be regarded as binding, both legally and factually, because that is a fundamental premise of the entire common regulatory framework. They submitted in the alternative that the EU principle of "sincere co-operation" arrives at the same result. It is unnecessary to rule on this alternative submission because in my judgment the first is obviously correct. The Commission has decided under Article 6(1) of the Directive that Tecfidera has its own GMA. Either that decision was correct, as I have found, or it must be treated as correct in this Court. As and when Tecfidera is chosen by a generic supplier as the reference medicinal product under Article 10(1), the competent authority following the abridged procedure is compelled to reach a conclusion under Article 10(1) which respects the rights which inhere in that product, express consideration to which has already been given. That consideration does not fall to be given *de novo*. In the same way as Article 10(1) operates in a case where there can be no dispute as to the scope of the initial MA but no decision was made at the outset, in a case where an Article 6(1) determination has been made there is simply no room for manoeuvre: the conclusion is mechanistic and predetermined; or, in the words of Advocate General Bobek in Novartis Europharm, "the latter notion [of the GMA] is instrumental in the determination of the conditions under which applicants in the abridged procedure may rely on the data contained in the file of the reference medicinal product" [33]. The present situation is clearly *a fortiori* Astellas: paragraphs [78-80] provide a legal matrix for determinations within the decentralised procedure, and it seems to me that the relevant matrix should be regarded as all the more binding and intractable in relation to decisions have been made under the centralised procedure pursuant to Article 6(1).

120. The position would be different if concerns were raised as to "potential serious risk to public health" within Article 29 of the Directive. No such concerns were raised and this avenue becomes a *cul de sac*.

121. Subordinate arguments were advanced on both sides as to whether Teva could and should have challenged the Commission's decision in 2014, and whether it has an alternative remedy. In my judgment, these arguments were largely irrelevant. If Teva's case on the substance of ground 1 were correct, it would be entitled to a ruling from me to that effect. I was not impressed by arguments along the lines that Teva should have sought to invoke the provisions of Articles 29-31 of the Directive. It could not do so on the available evidence, and even if it could that would not have obviated the need for a full analysis of Teva's case: I would not regard the public health provisions as constituting some form of alternative remedy. Further, if Teva's case on the substance of ground 1 were correct, I would also have been minded to hold that it would have been difficult for it to have challenged the Commission's decision. However, that factor cannot drive the analysis of the legal substance. One consequence of Teva's case being wrong is that the Commission's decision should be regarded as a "regulatory act" of direct concern to Teva notwithstanding that it was not named in it: see Case T-18/10, Inuit Tapiriit Kanatami v European Parliament [56] (General Court); Case C-583/11, Inuit Tapiriit Kanatami v European Parliament [60] (CJEU); and Case T-219/13, Ferracci v Commission [52].

122. For the reasons I have given, I cannot accept Teva's case on the first ground. This means that it must lose this application for judicial review, but in recognition of the full submissions I received on the second ground, I should now turn to address it.

G. The Second Ground

123. If, contrary to my conclusion on Ground 1, the MHRA was not bound by recital (3), then it was incumbent on it to decide whether MEF was an active substance in Fumaderm taking into account the Commission's reasoning and conclusion. The issue raised by Ground 2 is whether the MHRA applied the correct legal test.

124. Ms Bacon contended that the legal test applied by the MHRA was whether DMF and MEF are pharmaceutically active and have different therapeutic moieties. She submitted that this was the wrong test, and that the test that the MHRA should have applied was whether MEF makes a clinically relevant contribution to the therapeutic effect of Fumaderm.

125. Unfortunately, much of the debate at the Bar was about semantics and taxonomy. By this I mean that Ms Bacon spent time characterising the formulations of Ms Howard and Ms Stratford, only for the latter to complain that their cases had been mischaracterised; and then *vice versa*. I am not being critical; this often happens in cases of this nature. However, my function is not to enter this particular fray.

126. The key provision remains Article 1(3a) of the Directive which it is worth repeating:

> "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 diagnosis."

127. The subordinate clause "when used in its production" refers to the manufacture of the medicinal product, and has nothing to do with clinical use. In order to qualify as an active substance, there falls to be satisfied a composite test with two interconnected limbs: the substance must be intended to exert an action of a specific sort, and that must be with a view to changing a physiological function in a manner which may be described as beneficial (i.e. active substances which are purely toxic are excluded, unless they fall within the final limb – to make a diagnosis).

128. The phase "pharmacological, immunological and metabolic action" is extremely wide and it is not quantitative. There simply has to be "action" which, in context, I take to mean *some* action. Ms Howard submitted that there was no *de minimis* threshold. On one level she is right, because action either exists or it does not. On the other hand, there will be questions of scientific judgment at the margins. The point here is that the relevant "action" must be capable of being ascertained by a scientist even if its extent cannot necessarily be measured.

129. "Intended to exert" is there for a number of reasons, not least to make clear that the relevant action does not have to occur in all cases when the product is used in patients. However, I think that the scientific evidence must be such that it occurs sometimes, from which it may also be deduced that the notion of active substance within this provision is concerned with the capability or capacity of the product to exert the action in question.

130. The clause "with a view to restoring etc. physiological functions" harnesses the scope of active substance and confines it to therapeutic goals. I have mentioned toxic substances, but the effect of these limiting words is also to remove from scope food supplements and products not ever intended to have a therapeutic effect.

131. It was common ground before me that the issue of therapeutic moiety is irrelevant at this stage of the analysis. We are not yet at the stage of comparing putatively different active substances (which *are* active substances) with a view to ascertaining whether they do not share the same therapeutic moiety and should therefore be regarded as different. Nor are we at the stage of examining whether substances which do share a therapeutic moiety should be treated as different. At that stage of the analysis, should it arise, the discussion turns to questions of safety and efficacy.

132. In the context of safety and efficacy, issues of clinical relevance are both important and wide-ranging. The efficacy question entails an examination of degree of clinical effect, effect size, numbers needed to treat, and clinical judgment. These matters are both quantitative and evaluative, and to my mind have nothing to do with prior existential questions as to active substance.

133. It is quite true, as Ms Bacon strongly pressed on me, that the Commission's Notice to Applicants states in terms that in a combination case the applicant will need to demonstrate, or will have already demonstrated if other compound(s) are being removed, that "each active substance has a documented therapeutic contribution within the combination". I accept that this terminology lends some support to the proposition that what is required is clinically relevant therapeutic effect in the

medicinal product. However, it could also be read more neutrally as meaning "therapeutic effect in the product", and that would be my preferred approach, given the wording of Article 1(3a) and the various considerations I have already outlined. The adjective "demonstrated" is a synonym for "established on objective scientific principles".

134. To the extent, therefore, that Ms Bacon's case on ground 2 entails reliance on a formulation which includes "clinical relevance" in the sense defined under paragraph 132 above, I would reject it. However, the case advanced in oral argument was more nuanced and sophisticated. On my understanding of it, the clause "with a view to restoring etc. physiological functions" can be summarised as meaning "[the active substance] has a therapeutic effect in the medicinal product under consideration for the particular indication or condition which is sought to be treated". Furthermore, this effect must be discerned not just in a laboratory context (*in vitro* or *in vivo*) but in a clinical setting.

135. In short, on Ms Bacon's approach there are three issues here: first, the therapeutic effect cannot be considered in abstract but must be tethered to the medicinal product which is sought to be authorised; secondly, the therapeutic effect must be assessed in the context of a particular indication or disease process; and, thirdly, the assessment must include a clinical rather than a laboratory setting.

136. I entirely agree with Ms Bacon at the first stage: the issue is whether the substance is active in the medicinal product being applied for. Ms Stratford accepted that the issue was whether MEF exerted a pharmacological action in Fumaderm. In my judgment, it is clear that the relevant action must be occurring in the context of a particular medicinal product. Article 1(3a) states in terms that the substance must be active when used in the production of a medicinal product.

137. Further, I have no doubt but that Article 1(3a) is concerned with the notion of pharmacological etc. action which is intended to be therapeutic. This is entirely consistent with (i) the wording of the provision under scrutiny ("with a view to restoring, correcting or modifying physiological functions"), (ii) the Opinion of Advocate General Jacobs in the SmithKline Beecham case (see paragraph 26 above), and (ii) the MHRA's own internal documents (see, for example, the email dated 16th January 2017 referred to under paragraph 74 above). Accordingly, I would accept Ms Bacon's submission that if the MHRA applied an entirely abstract test, divorced as it were from therapy in or for *homo sapiens*, it would have erred.

138. At Ms Bacon's second stage, the issue is whether the therapeutic effect must be for the specific indication or disease process specified in the application for the medicinal product. In the circumstances of this case, does it have to be shown that MEF has a discrete pharmacological action with a therapeutic effect in, or for, psoriasis?

139. If the answer to that question is "yes", it is naturally easier for Ms Bacon to submit, as she does, that the pharmacological action must be clinically relevant in the sense in which she is using that term. Furthermore, the difference between (i) salient activity in Fumaderm which is therapeutic, and (ii) salient activity in Fumaderm which is therapeutic for psoriasis is somewhat slender. The exiguity of the distinction has been demonstrated by the fact, as I have pointed out, that the CHMP in 2013 did touch on

the issue of whether the MEF exerted pharmacological activity of relevance for psoriasis.

140. However, there remains a point of principle to be determined, and I have concluded that on this issue the submissions of Ms Stratford in particular are to be preferred. As I have said, the substance when used in the product must be intended to bring or capable of bringing about a pharmacological action which in some way is of benefit to a patient. The "intended to" and "with a view to" are all part and parcel of the same test. Article 1(3a) refers to "*a* physiological function" in very general terms, and neither expressly nor by necessary implication anchors or relates that function to any particular disease process. I would construe the indefinite article as meaning "any". Furthermore, the issue of whether the medicinal product "works" for the disease or condition indicated in the application for an MA is, in my view, necessarily part of the risk-benefit analysis which experts will be conducting at a later stage in the decision-making process.

141. This approach is fortified by two further considerations. First, the concept of GMA is not linked to therapeutic indications; its second constitutive element is solely the active substance: see Advocate General Bobek in Novartis Europharm, [47-71] and the judgment of the CJEU [56]. If the therapeutic indication changes, the active substance does not. If, however, the notion of active substance depended to any extent on therapeutic indication, any change in the latter would alter the active substance. Secondly, and connectedly, the fourth subparagraph of Article 10(1) makes clear that an application for a new therapeutic indication may in exceptional circumstances lead to a one-year extension to the GMA. However, the GMA itself, tied to the concept of the active substance which was initially authorised, remains constant.

142. The "product characteristics" of the medicinal product for the purposes of Article 11 of the Directive separately itemise the active substance(s) and the therapeutic indications. This underscores the point that the two are discrete.

143. According to paragraph 19 of Dr Peter Feldschreiber's witness statement, there are examples of substances which are active substances or excipients depending on the medicinal product in which they are found. This evidence has not been disputed. Ms Bacon relies on it in support of the proposition that the concept of active substance is inextricably bound with its therapeutic value for a particular indication or condition. I have reflected on Dr Feldschreiber's point but have concluded that this apparent conundrum is illusory. Imagine a substance which has been demonstrated to be active in a particular medicinal product. In my view, there is nothing to preclude that self-same substance being used in a different product - and presumably for a different indication - as an excipient because in that case the substance would not be *intended* to exert a relevant action *with a view* to having a therapeutic effect. Any activity which that substance might be producing would not be with a view to being therapeutic.

144. Overall, in my judgment, Ms Bacon's submissions fail to give sufficient view to the composite nature of the test in Article 1(3a) and the wording, "intended to" and "with a view to".

145. Thus, and by way of summary of the position, there are three potentially relevant stages in the analysis. In the context of this case, the first stage is whether MEF exerts

a therapeutic pharmacological action in Fumaderm. This is a bimodal question inasmuch as the action either occurs or it does not. However, there is a scientific judgment to be made, which will be conducted on the basis of such tests, trials and literature as the experts may consider relevant. The second stage, which only arises if the answer at the first stage is in the affirmative, is whether the pharmacological action exerted by MEF salt shares the same therapeutic moiety as that exerted by DMF. The third stage, which only arises if the answer at the second stage is in the affirmative, is whether the two active substances differ in their safety and efficacy profile: see, for example, paragraph 3 of Annex 1 to the Directive. I have already stated that the idea of "clinical relevance" is only properly germane at this third stage. I should add, for the avoidance of doubt, that the issue of whether the medicinal product should be authorised at all is an overarching question which experts will consider having regard to a suite of considerations amongst which clinical relevance will undoubtedly form an important part.

146. I am not for one moment suggesting that the MHRA was required to proceed through these three stages. It is common ground that the MHRA was entitled to take into account recital (3) and the evidence which supported it. In my preceding paragraph I am setting out how the issue falls to be addressed as a matter of principle.

147. Having identified the correct legal test, I must now consider whether the MHRA properly applied it. It is clear that the MHRA did not ask itself whether the pharmacological action exerted by MEF in Fumaderm was clinically important. In my judgment, this was not the question which should have been asked. Instead, the MHRA asked itself, in my view correctly, whether the evidence continued to show that MEF exerted a pharmacological action in Fumaderm. On any view, the MHRA could not ignore all the work that had been done in 2013/14; it was entitled to consider whether there had been any relevant change in the evidence base. The MHRA's scientific advisors recognised that Dr Warren's evidence in particular placed a mark of doubt against that proposition, but it remained valid. Ms Bacon submitted that the MHRA has failed to grapple properly with the issues relating to doses of MEF in Fumaderm, but in the same way as therapeutic indications are irrelevant to the concept of active substance, so too are doses: see [73] of Novartis Europharm where Advocate General Bobek equates the two. In my opinion, the MHRA applied the right test and Ms Bacon's second ground must fail.

148. The parties devoted time and careful submission directed to the legal test the Commission applied in 2013/14. In my view these submissions ultimately led nowhere. The Commission concluded that DMF and MEF are different active substances. Whether that conclusion was reached for the right reasons is, to my mind, entirely irrelevant, not least because Teva cannot challenge in these proceedings a decision of an EU institution made several years ago, or at all.

149. For completeness, and in deference to the submissions I received, there are two further answers to Teva's case on this aspect. First, although the question posed to the CHMP could be interpreted as presupposing or predicating that DMF and MEF were different active substances, some of the scientific analysis that was in fact undertaken was directed to the validity of that premise. Thus, the CHMP did not just consider whether DMF and MEF shared the same therapeutic moiety; consideration was given to whether MEF was pharmacologically active in Fumaderm in its own right. Paragraph 37 of Mr Hemmings' first witness statement explains this clearly. The

pharmacological effects to which he refers are therapeutic because they are protective against inflammatory and oxidative stress in the human species. This, I infer, is part of the disease process relevant to psoriasis as an auto-immune condition. Moreover, the issue was considered not just theoretically but also experientially because the CHMP referred to clinical studies.

150. In any event, and *pace* Ms Bacon's analysis, there is no rigid distinction for these purposes between *in vitro* studies, *in vivo* animal studies, and *in vivo* human studies and/or clinical studies. These all fall across different points on a spectrum. Clinical relevance would require studies in my last category, but ascertainment of pharmacological action would not necessarily do so. This is because the demonstration of action of or along a particular pathway with a particular cellular response is, or at least may be, capable of being demonstrated in a laboratory setting.

151. Secondly, even if the Commission in 2013/14 proceeded on the basis of a premise which it took as a "given", thereby applying an independent assessment only to the issue of therapeutic moiety at stage 2, I cannot see how that avails Teva. On that interpretation of the Commission's decision-making process in 2013/14 (I emphasise, not my preferred interpretation), the Commission would have proceeded on this basis because it was applying *avant la lettre* subparagraph 3 of paragraph 2.3 of its Notice to Applicants. Either the Commission was right to do this, in which event no possible point arises; or it was wrong to do this, in which event the issue is not justiciable in this Court. The stumbling block for Teva's purposes is that the present challenge, however it may be formulated, cannot in any way entail a challenge to the Commission. Further, and relatedly, the issue of whether BfArM came to any decision as to the separate effect or role of MEF salts in Fumaderm is equally not justiciable.

H. Conclusion

152. My initial reaction to Teva's case when I was reading into these papers was that it appeared to be an ingenious attempt to exploit a loophole in the scheme of the Directive, and a classic instance of having one's cake and eating it. The skill and rigour of Ms Bacon's arguments compelled me to examine the merits of her client's case far more critically, but at the end of this exercise I confess that I find myself having travelled more or less full circle; albeit I hope that I am very much the wiser having undertaken that circuit.

153. I have rejected Teva's case on both its first and second grounds. This application for judicial review must therefore be dismissed.