Case C-616/20

Summary of the request for a preliminary ruling pursuant to Article 98(1) of the Rules of Procedure of the Court of Justice

Date lodged:

19 November 2020

Referring court:

Verwaltungsgericht Köln (Germany)

Date of the decision to refer:

27 October 2020

Applicant:

M2Beauté Cosmetics GmbH

Defendant:

Federal Republic of Germany

Subject matter of the main proceedings

Classification of a cosmetic product to promote eyelash growth as a medicinal product by function within the meaning of Paragraph 2(1), point 2(a), of the German Arzneimittelgesetzes (Law on Medicinal Products), which transposes Article 1(2)(b) of Directive 2001/83 on the Community Code relating to medicinal products for human use.

Subject matter and legal basis of the reference

Interpretation of EU law, Article 267 TFEU

Questions referred

1. Is a national authority, when classifying a cosmetic product as a medicinal product by function, within the meaning of Article 1(2)(b) of Directive 2001/83/EC of 6 November 2001, and, in so doing, examining all the characteristics of that product, entitled to base the necessary scientific assessment

of the pharmacological properties of that product and the risks associated with it on a 'structural analogy', in a case where the active substance used has only recently been developed, is comparable in its structure to pharmacological active substances which are already known and studied, but no comprehensive pharmacological, toxicological or clinical studies of the new substance in relation to its effects and its dosage, which are necessary only if Directive 2001/83/EC is applicable, have been submitted by the applicant?

2. Is Article 1(2)(b) of Directive 2001/83/EC of 6 November 2001 to be interpreted as meaning that a product which is placed on the market as a cosmetic and which significantly modifies physiological functions by producing a pharmacological effect is to be regarded as a medicinal product by function only in the case where it has a specific positive health-promoting effect? Is it sufficient in this regard even that the product has on a person's appearance a predominantly positive effect which, by increasing self-esteem or wellbeing, is of indirect benefit to health?

3. Or is that product also a medicinal product by function in the case where its positive effect is confined to an improvement in a person's appearance, without being of direct or indirect benefit to health, but where it does not have properties that are exclusively harmful to health and is not therefore comparable to a narcotic?

Provisions of EU law relied on

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, in particular Article 1(2)(b) and Article 2(2)

Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, in particular recital 7 and Article 2(1)(a)

Provisions of national law relied on

Gesetz über den Verkehr mit Arzneimitteln (Law on the Marketing of Medicinal Products) (Arzneimittelgesetz (Medicinal Products Law) – AMG), in particular Paragraph 2

Lebensmittel-, Bedarfsgegenstände- und Futtermittelgesetzbuch (Food, Commodities and Feed Code) (Lebensmittel- und Futtermittelgesetzbuch (Food and Feed Code) – LFGB), in particular Paragraph 2

Neue-psychoaktive-Stoffe-Gesetz (Law on New Psychoactive Substances) (NpSG), in particular Paragraph 2, point 1, and Paragraphs 3 and 4

Brief presentation of the facts and the proceedings

1 The applicant has developed the product 'M2 Eyelash Activating Serum' and placed it on the market as a cosmetic product. The product consists of a gel-like liquid containing, inter alia, an active substance known as 'methylamide-dihydro-noralfaprostal' (MDN) in a concentration of 0.02%. This is a new synthetic active substance which is structurally related to the human tissue hormone prostaglandin and is known as a prostaglandin derivative or prostaglandin analogue.

2 Prostaglandins make up a group of substances which, when needed, are produced by biosynthesis from fatty acids in various organs of the body and control numerous physiological processes by binding to specific receptors. They are involved, in particular, in the regulation of reproduction (e.g. the initiation of contractions), the cardiovascular system, respiration, pain and the ocular and sensory system. Pharmaceutical research has led to the development of some synthetic prostaglandins which are structurally related to human prostaglandins and have effects which are deployed therapeutically.

3 Prostaglandin derivatives of the type PGF2alpha, for example, are used in ophthalmology as an ingredient in eye drops for the treatment of glaucoma ('green star'). They lower intraocular pressure by increasing the outflow of intraocular fluid. A known side effect which has come to light in clinical studies is increased eyelash growth. For example, a prostaglandin derivate by the name of 'bimatoprost' (BMP) has been authorised as a medicinal product in Germany in its capacity as an active ingredient in eye drops for the treatment of glaucoma. In the USA, moreover, bimatoprost has been authorised as a medicinal product to promote eyelash growth ('Latisse') in the treatment of 'eyelash hypotrichosis'. These products contain BMP in 0.03% solution.

4 According to the current state of scientific knowledge, bimatoprost works by prolonging the growth phase of eyelashes and delaying the subsequent transition phase. This leads to an increase in the number of hair shafts, which form thicker and longer eyelashes. A regeneration of hair follicles does not take place.

5 The substance MDN that is used in the product at issue is largely identical in its molecular structure to the active substance bimatoprost used in medicinal products. The only difference between the two substances lies in a single group of molecules.

6 The applicant advertises the product as an innovative beauty product which promotes the natural growth and density of eyelashes by up to 50% on average. The serum is contained in an elongated bottle with an integrated brush that resembles a mascara or eyeliner container. The liquid is to be applied once a day, with the brush, to the base of the upper eyelashes, like an eyeliner.

7 By decision of 29 April 2014, the Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices) (BfArM) held that that product was not a cosmetic but a medicinal product requiring

authorisation. the institute stated that that product has the characteristics of a medicinal product by function.

8 Following completion of the administrative objection proceedings, the applicant, on 9 November 2017, brought before the referring court an action seeking the annulment of that decision.

Essential arguments of the parties to the main proceedings

9 In the view of the *BfArM*, the product at issue is a medicinal product by function. The reason is that the effects of MDN and BMP, which is used as an ophthalmic medicine, are comparable. The molecular structure of the two substances is comparable from the point of view of their characteristic components. Because of the known relationships between the structure and effect [of substances], it can therefore be assumed that the effects of those substances are comparable too. This is confirmed by the applicant's finding in its own trials that use of the active substance MDN has the same effect of increasing eyelash growth as BMP is known to produce. MDN has a pharmacological effect because – like BMP – it interacts with the prostamide receptor. The lengthening and thickening of eyelashes also has a significant impact on physiological functions. What is more, the product's classification as a medicinal product by function is supported by the fact that a risk to health from its use cannot be excluded. Because of the structural similarity of the two, its side effects are likely to be similar to those of 'Latisse', too.

10 The *applicant* takes the view that its product and the active substance MDN do not have a pharmacological effect. The in-vitro comparative studies conducted by the manufacturer of the active substance show that, notwithstanding their structural similarity, the substances MDN and BMP are not comparable from the point of view of their biological and chemical properties. MDN is likely to work in the same way as the group of substances known as ceramides, and its effects, like those of ceramides, are not therefore pharmacological either. What is more, the promotion of eyelash growth does not constitute a significant modification of physiological functions. The health risks assumed to be present by the BfArM were drawn from experience in the use of medicinal products and have not been proved to apply in the case of the product at issue. Finally, the applicant takes the view that classification of the product at issue as a medicinal product by function is contrary to the case-law of the Court of Justice of the European Union concerning products which are consumed not for therapeutic purposes but exclusively for the purposes of relaxation or intoxication and, as such, are harmful to health (Court of Justice, judgment of 10 July 2014, C-358/13 and C-181/14, *Markus and G.*, concerning, inter alia, 'legal highs').

Brief presentation of the grounds for the reference

11 The decision on the lawfulness of the BfArM's finding that the eyelash growth product at issue is a medicinal product by function is dependent on the interpretation of the concept of medicinal product under EU law and, therefore, on the answers to the questions referred. The reason for this is that the national definition of a medicinal product by function given in Paragraph 2(1), point 2(a), of the AMG corresponds almost verbatim to the provision contained in Article 1(2)(b) of Directive 2001/83.

12 The finding that a product has a pharmacological effect, upon which its classification as a medicinal product by function is contingent, is possible only if the active substance used, MDN, is found to be structurally analogous to BMP, as the BfArM considers it to be. The reason is that no conclusive pharmacological studies have been carried out into the pharmacological effects of MDN at a particular dosage.

13 The capacity to be of direct or indirect benefit to health, [note: this criterion is a reference to Joined Cases C-358/13 and C-181/14, cited above. See the operative part and paras 36 and 38 of that judgment, German being the language of the case. The French 'des effets bénéfiques, immédiats ou médiats, sur la santé humaine' is translated as 'der menschlichen Gesundheit unmittelbar oder mittelbar zuträglich' (DE); beneficial effects, either immediately or in the long term, on human health (EN); ευεργετικά αποτελέσματα, άμεσα ή έμμεσα, για την ανθρώπινη υγεία (EL); efectos beneficiosos, mediatos o inmediatos, sobre la salud humana (ES); effetti benefici, immediati o mediati, sulla salute umana (IT); nyttige virkninger, direkte eller indirekte, på menneskers sundhed (DA): the EN translation appears to be an outlier] upon which classification as a medicinal product by function is also contingent, is dependent on how that unwritten criterion for the application of Article 1(2)(b) of Directive 2001/83 – which has been developed in the case-law of the Court of Justice – is to be interpreted. In particular, the question is whether a cosmetic too must have an additional positive effect on health in order to be a medicinal product.

14 Since the product at issue is marketed as a 'cosmetic product' and does not claim to be a means of curing, alleviating or preventing human disease, it is not a 'medicinal product by presentation' within the meaning of Article 1(2)(a) of Directive 2001/83/EC.

15 The BfArM takes the view, however, that, because of the ingredient MDN, that product is a medicinal product by function within the meaning of Article 1(2)(b) of Directive 2001/83. This is doubtful, however. First, it is unclear how far the obligation incumbent on the national authorities and the courts to establish the pharmacological effects of the product and the risks associated with it extends, in the absence of adequate scientific evidence on the active substance used at the dosage in question and its use on the eyelid (see section I below).

16 Secondly, it is open to question whether cosmetic products which alter a person's appearance by means of a pharmacologically active substance have an effect as a medicinal product by function which is of direct or indirect benefit to health (see section II below).

17 In accordance with the settled case-law of the Court of Justice, the competent national authority must make the decision as to whether a product falls within the definition of a medicinal product by function on a case-by-case basis, taking into account all of the characteristics of the product, in particular its composition, its pharmacological, immunological or metabolic properties, in so far as these can be established in the present state of scientific knowledge, the manner in which the product is used, the extent of its distribution, its familiarity to consumers and the risks which its intended use may entail.

18 In this regard, it is not sufficient for a product to contain a physiologically active substance. The pharmacological, immunological or metabolic properties of a product are the factor on the basis of which it must be ascertained, in the light of the potential effects of the product, whether it may be used in or on the human body with a view to restoring, correcting or modifying physiological functions.

19 However, products cannot be classified as a medicinal product by function in the case where, although they have an effect on the human body, they do not significantly affect physiological functions and thus do not actually modify the way in which it functions.

20 Neither is it sufficient, in and of itself, that the use of a product presents a risk to health. This is an autonomous factor in the classification of a product as a medicinal product by function. Risks to health are not, however, indicative of the presence of the necessary pharmacological effects (see Court of Justice, judgment of 30 April 2009, *Bios Naturprodukte*, C-27/08, paragraph 18 *et seq*.).

21 Finally, the concept of a medicinal product by function does not cover substances the effects of which merely modify physiological functions and which are not such as to entail direct or indirect beneficial effects for human health. In particular, substances which are consumed solely to induce a state of intoxication and are, as such, harmful to human health (see Court of Justice, judgment of 10 July 2014, C-358/13 and C-181/14, *Markus and G.*, inter alia, paragraphs 38 and 50).

I. Pharmacological effect of the ingredient MDN

22 In the light of the foregoing, it is doubtful whether the BfArM has scientifically substantiated, to a sufficient extent, its finding that the ingredient MDN has a pharmacological effect on the basis of the dosage, form of administration and particular mode of use (application to the rim of the eyelid) present here.

23 According to the definition given in the ‘Borderline Guideline’, MEDDEV 2.1/3, rev. 3, a pharmacological effect is present where there is an interaction between the molecules of the substance concerned and a cell component usually described as a receptor.

24 The substance used here is a newly developed one the pharmacological effects of which have not been the subject of sufficient scientific study. The applicant has submitted an in-vitro study to establish the affinity of MDN to known prostaglandin receptors which was able to establish only a weak binding to those receptors and could not therefore confirm any relevant pharmacological effect. In the estimation of the Institut für Risikobewertung (Institute of Risk Assessment) of July 2018, however, it is unclear whether that testing regime is physiologically relevant, that is to say whether it is transposable to the rim of the human eyelid. The applicant has not, however, been able to substantiate its assertion that the effect is based on a similarity with another group of substances (ceramides) and is non-pharmacological in nature.

25 The proposition put forward by the BfArM that MDN has a pharmacological effect by interacting with an as yet unidentified prostamide receptor has likewise not been the subject of any study that would support that assumption. For that reason, the BfArM falls back on a so-called structural analogy with previously known prostaglandin analogues, in particular BMP. From the fact that the two substances, MDN and BMP, have a largely identical molecular structure and produce the same effect on eyelash growth, the conclusion is drawn that they also have a comparable pharmacological mode of operation and comparable side effects. There is as yet no positive evidence to support that proposition. However, not even the comparative studies of the hydrolysis and binding behaviour of MDN and BMP are capable of refuting the structural analogy proposition, since, in the BfArM’s assessment, those studies show that the substances in question exhibit not identical but similar properties. The referring court concurs with that assessment.

26 The precise mode of operation of BMP is also as yet unknown and scientifically contentious. There is general agreement, however, that BMP has a pharmacological effect because it is a prostaglandin analogue and, like that class of substances, controls physiological functions via certain receptors, even though the receptor in question has not yet been identified.

27 MDN can therefore be said to have a pharmacological mode of operation in the product at issue only if it is confirmed that its effect is comparable to that of BMP because it is structurally analogous to that substance and to other prostaglandin analogues.

28 The referring court wishes to ascertain whether a scientific finding of pharmacological properties on the part of a new unknown substance may be reached even on the basis of a structural analogy, that is to say the fact that that substance belongs to a particular known group of substances, or whether, given

that substance-specific study is largely lacking, it must be concluded that that substance does not have a pharmacological effect.

29 The conclusion that the pharmacological properties of a new, slightly modified substance cannot be established on the basis of a structural analogy would mean that products that may have pharmacological effects could be placed on the market as a medicinal product without a marketing authorisation because there is no way of establishing those effects in the absence of any scientific studies in this regard. The referring court is therefore inclined to endorse the permissibility of adducing the necessary proof of pharmacological effects on the basis of a structural analogy in the case where the manufacturer cannot unequivocally refute those effects by reference to its own conclusive studies. After all, the manufacturer decides on the composition of the product and its properties. He is responsible for placing the product on the market in a legal manner. If, in so doing, he uses a substance the molecular structure of which is indicative of a pharmacological mode of operation, he must rebut this if he does not wish to place the product on the market as a medicinal product. Currently, he would not have been able to do this in the present case, because the limited affinity to known prostaglandin receptors does preclude that affinity being sufficient for the purposes of the established effect of promoting eyelash growth *in vivo* or the substance in question binding to another as yet unidentified receptor.

30 If it is found that the product at issue does have a pharmacological mode of operation, the referring court will assume, in accordance with the foregoing considerations, that that product, when used as intended, has a significant effect on the body's physiological functions (Court of Justice, judgment of 15 November 2007, *Commission* v *Germany* C-319/05, paragraph 68).

31 By comparison with products to combat hair loss and dandruff, which, notwithstanding their effect on physiological functions, are not perceived by the general public as being medicinal, the product at issue here is applied to the rim of the eyelid and thus in the vicinity of the eye, that is to say near a particularly sensitive and important organ. Since that product is effective only if applied over a prolonged period and the active substance used is likely to have a broad range of effects in its capacity as a tissue hormone, there would appear to be good reason to assume that the product at issue here has a significant impact on the body's physiological functions.

II. Capacity of the product to be of direct or indirect benefit to human health

32 The character of the product at issue as a medicinal product by function therefore depends on whether its effect on eyelash growth is of direct or indirect benefit to human health (Court of Justice, judgment of 10 July 2014, C-358/13 and C-181/14, *Markus and G.*, paragraphs 38 and 46).

33 Whether the product is objectively capable of being used for therapeutic purposes is not decisive from the point of view of its character as a medicinal product. The

finding that a product has the objective capacity to be used for therapeutic purposes is tantamount to proof that it is therapeutically effective. However, its capacity to do so is a component not of the definition of a medicinal product by function but of the downstream examination of a positive risk-benefit ratio that forms part of the procedure for authorising medicinal products. The Court of Justice confirmed this in the judgment of 15 December 2016, C-700/15, *LEK Farmacevtska Družba*, paragraph 35.

34 Accordingly, it is not necessary for a product to be capable of being used to treat a disease. That said, a product would automatically be regarded as having a significant pharmacological effect if it were proven to be therapeutically efficacious (Court of Justice, judgment of 30 November 1983 *Leendert van Bennekom*, C-227/82).

35 That is not the case with the product at issue, however. In the European Union, there is no medicinal product authorisation for the active ingredient MDN and there are no clinical efficacy studies either.

36 Even if a structural analogy were found to be permissible, BMP is likewise not the subject of any efficacy studies that could be transposed to the product at issue. It is true that the active ingredient BMP is authorised in the USA for the indication of 'eyelash hypotrichosis'. It is open to question, however, whether this constitutes a medical condition. The registration trials – in so far as these have been presented [to the court] – were carried out on healthy volunteers. Even in the 2014 study submitted, carried out on Japanese volunteers, the only indications examined were eyelash loss after chemotherapy and 'idiopathic hypotrichosis', which is to say impaired eyelash growth for no recognisable cause. After chemotherapy, eyelashes and hair usually grow back on their own. Whether the product is efficacious even in the case where natural hair growth does not resume was not examined. The study therefore focused on strengthening natural eyelash growth, and thus on an aesthetic benefit.

37 In so far as hypotrichosis has a pathological cause, such as hair loss, nutritional deficiencies or autoimmune diseases, it is open to question whether the product at issue, even assuming a structural analogy to be permissible, will be therapeutically effective so long as the cause is not treated. There are no clinical studies on pathological eyelash loss.

38 Whether the product at issue – like 'Lumigan' – could be used to reduce intraocular pressure and thus to treat glaucoma is open to question and has not been proved. It has a lower concentration, is applied not to the conjunctival sac but to the eyelid, is not a liquid but in a gel-like form and is, as such, bioavailable in a much smaller quantity in the eye.

39 Finally, the defendant has not adduced any evidence to show that the psychological stress brought on by sparse eyelash growth is so serious as to

warrant classification as pathological and can be cured with an eyelash growth product.

40 If, therefore, no demonstrable therapeutic efficacy can be established, what matters here is whether the promotion of eyelash growth is an effect which has direct or indirect health benefits (Court of Justice, judgment of 10 July 2014, C-358/13 and C-181/14, *Markus and G.*, paragraph 38).

41 That examination depends on how that unwritten criterion is to be interpreted. If health must be specifically and identifiably promoted in the sense of being improved or maintained, the product at issue would not be a medicinal product by function.

42 The reason is that the positive effect of the product in this case is confined to strengthening eyelash growth, and thus to aesthetics. The improvement of a person's appearance by longer and thicker eyelashes is an effect which has no bearing on health. It is an effect typical of cosmetics but not of medicinal products.

43 Nor can it be established that strengthened eyelashes have a significant positive effect on the protective function of eyelashes as protection against foreign bodies, dust or sunlight. The form taken by eyelashes in different individuals varies within a natural range which is determined largely by genetics. No evidence is available to indicate that eyelashes have a diminished protective effect if there are fewer of them or they are shorter. That protection is probably of little importance to the individuals in the product's target market nowadays anyway, most of whom enjoy a modern urban lifestyle that takes place largely indoors. One study even suggested that artificially lengthened eyelashes may even be counterproductive.

44 If, on the other hand, an improvement in a person's appearance were regarded as having a positive effect on self-esteem, personal wellbeing or the quality of social relations, and as thus indirectly promoting health, the product could be a medicinal product by function.

45 Even if it is found that a product has health benefits as soon as it produces an effect which is in any way positive and is not exclusively harmful to health, a cosmetic which simply brings about a positive change in a person's appearance and whose effects are not therefore confined to being harmful, as intoxicants are, for example, could also be a medicinal product by function.

46 The decisions of the Court of Justice concerning the definition of the concept of medicinal product by function do not offer a clear interpretation for the purposes of the cosmetic product at issue.

47 The judgment of the Court of Justice of 16 April 1991, C-112/89, *Upjohn* paragraphs 19 and 21, points rather towards a broad interpretation of the concept of medicinal product by function. On this interpretation, cosmetic products intended to combat hereditary and non-pathological hair loss are also medicinal

products if they significantly modify physiological functions. In that judgment, the Court of Justice did not at that stage require that a medicinal product by function must, as an unwritten characteristic, have an effect that is beneficial to health. That decision could therefore be interpreted as meaning that, in the case of cosmetic products at least, classification as being in the nature of a medicinal product is subject only to the requirement that the product's pharmacological properties should significantly modify physiological functions, and that a more extensive positive effect on health is **not** necessary.

48 The decision of the Court of Justice of 10 July 2014, C-358/13, and C181/14, *Markus and G.*, paragraphs 38 and 50, points rather towards a narrower interpretation of the concept of medicinal product by function. According to this interpretation, 'legal highs', that is to say intoxicants containing cannabinoids, are not medicinal products because, although they significantly modify physiological functions, they are of neither direct nor indirect benefit to health, but serve only relaxation purposes. That decision could be construed as meaning that cosmetic products too are subject to the further requirement that the product must be of direct or indirect benefit to health. That construction is supported by the Court's reference to the schematic connection with the concept of a medicinal product by presentation mentioned in Article 1(2)(a) of Directive 2001/83/EC and to the objective of health protection referred to in recital 3 of amending Directive 2004/27. In that regard, the Court is silent on the matter of what it understands by an indirect positive effect on health. This might also include a positive effect on a person's appearance the health benefits of which are not direct but indirect, in the form of an improvement in an individual's wellbeing or self-esteem.

49 That said, the judgment of 10 July 2014 cited in the preceding paragraph related to narcotics, not to cosmetics. The earlier decision of 16 April 1991 (*Bios Naturprodukte*, C-27/08) on cosmetic products for hair loss was mentioned but not abandoned. The requirement that a product must be of direct or indirect benefit to health might therefore serve only to exclude products whose effects on health are exclusively harmful, such as the synthetic cannabinoids referred to above, from the concept of medicinal product, without introducing the need for the further positive characteristic of having a health-promoting effect. If that were the case, nothing about the decision of 16 April 1991 would have changed and the cosmetic product at issue would be a medicinal product by function even in the absence of a positive finding in relation to its health-promoting effect.

50 It is mentioned only for the sake of completeness that the presence of health risks is unlikely to have a decisive bearing in the matter of the classification of products as medicinal products. If the answer to the questions referred is that the product at issue can be said to have both a pharmacological mode of operation and a health-promoting effect, that product would be a medicinal product by function. The danger of the health risks posed by prolonged use of that product would serve only to confirm that classification. In the event that the product at issue cannot be said to have a pharmacological mode of operation or a health-promoting effect, that product would be a cosmetic product irrespective of the risks associated with it. In

that event, Regulation No 1223/2009 makes available a procedure, for which it provides in Annex 2 thereto, for prohibiting substances which present risks to health.