Clarification of the conditions for establishing that a substance constitutes a product within the meaning of article 1 of regulation no. 469/2009, enabling a supplementary protection certificate to be obtained for medicina (Ruling n° 101 - 21-15.221)

01/02/2023

Ruling No. 101

DISMISSAL

FRENCH REPUBLIC

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ON BEHALF OF THE FRENCH PEOPLE

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RULING OF THE COMMERCIAL, FINANCIAL AND ECONOMIC CHAMBER OF THE *COUR DE CASSATION* (COURT OF CASSATION) OF 1 FEBRUARY 2023

Halozyme Inc., a company incorporated under US corporation law, with registered office at [Address 1], lodged appeal No. D 21-15.221 against the ruling delivered on 15 December 2020 by the *cour d'appel* (Court of Appeal) of Paris (Division 5, Chamber 1) in the dispute between said company and the Director General of the National Institute of Industrial Property (INPI), with registered office at [Address 5], respondent to the quashing.

The applicant bases its appeal on the single plea for quashing appended to this ruling.

The case file has been sent to the Prosecutor-General.

On the report by Ms Bessaud, judge referee, the observations of SCP Duhamel-Rameix-Gury-Maitre, lawyers of Halozyme Inc., SARL Le Prado - Gilbert, lawyers of the Director General of the National Institute of Industrial Property, and the advisory opinion of Mr Douvreleur, Advocate-General, following which the President asked the lawyers whether they wished to make further comments, following debate in the public hearing of 6 December 2022 in the presence of Mr Vigneau, President, Ms Bessaud, judge referee rapporteur, Ms Darbois, elder judge of the chamber, Ms Vissette, elder judge of the section,

Mr Mollard, elder judge of the section, Ms Vallansan, Ms Poillot-Peruzzetto, Ms Graff-Daudret, Ms Belaval, Ms Champalaune,

Ms Daubigney, judges, Mr Guerlot, Ms Barbot, judge referees, Mr Douvreleur, Advocate-General, and Ms Labat, Chamber Registrar,

the Commercial, Financial and Economic chamber of the *Cour de cassation* (Court of Cassation), composed, pursuant to Articles R. 421-4-1 and R. 431-5 of the Judicial Code, of the above-mentioned President and Judges, having deliberated in accordance with the law, has delivered the present ruling.

Account of the dispute

Facts and Procedure

1. According to the ruling under appeal (Paris, 15 December 2020), on 20 July 2015, Halozyme Inc., a US biotechnology laboratory that develops innovative cancer therapies, filed an application for supplementary protection certificate No. 15C0053 (SPC No. 053) for the product "trastuzumab and recombinant human hyaluronidase". This application mentions the French part of the European patent filed on 5 March 2004, published under No. EP 2163643 (EP 643) under the title "Soluble hyaluronidase glycoprotein, process for its preparation, uses and component pharmaceutical compositions", issued on 21 January 2015, of which Claim No. 18 covers a combination of substantially purified hyaluronidase polypeptide and an anti-cancer agent, and of which Claim No. 21 covers such a composition for use in the treatment of cancer wherein the anti-cancer agent is a monoclonal antibody.

2. On 20 July 2015, on the basis of the French part of patent EP 643 and a Community marketing authorisation issued to Roche Registration Limited (the company Roche) on 26 August 2013 for the subcutaneous formulation of an anti-cancer medicinal product called "Herceptin", composed of the combination of trastuzumab, a monoclonal antibody presented in the marketing authorisation as the "active ingredient", and recombinant human hyaluronidase, presented as an "excipient", Halozyme submitted an application for a*certificat complémentaire de protection (CCP)* (supplementary protection certificate (SPC))for the product "trastuzumab and recombinant human hyaluronidase".
3. On 28 August 2000, Roche obtained a Community marketing authorisation for the intravenous formulation of "Herceptin", which does not contain recombinant human hyaluronidase.
4. By decision of 7 March 2018, the Director General of the French national institute of industrial property (INPI, *Institut National de la Propriété Industrielle*) rejected the SPC application on the grounds that recombinant human hyaluronidase is not an active ingredient with its own therapeutic effect but rather constitutes an excipient, as follows from the summary of the product characteristics referring to the marketing authorisation of 26 August 2013, and that the product, which is the subject of the SPC applied for, can only be the active ingredient appearing in the marketing authorisation, namely trastuzumab, which is the subject of a prior marketing authorisation of 28 August 2000.
5. The company Halozyme appealed this decision.

Pleas

Review of the plea

On the third part of the plea, appended hereto

Statement of reasons

6. Pursuant to Article 1014(2) of the Code of Civil Procedure, there is no need to have a specially reasoned decision on this plea, which is clearly not of such a nature as to entail quashing.

Pleas

On the first and second parts of the plea

Statement of plea

7. Halozyme objects to the ruling for dismissing its appeal against the decision of the Director General of the INPI of 7 March 2018, rejecting SPC application No. 053, relating to the French part of patent EP 643, for the product "trastuzumab and recombinant human hyaluronidase", whereas:

"(1) a substance presented in the marketing authorisation as an excipient, but which has been demonstrated to have a specific pharmacological, immunological or metabolic effect on the bodies of patients when combined with another substance presented as an active ingredient, must itself be considered as an "active ingredient" as defined in Article 1(b) of Regulation (EC) No. 469/2009 of 6 May 2009; whereas, in this case, as argued by the plaintiff and as noted by the decision of the director of the INPI company, presented as an excipient in the marketing authorisation, hyaluronidase acts directly on the body of patients suffering from breast cancer by modifying their cellular tissues to allow better assimilation of trastuzumab, a monoclonal antibody, and its more targeted administration by subcutaneous rather than intravenous route; whereas it follows that the interaction of the two chemical components produces effects specific to hyaluronidase and that, combined with trastuzumab, this substance has a pharmacological, immunological or metabolic effect such that it can be considered an "active ingredient" as defined in Article 1(b) of Regulation (EC) No. 469/2009 of 6 May 2009; whereas, by holding, however, that hyaluronidase, alone or in combination with trastuzumab, was devoid of its own pharmacological, immunological or metabolic effect, without ruling on the physiological effect of hyaluronidase itself, acting directly on the cell tissues of the patients to whom it was administered, the*cour d'appel* (Court of Appeal) deprived its decision of a legal basis in the light of Articles 1, 2, 3 and 4 of said regulation;

(2) whereas it is up to the courts dealing with the substance of the case to verify, in the light of all the facts characterising the dispute, whether a component presented as an excipient in a marketing authorisation has its own pharmacological, immunological or metabolic effect when it is combined with another active ingredient, regardless of whether the marketing authorisation does not expressly mention the specific effects of the substance in question; whereas, by nevertheless stating that Halozyme produced only documents written in English which did not make it possible to identify the pharmacological, immunological and metabolic effect of hyaluronidase for the treatment of breast cancer, which did not reveal anything about the effects of the enzyme when combined with trastuzumab, and that the marketing authorisation, assimilating hyaluronidase to an excipient, did not conclude that there was a pharmacological, immunological or metabolic effect specific to that component "in its association with trastuzumab", the*cour d'appel* (Court of Appeal) therefore ruled on grounds that were both insufficient and unsuitable for holding, in the light of all the facts of the dispute, that hyaluronidase did not have a pharmacological, immunological or metabolic effect of its own in its association with trastuzumab, thus infringing Articles 1, 2, 3 and 4 of Regulation (EC) No. 469/2009 of 6 May 2009."

Statement of reasons $

Court's response

8. In its ruling of 15 January 2015 (Forsgren, C-631/13), the Court of Justice of the European Union ruled that "Article 1(b) of No. 469/2009 must be interpreted as meaning that a vector protein combined with a polysaccharide antigen by means of a covalent binding can only be characterised as an "active ingredient", as defined in that provision, if it is established that it produces a pharmacological, immunological or metabolic effect of its own covered by the therapeutic indications of the marketing authorisation, which it is for the referring court to verify in the light of all the facts characterising the dispute in the main proceedings."
9. It follows that when the marketing authorisation does not classify a substance as an "active ingredient", it is rebuttably presumed that said substance does not produce any specific pharmacological, immunological or metabolic effect covered by the therapeutic indications referred to in the marketing authorisation.
10. After having specifically stated that the specific pharmacological, immunological or metabolic effect covered by the therapeutic indications of recombinant human hyalorunidase should be assessed with regard to the content of the marketing authorisation, the ruling notes that the marketing authorisation only refers to trastuzumab as the active ingredient and only cites recombinant human hyalorunidase as one of the excipients of the composition, holding that no element contained in the marketing authorisation or in an external document justifies an effect

specific to hyaluronidase alone, or in its association with trastuzumab for the therapeutic indications in the marketing authorisation.

11. On the basis of these statements, findings and assessments, the *cour d'appel* (Court of Appeal), which pointed out that human recombinant hyaluronidase was presumed to be an excipient in the light of the statements of the marketing authorisation and its preparatory documents, and held that no evidence to the contrary was provided, legally justified its decision on these grounds alone.
12. The plea is therefore unfounded.

Operative part of the ruling

ON THESE GROUNDS, the Court:

DISMISSES the request;

Orders the company Halozyme Inc. to pay the costs;

In application of Article 700 of the Code of Civil Procedure, orders Halozyme Inc. to pay the Director General of the National Institute of Industrial Property the sum of EUR 3,000;

Thus ordered and adjudged by the Commercial, Financial and Economic Chamber of the *Cour de cassation* (Court of Cassation), and delivered by the President in public hearing on the first day of the month of June of the year two thousand and twenty-two.

Pleas attached

PLEA ATTACHED to this ruling

Plea submitted by SCP Duhamel-Rameix-Gury-Maitre, Supreme Court Lawyer, for Halozyme Inc.

Halozyme objects to the ruling under appeal for having dismissed its appeal against the decision of the Director General of the INPI of 7 March 2018, refusing to grant its application for supplementary protection certificate No. 16C0053 ("SPC 053"), relating to the French part of patent EP 643, for the product "trastuzumab and recombinant human hyaluronidase".

(1) WHEREAS a substance presented in the marketing authorisation as an excipient, but which has been demonstrated to have a specific pharmacological, immunological or metabolic effect on the bodies of patients when combined with another substance presented as an active ingredient, must itself be considered as an "active ingredient" as defined in Article 1(b) of Regulation (EC) No. 469/2009 of 6 May 2009; whereas, in this case, as argued by the plaintiff and as noted by the decision of the director of the INPI (p. 4(1)), presented as an excipient in the marketing authorisation, hyaluronidase acts directly on the body of patients suffering from breast cancer by modifying their cellular tissues to allow better assimilation of trastuzumab, a monoclonal antibody, and its more targeted administration by subcutaneous rather than intravenous route; whereas it follows that the interaction of the two chemical components produces effects specific to hyaluronidase and that, combined with trastuzumab, this substance has a pharmacological, immunological or metabolic effect such that it can be considered an "active ingredient" as defined in Article 1(b) of Regulation (EC) No.

469/2009 of 6 May 2009; whereas, by holding, however, that hyaluronidase, alone or in combination with trastuzumab, was devoid of its own pharmacological, immunological or metabolic effect (order, p. 8(6)), without ruling on the physiological effect of hyaluronidase itself, acting directly on the cell tissues of the patients to whom it was administered, the cour d'appel (Court of Appeal) deprived its decision of a legal basis in the light of Articles 1, 2, 3 and 4 of said regulation;

(2) WHEREAS it is up to the courts dealing with the substance of the case to verify, in the light of all the facts characterising the dispute, whether a component presented as an excipient in a marketing authorisation has its own pharmacological, immunological or metabolic effect when it is combined with another active ingredient, regardless of whether the marketing authorisation does not expressly mention the specific effects of the substance in question; whereas, by nevertheless stating that Halozyme produced only documents written in English which did not make it possible to identify the pharmacological, immunological and metabolic effect of hyaluronidase for the treatment of breast cancer (order, p. 8(3) and (4)), which did not reveal anything about the effects of the enzyme when combined with trastuzumab, and that the marketing authorisation, assimilating hyaluronidase to an excipient, did not conclude that there was a pharmacological, immunological or metabolic effect specific to that component "in its association with trastuzumab" (order, p. 8(5)), the *cour d'appel* (Court of Appeal) therefore ruled on grounds that were both insufficient and unsuitable for holding, in the light of all the facts of the dispute, that hyaluronidase did not have a pharmacological, immunological or metabolic effect of its own in its association with trastuzumab, thus infringing Articles 1, 2, 3 and 4 of Regulation (EC) No. 469/2009 of 6 May 2009;

(3) WHEREAS, finally, by holding that hyaluronidase could not be considered an "active ingredient", without responding to Halozyme's submissions arguing that the length of the clinical studies that preceded the marketing authorisation for the trastuzumab/hyaluronidase composition "could only be explained by the addition of hyaluronidase to trastuzumab", since trastuzumab had already been the subject of a marketing authorisation (concl., p. 33(67)) and that "if the addition of hyaluronidase had been so neutral, and even though it allows a more effective treatment and a subcutaneous injection, the obtaining of a marketing authorisation would have been much faster" (concl., p. 33, in fine), from which it nevertheless resulted that the length of the phase of clinical tests relating to the specific effects attached to the combination of hyaluronidase with trastuzumab revealed the specific pharmacological, immunological and metabolic effect attributed to hyaluronidase in combination with trastuzumab, the *cour d'appel* (Court of Appeal) violated Article 455 of the Code of Civil Procedure.

President : Mr Vigneau
Advocate-general : Mr Douvreleur
Judge referee : Ms Bessaud
Lawyer(s) : SCP Duhamel-Rameix-Gury-Maitre - SARL Le Prado - Gilbert

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