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Trastuzumab x recombinant human hyaluronidase: the French Supreme Court clarifies the interpretation of article 1 b) of the SPC Regulation

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"*Jamais deux sans trois*". The French Supreme Court ("*Cour de Cassation*") has issued no less than seven decisions relating to SPCs on February 1st, 2023. After having reported the two relating to the interpretation of article 3 a) of the SPC Regulation last week (nivolumab and pembrolizumab cases), I will report today a decision rendered on the interpretation of article 1 b) of said Regulation.

We should note, as a preliminary remark, that this week's judgement is a little unusual in that it is the only one of the "February 1st series" to have been published in the "*Bulletin*", an honor reserved only for the Cour de Cassation's decisions of principle.

In this case, Halozyme Inc. had applied for an SPC (FR15C0053) for a combination product of trastuzumab and recombinant human hyaluronidase on the basis of a marketing authorization ("MA") granted on August 26, 2013.

Trastuzumab is a monoclonal antibody targeting HER2 and thereby inhibiting the proliferation of human tumor cells that overexpress HER2, while recombinant human hyaluronidase enhances the dispersion and absorption of the drugs administered with it when delivered subcutaneously, by catalyzing the hydrolysis of hyaluronan, a component of the extracellular matrix. The combination of trastuzumab and recombinant human hyaluronidase, which is covered by the marketing authorization, is indicated for the treatment of breast cancer and gastric cancer.

The French PTO ("*INPI*") rejected the application for a SPC for this combination on the basis of Article 3 d) of the SPC Regulation, because the summary of product characteristics of the 2013 MA only mentioned trastuzumab as an active ingredient and hyaluronidase was listed among the excipients. The INPI considered that recombinant human hyaluronidase could not constitute an active ingredient with its own therapeutic action within the SPC, but that it could only be an excipient, according to the summary of product characteristics of the MA. The Court of Appeal confirmed this decision (December 15, 2022), ruling that according to Article 1 b) of the SPC Regulation, within the meaning of the Arne Forgsen decision (C-631/13) of the CJEU, only trastuzumab could be an active principle, since it was the only one referred to as such in the summary of product characteristics of the MA and that no other element included in the said MA justified that hyaluronidase alone, or combined with trastuzumab, would produce a specific

pharmacological, immunological or metabolic action falling within the therapeutic indications of the MA.

The *Cour de Cassation* dismissed the appeal against this decision, thus confirming the position taken by the Court of appeal. According to the Supreme Court, it follows from the above-mentioned case law of the CJEU that "*when the marketing authorization does not qualify a substance as an "active principle", it is rebuttably presumed that this substance does not produce its own pharmacological, immunological or metabolic effect covered by the therapeutic indications referred to in that marketing authorization*". As a consequence, "*after having precisely stated that the assessment of the pharmacological, immunological or metabolic effect covered by the therapeutic indications of recombinant human hyaloronidase had to be carried out with regard to the content of the marketing authorization, the judgment noted that the latter refers only to trastuzumab as the active ingredient and mentions recombinant human hyaloronidase only as one of the excipients of the composition, and held that no element contained in the marketing authorization or in an external document justifies an effect specific to recombinant human hyaloronidase alone, or in its combination with trastuzumab, for the therapeutic indications of the marketing authorization*".

The French Supreme Court approved the method of assessment of the Court of Appeal which analyzed the entire content of the MA and not only the summary of product characteristics, as well as external documents, such as scientific articles, to assess the action of hyaluronidase and to judge whether it could be qualified as an "*active ingredient*". The Court of Appeal also reiterated this method in a subsequent decision (January 18, 2022) by confirming the rejection of an SPC application for the combination of rituximab (anti-CD20 monoclonal antibody) and recombinant human hyaloronidase for the treatment of non-Hodgkin lymphoma.

Thus, even if an active ingredient is not mentioned as such in the summary of product characteristics of the MA, it would seem a combination SPC could still be possible in France, if data on the specific therapeutic action of this ingredient are provided in in other parts of the MA or in an external document.

In any case, and to conclude, it must be noted that with its series of 7 decisions of February 1st, particularly those relating to article 3 a) of the SPC regulation and the one commented on today, the *Cour de Cassation* has established the framework of a clear method of SPC applications assessment, and therefore a guarantee of security, for the applicants. Oyez! Oyez! Oyez!

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This entry was posted on Monday, February 20th, 2023 at 1:23 pm and is filed under Case Law, France, SPC
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