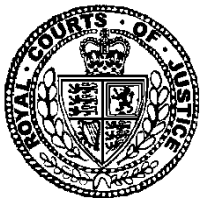

Neutral Citation Number: [2024] EWHC 3202 (Pat)
Appeal No: CH-2024-000108

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
INTELLECTUAL PROPERTY LIST (ChD)
PATENTS COURT

The Rolls Building
7 Rolls Buildings
Fetter Lane
London EC4A 1NL
16 December 2024

Before:
MR. JUSTICE MEADE

Between:

HALOZYME, INC. **Appellant**

- and –

THE COMPTROLLER-GENERAL OF PATENTS, DESIGNS AND TRADE MARKS **Respondent**

- -

Hearing date: 14 November 2024

TOM MITCHESON KC and DANIEL SELMI (instructed by **Wiggin LLP**) for the **Appellant**

STUART BARAN (instructed by the **Treasury Solicitor**) for the **Respondent**

- -

JUDGMENT

Remote hand-down: This judgment will be handed down remotely by circulation to the parties or their representatives by email and release to The National Archives. A copy of the judgment in final form as handed down should be available on The National Archives website shortly thereafter but can otherwise be obtained on request by email to the Judicial Office (press.enquiries@judiciary.uk).

Mr Justice Meade:

1. This is an appeal from decision BL O/0257/24 of the Hearing Officer, Dr Lawrence Cullen ("the Decision"). The Decision is dated 27 March 2024.

2. In the Decision the Hearing Officer refused two SPC applications ("the Applications" or "the first/second Application"; for reasons appearing below I refer also to the first as the "Herceptin Application"). Details of the Applications are given in paragraphs 1 to 3 of the Decision. Details of the relevant basic patents relied on are given in paragraph 4 of the Decision. Details of the marketing authorisations concerned ("the MAs") are given in paragraphs 2, 3 and 5 of the Decision. There is no dispute about any of the details and so I do not set them out here.

3. The Appellant is Halozyme, Inc. ("Halozyme") as SPC applicant, and the Respondent is, of course, the Comptroller-General of Patents, Designs and Trade Marks ("the Comptroller"). At the hearing, Mr Mitcheson KC appeared for Halozyme leading Mr Selmi and Mr Baran appeared for the Comptroller. I am grateful for their concise and helpful written and oral submissions.

4. The central issue is, as described in paragraph 6 of the Decision:

> 6. The applicant considers that both of these MAs relate to a product that is a combination of active ingredients and the examiner does not. This disagreement centres on the role of the human recombinant hyaluronidase component in the medicinal product and whether it can be regarded as an active ingredient or not.

5. As paragraph 1 of the Decision records, the first Application concerns trastuzumab (Herceptin) together with recombinant human hyaluronidase and the second Application concerns rituximab (MabThera) together with recombinant human hyaluronidase. As paragraph 9 of the Decision goes on to state, the arguments before the Hearing Officer focused on the first Application with references to the second only where necessary, and before me matters went just a little further, to the extent that I only need to consider the first Application. It was accepted for Halozyme that if that application failed (as I find it does) then so does the second Application.

6. For reasons explained later in the Decision, at paragraphs 26 to 29, if recombinant human hyaluronidase is not an active ingredient in its own right then the Applications must fail (in the Decision, for understandable reasons of brevity, the Hearing Officer often just referred to "hyaluronidase" even where he specifically meant the recombinant enzyme the subject of the MA, but I will continue to refer to "recombinant human hyaluronidase"; nothing turns on this).

7. The Decision contains detailed and helpful analysis of the Relevant Law (paragraphs 30 to 35), and the Relevant Case Law (paragraphs 36 to 67). It then considers the MAs from paragraph 75, and in particular the Herceptin MA from paragraph 78 onwards. In the course of doing so, it covers the SmPC and the EPAR, whose roles are explained in the Relevant Law section (the SmPC is part of the MA and the EPAR is, formally, not, although it is derived directly from

the full scientific assessment report produced by the CHMP for the EMA – see paragraph 24 of the Decision). There is also a section on the MabThera MA from paragraph 86 but for reasons already explained I do not need to say anything about that separately.

8. The Decision then comes on to consider the role of recombinant human hyaluronidase based on the MAs from paragraph 94 and concludes that they contain nothing to indicate that recombinant human hyaluronidase is an active ingredient, as opposed to an excipient.

9. However, the Decision then has a section from paragraph 101 onwards asking "Is analysing the marketing authorisation the whole story?". The Hearing Officer concluded that the UKIPO's approach is "SmPC/EPAR-led". He explained that this means that those documents (and the Commission Implementing Decision) must be considered and lead the analysis; they may be the only ones needed; but additional materials may be considered, although if they are then they are not to be considered in isolation but as a whole alongside these primary materials.

10. Then the Decision goes on to analyse whether recombinant human hyaluronidase is an active ingredient from paragraph 107 onwards. At this stage the Hearing Office considered, in addition to the primary materials, passages from the basic patent for the first Application (referred to as '643), three scientific papers by Baumgartner (at paragraph 109 (iv)), De Maeyer (at paragraph 109(v)) and St Croix (paragraph 109(vi)). He also referred at paragraph 110 to a clinical trial from the MA, which is key to aspects of Halozyme's arguments.

11. In view of the centrality of these paragraphs to my conclusion, I will, for convenience, set them out in full here (footnotes, which are the references to the papers, omitted):

> 107 In their skeleton argument (see para 31), filed in advance of the hearing, the applicant, referring to the CJEU decisions in *MIT, GSK, Forsgren, Bayer* and *Abraxis* (see above), stated that this caselaw establishes two conditions which must be met to define an active ingredient:
>
> > • Firstly, the ingredient in question has an effect on the human body i.e. a metabolic effect.
> >
> > • Secondly, that the presence and effect of the ingredient is reflected in the technical information submitted as part of the MA and contributed to the delay in obtaining authorisation, i.e. covered by the therapeutic indication of the MA.
>
> The applicant then goes on to say, taken together, these two conditions indicate "In other words, that it [the active ingredient] *has a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indications of the marketing authorisation*".

108 The applicant considers that the first condition for hyaluronidase to act as an active ingredient is met because of "*the basic science underlying its use*" as explained in the '643 patent filed in support of this SPC application and in some of the references identified in that patent. Mr Mitcheson argued that hyaluronidase has been shown to have both general and specific effects regarding the treatment of cancer and that its "*presence leads to a significant advance in the treatment of cancer*". The general effects were those referred to in the literature such as the papers cited in the patent which show that "*hyaluronidase has been shown to inhibit tumour growth*" and that it has a metabolic effect of its own i.e. "*It has specific enzymatic activity which modifies the structure, and thus the function, of the subcutaneous extracellular matrix*".

109 In support of this argument, Mr Mitcheson asked me to consider the basic patent '643 and several other documents, including a number of journal references, cited in the basic patent which, the applicant believes, supports their argument that recombinant human hyaluronidase has an effect, be it pharmacological, immunological or metabolic, on cancer. He directed me to several paragraphs in basic patent '643 which, he asserted, provided evidence of an effect of recombinant human hyaluronidase in cancer, including:

(i) paragraphs [0046] and [0049] show that recombinant human hyaluronidase has a metabolic effect on the body (my emphasis added):

[0046] Methods for the use of sHASEGP's in the removal of glycosaminoglycans are also provided. ***sHASEGP's open channels in the interstitial space through degradation of glycosaminoglycans that permit the diffusion of molecules*** *less than 500nm in size. These channels remain for a period of 24-48 hours depending on dose and formulation. Such channels can be used to facilitate the diffusion of exogenously added molecules such as fluids, small molecules, proteins, nucleic acids and gene therapy vectors and other molecules less than 500nm in size.*

……

[0049] In other indications, a single short acting dose is preferable. ***Temporary removal of glycosaminoglycans can be used to enhance the delivery of solutions and drugs into interstitial spaces****. This can be very useful for the diffusion of anesthesia and for the administration of therapeutic fluids, molecules and proteins.* ***Subcutaneous*** *and intramuscular* ***administration of molecules in the presence of sHASEGP's also facilitate their systemic distribution more rapidly****. Such methods are very useful when intravenous access is not available or where more rapid systemic delivery of molecules is needed. Delivery of other large molecules such as Factor VIII, that are poorly bioavailable upon subcutaneous administration, made be injected with sHASEGP's to increase their availability.*

(ii) paragraph [0047] discloses a number of possible uses and effects of glycosaminoglycans (GAG, such as hyaluronidase) as follows:

"[0047] sHASEGPs can also be used to remove excess glycosaminoglycans such as those that occur following ischemia, reperfusion, inflammation,

arteriosclerosis, edema, cancer, spinal cord injury and other forms of scarring. In some instances, sHASEGP's can be delivered systemically by intravenous infusion. This can be helpful when local access is not readily available such as at the heart or brain or in the case of disseminated neoplasm wherein the disease is through the body. Super-Sialated sHASEGP's are preferable to increase serum half-life and distribution over native hyaluronidase enzymes that lack terminal sialic acids".

Mr Mitcheson further pointed out, in this regard, that "*There is a direct action where the molecules of the invention can be used to remove the GAGs that are made during diseases such as cancer*";

(iii) paragraph [281] and [283] which indicate that sHASEGP polypeptides "*can be formulated as pharmaceutical compositions*" and that these "*polypeptides can be formulated as the sole pharmaceutically active ingredient in the composition or can be combined with other active ingredients"*.

(iv) paragraph [0361] and the scientific journal articles referenced therein, particularly *Baumgartner et al.*, Counsel highlighted a passage from the introduction of *Baumgartner et al*. (reproduced below, my emphasis in bold):

"There is much evidence indicating that alterations in the extracellular matrix composition of tumour stroma can arise as a result of altered synthesis by host cells in response to tumour cell influences, inducing resistance to a variety of drugs.

Therefore, the concept of cancer therapy by means of (bio)chemical modification of tumour cells or normal tissue and extracellular matrix such that a therapeutic gain can be achieved using conventional therapeutic modalities is a promising one.

We report here on a phase I study of the improvement in therapeutic efficacy in loco-regional treatment of chemo-resistant malignant diseases achieved by adding hyaluronidase to the appropriate chemotherapy protocol."

He then went on to argue that "*there can be no doubt that the hyaluronidase is an active ingredient in the sense required by law because it is achieving biochemical modification of the tumour cell. It is an enzyme, so it is dissolving or, in chemical reaction, the molecules around the tumour cells, and that is improving the ability of the other ingredient to overcome the resistance which has occurred"*.

(v) paragraph [0362] where Mr Mitcheson directed me to the statement in this paragraph that "*In addition to its indirect anticancer effects, cattle derived hyaluronidase has direct anticarcinogenic effects. Hyaluronidase prevents growth of tumours transplanted into mice*". He also took me to the paper by *De Maeyer et al.* referenced therein which concerned a study examining two mouse strains, C57BL/6 and HW23, which have different levels of circulating hyaluronidase, and investigated the effects of these hyaluronidase levels on

resistance to tumour development. This study appears to indicate that higher levels of circulating hyaluronidase increase resistance to tumour development in lung carcinoma and melanoma.

(vi) paragraph [0372] and the 1998 *St. Croix et al.* paper referenced therein. This paper discusses the use of bovine testicular hyaluronidase to treat intact multicellular spheroids of a mouse mammary tumour EMT-6 by disaggregating and dispersing the spheroids making them more susceptible to the effects of chemotherapeutics. The hyaluronidase in this case was administered intraperitoneally.

(vii) Mention is also made in paragraphs [0373] and [0374] that "*sHASEGP can be used as a chemotherapeutic agent (alone or in combination with other chemotherapeutics) in the treatment of any of a variety of cancers, particularly invasive tumours. For example, sHASEGP can be used in the treatment of small lung cell carcinoma ……*" and that the sHASEGP can also be used to increase the sensitivity of tumours that are resistant to conventional chemotherapy.

(viii) In addition to the paragraphs identified above, Mr Mitcheson also took me to paras [0001]-[0003], [0007], [0008], [0359] and [0363] which illustrate that there is a need for hyaluronidase of human origin that can be used in chemotherapy as a therapeutic agent itself or in conjunction with other chemotherapeutic agents.

110 In relation to the second condition, the applicant makes reference to the specific effect of hyaluronidase (see para 41 of skeleton argument), citing clinical trial BO2222Y from the MA, as follows:

> *"As for the specific effect in combination with trastuzumab, this is demonstrated by the clinical trial BO22227 reported at p.50 of the Herceptin SmPC/EPAR (cf the Forsgren case). Whilst 40.7% of patients in the control group receiving trastuzumab alone (intravenously) lacked cancer cells in the breast, some 45.5% of patients receiving trastuzumab and hyaluronidase achieved the same status, an improvement rate of over 10%. This is an important advance given the seriousness of the disease in question."*

111 In the above-mentioned clinical study, the effect of hyaluronidase on the pharmacokinetics of trastuzumab in the subcutaneous formulation (Herceptin SC) was compared to that of trastuzumab in the intravenous formulation (Herceptin IV, see SmPC, Section 5.2: Pharmacokinetic properties, page 51). As a consequence, the legal test outlined by the applicant (see above) is fulfilled in their view. The applicant argued that this shows, not only that the hyaluronidase is having an effect on the human body, but it is doing so in a way that is consistent with the granted marketing authorisation. As such, hyaluronidase can be considered to have all the features of an active ingredient – it has a metabolic effect, it is part of the clinical testing that contributed to the delay in obtaining authorisation and according to the

applicant, citing the CJEU decision in *Bayer*, the hyaluronidase "*is at least as active as the safener in Bayer*".

12. The Hearing Officer then gave conclusions to this section at paragraphs 112 to 115 (paragraph 116 explains that the same reasoning applies to the second Application):

> 112 I do not agree with this characterisation by the applicant of the conditions to be met to determine if a substance is an active ingredient. I do not consider that the first condition proposed by the applicant is correct – it is not a question of whether the substance is an active substance because it has a metabolic effect on the body. This is too general. I believe that the case law is clear in that the condition to be met is more specific, i.e., does the substance in question have a pharmacological, immunological or metabolic action of its own **which is covered by the therapeutic indications of the marketing authorisation** (as the CJEU concluded in *Forsgren*, my emphasis added in bold).
>
> 113 Such references as those referred to by Mr Mitcheson and described above from the '643 patent and the related documents cited therein fall short in my view of showing that something is acting as an active agent for a particular disease. This is especially true when set alongside the fact that the MA indicates it is acting as an excipient. I consider that while these references indicate that hyaluronidase has properties that show it has potential to be used to treat cancer in general and that it is worth investigating further, it does not provide information on how hyaluronidase acts in the treatment of the specific cancers of interest, e.g., HER2 breast cancer or NHL, the specific treatments referred to by the respective MAs.
>
> 114 In his argument that this "*metabolic effect*" supports hyaluronidase as an active ingredient, Mr Mitcheson suggests that rHuPH20 is having an indirect effect on breast cancer, by allowing diffusion of trastuzumab into the body, and pointed to the decision of *Bayer*, to support his position. However, I do not think that this takes sufficiently into account the decision in *Forsgren*, which confirms that the active ingredient must have an effect of its own in the relevant therapeutic indication. In my view, it is clear from the MA that the therapeutic effect that has to be taken into account for Herceptin is not cancer in general but is the rather more specific HER2 breast cancer. The latter is the therapeutic indication that has been approved by the MA for Herceptin, not the former. Similarly, for MabThera, the indication is for NHL rather than cancer in general.
>
> 115 While I appreciate Mr Mitcheson's eloquence in presenting the applicant's case in the best light he can, I do not think that I can stretch or redefine the meaning of excipient so that it covers active ingredient in the way that the applicant is inviting me to do so.

13. I will return to the *Forsgren* test shortly.

14. The Decision then contains a section from paragraph 117 onwards about whether the metabolic effect of recombinant human hyaluronidase that Halozyme relies on is discussed in the Herceptin MA. This touches once more (at paragraph 119) on the BO22227 clinical trial. At the end of paragraph 121 the Hearing Officer said that he considered that additional materials beyond the MA/SmPC/EPAR could be used to supplement them, but not to "provide information for which there is no basis in the SmPC or EPAR". He went on to give reasons for this.

15. Then there is a section in the Decision entitled "*What is the role of the marketing authorisation in identifying the different components of the medicinal product*". This section contains two paragraphs, 127 and 133, which revert to the technical issues at play, and since they are (or at least at one point, were) important to Halozyme's arguments I will set them out here:

> 127 Following on from the points discussed in the previous section, I consider, firstly, that the starting point for identifying the active ingredient and the other components in the medicinal product is the marketing authorisation and not the patent. When considering if an SPC application meets the requirement of Article 3(d) it is correct to start this consideration with the authorisation and what it covers. Just because the patent may include additional information about the hyaluronidase does not in my view mean that you can ignore or not place suitable weight on the role that the hyaluronidase plays in the medicinal product as explained in the MA. In this instance, the MA refers to the hyaluronidase as an excipient, making the delivery of the active ingredient trastuzumab (or rituximab) possible by the subcutaneous route. It seems logical that the hyaluronidase is only necessary for subcutaneous administration of trastuzumab because there are GAGs present in the application site.
>
> …..
>
> 133 Nothing in the SmPC or the EPAR suggests, in my view, that the hyaluronidase is acting in any fashion other than as an excipient, i.e., it is breaking down GAGs at the injection site and making it easier for trastuzumab to penetrate into the blood stream and so exert its therapeutic effect on HER2 breast cancer cells. It is only the latter role that has been identified and assessed for the purpose of the extension to the MA for Herceptin (and also for the purpose of the extension to the MA for MabThera). Any other contribution made by the hyaluronidase, unless it is specifically accounted for and referred to in the marketing authorisation is, in my view, not relevant for the purposes of deciding the grant of an SPC.

16. At paragraph 135 the Hearing Officer said that because the MA/SmPC/EPAR provided no support for recombinant human hyaluronidase being an active ingredient, it was not legitimate for Halozyme to rely on anything else, such as the basic patent or scientific materials. So it was not an active ingredient.

17. At paragraphs 141 to 152 in a section entitled "Conclusions" the legal effect of this is spelled out systematically: both Applications are rejected.

18. In between, the Decision refers to parallel decisions from other jurisdictions. These have gone both ways. The Hearing Office did not draw assistance from them and neither do I, not least because my ultimate decision on this appeal is based on the facts and the arguments about the facts that I have received, not disputes about the law.

The test for "active ingredient"

19. Although a large number of CJEU decisions were cited to the Hearing Officer and to me, it was not in dispute that the basic, relevant test for "active ingredient" under Article 1(b) is that from *Forsgren* (C-631/13), set out at paragraph 53 of the Decision, which is mentioned in the parts of the Decision that I have quoted above:

> 53 In the operative part of the CJEU judgement (reproduced below) it makes clear that finding a "*pharmacological, immunological or metabolic action of its own*" is not the only requirement, this action must be in relation to the therapeutic indications of the marketing authorisation (my emphasis added in bold):
>
> > *Article 1(b) of Regulation No 469/2009 must be interpreted as meaning that a carrier protein conjugated with a polysaccharide antigen by means of a covalent binding* ***may be categorised as an "active ingredient" within the meaning of that provision only if it is established that it produces a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indications of the marketing authorisation, a matter which it is for the referring court to determine, in light of all the facts of the dispute in the main proceedings.***

20. A key point, stressed by the Hearing Officer and in the arguments before me, is that merely finding a "pharmacological, immunological or metabolic action of its own" is not enough for something to be an active ingredient. The effect has to be in relation to the therapeutic indications of the MA.

21. Halozyme did not dispute this as a matter of law. The legal arguments before me were not on the nature of the test to be applied but on the materials to be considered as inputs to it: as is recorded in the parts of the Decision which I have narrated above, the Hearing Officer decided that it was not legitimate to go beyond the MA/SmPC/EPAR in pursuit of an effect they did not support at all, and Halozyme wanted to rely on the basic patent and the scientific papers identified above.

The Respondent's Notice

22. The Comptroller submitted a Respondent's Notice by which it is sought to argue (I paraphrase) that whether a substance is an active ingredient or not should be determined conclusively by reference only to Section 2 of the SmPC. In a nutshell this means that if the medicines regulator concludes that something is an excipient and says so in Section 2, there can be no contrary argument, not even based on any other part of the SmPC, or the EPAR. Conversely, as I understand it, if the regulator decided something to be an active ingredient that would also be conclusive in the applicant's favour.

23. This radical approach, much stricter than the SmPC/EPAR-led approach, was urged on me as giving certainty, and being simple in its application for the UKIPO, simplicity of application, it was said, being a key objective of the SPC system. Formally speaking the Respondent's Notice also urged that consideration should be limited to the whole of the SmPC and nothing else but this was not the real thrust of the argument and little time was spent on it at the hearing.

Reference to the CJEU

24. On 18 June 2024 the Supreme Administrative Court of the Czech Republic referred six questions to the CJEU in a case concerning an SPC application by Halozyme which I understand to be essentially the same as the Herceptin Application the subject of this appeal. The six questions ask whether the MA is conclusive on the question of whether a substance is an active ingredient or an excipient (i.e. going directly to the Respondent's Notice point). And they ask, if it is not conclusive, what documents should be taken into account (including inquiring about the basic patent). The result of the reference will not be binding on this Court but could well be persuasive.

Structure of the issues on this appeal

25. There are two different categories of issue in play in this appeal.

26. The first category concerns what it is legitimate to consider to decide whether recombinant human hyaluronidase is an active ingredient. The Hearing Officer proceeded on the SmPC/EPAR-led approach. Halozyme argues that it is also legitimate to consider other materials and in particular the basic patent and the three scientific papers mentioned above. By the Respondent's Notice the Comptroller says that the only relevant matter is section 2 of the SmPC.

27. The second category concerns what should be the factual finding as to whether recombinant human hyaluronidase is an active ingredient based on the materials that it is legitimate to consider.

28. Although the second in a sense logically comes after the first, it is in my view critical to note that although the Hearing Officer held that the SmPC/EPAR-led approach was the right one and rejected Halozyme's ability to rely on the basic patent and the scientific literature, he also made factual findings that even taking into account the basic patent and the literature on top of the MA/SmPC/EPAR it was not shown that there was a basis for thinking that recombinant human hyaluronidase has a treatment effect for the particular indications approved by

the MAs. He said that this was "especially" true given that the MA says recombinant human hyaluronidase is an excipient (see paragraph 113), but that just means that he gave some non-decisive weight to the MA, which Halozyme did not say was wrong as a matter of approach. In short, his findings mean that if Halozyme was right about the materials to be considered, it would still lose on the facts; he rejected critical parts of Halozyme's arguments on the facts based on the basic patent and the literature.

29. So unless Halozyme were to convince me that the Hearing Officer was wrong about the facts, the question of what materials it is legitimate to consider does not matter and does not need to be decided, and the Respondent's Notice does not arise, either.

Standard of review on the facts

30. The UKIPO is an expert tribunal with a high degree of competence in deciding technical/scientific matters. It was, rightly, not argued by Halozyme that I should conduct a rehearing. I am, rather, reviewing the decision of the Hearing Officer.

31. The many authorities on the deference to be given by appellate tribunals to fact-finding decisions at first instance in this sort of situation were not specifically cited to me but they are very well known. I am not to ask myself whether I would have reached the same decision, but rather whether the decision was one that was reasonably open to the Hearing Officer or, on the other hand, whether he made an unsupportable decision because, for example, he failed to take something relevant into account, or reached an irrational conclusion. The appellate tribunal has to be particularly alert to the danger of "island hopping".

32. Initially in his oral submissions Mr Mitcheson accepted in answer to questions from me that the question was whether, on the evidence, it was shown to the ordinary civil standard that recombinant human hyaluronidase actually has the necessary effect. Following further consideration over the short adjournment he modified this to argue that on an application for the grant of an SPC (as opposed to *inter partes* validity proceedings, I think) it was only necessary that the effect be plausible or possible. This was only very faintly persisted in and I reject it; decisions about SPC grant always determine whether the requirements of validity are actually met, not whether they might possibly be met. Further, the argument before the Hearing Officer was directed to whether the requirements were actually met and this point was not part of the grounds of appeal. It is not open to Halozyme to seek to argue for a different standard at this stage.

Analysis on the factual conclusions taking the basic patent and literature into account

33. I have set out the relevant parts of the Decision above. Although the key findings are mainly at paragraphs 110 to 115, I also need to bear in mind what the Hearing Officer said later, especially at paragraphs 120 and 133. I do not think it is any criticism of the Hearing Officer that he made those later

comments in dealing with other legal arguments, but I bear them in mind because Halozyme's arguments deployed them.

34. In relation to the parts of the basic patent relied on, I positively agree with the Hearing Officer's overall assessment that they assert some potential in treating cancer at a general level but do not provide information on how recombinant human hyaluronidase acts in treating the specific cancers of interest. They are general and prophetic and do not provide any experimental evidence, and in many instances they are about improving access to tumours for other drugs, which would not meet the *Forsgren* test. In any event, it is not necessary that I positively agree (though I do), it is a matter of whether the Hearing Officer's analysis was open to him, and I conclude that it was.

35. To be fair, Mr Mitcheson did not rely very heavily on the basic patent itself, and rather more so on the three papers. Of these:

    a. Baumgartner: the Hearing Officer quoted this at paragraph 109(iv) and emphasised the part that says that the "therapeutic gain" is achieved by "conventional …modalities". He also quoted Mr Mitcheson's submission that the recombinant human hyaluronidase "improves the ability of the other ingredient".

    b. De Maeyer: this was addressed at paragraph 109(v) of the Decision. In a sense this was the high point of Halozyme's case on the literature references because on one view (I think a rather generous one) it might be said that the recombinant human hyaluronidase could be having an effect of its own and not just assisting another drug. But that does not meet the Hearing Officer's later reasoning at 112-114 that Halozyme's argument was too general. De Maeyer is a study in mice only, and not in relation to the specific cancers of the MA.

    c. St Croix: this was addressed at paragraph 109(vi) of the Decision and is another one where increased susceptibility to other therapeutics is asserted. So this is in the same category as Baumgartner.

36. Overall on the three literature references I again actually agree with the Hearing Officer but in any event am confident that his analysis was properly open to him.

37. Although Halozyme relied more heavily on the literature references than on the basic patent it seemed to me that it sensed that it would not realistically be able to say that the Hearing Officer was going beyond that which was reasonably open to him from them, and the area where it argued that he made a fundamental error was in relation to the clinical trial referred to above.

38. The following is what is said about clinical trial BO22227, at page 50 of the Herceptin SmPC (so this is part of the MA):

Subcutaneous formulation

Study BO22227 was conducted to demonstrate non-inferiority of Herceptin subcutaneous formulation versus Herceptin intravenous formulation based on co-primary PK and efficacy endpoints. A total of 595 patients with HER2-positive, operable or locally advanced breast cancer (LABC) including inflammatory breast cancer received eight cycles of either Herceptin intravenous formulation or Herceptin subcutaneous formulation concurrently with chemotherapy (4 cycles of docetaxel, 75 mg/m^2 intravenous infusion, followed by 4 cycles of FEC ([5-Fluorouracil, 500 mg/m^2; epirubicin, 75 mg/m^2; cyclophosphamide, 500 mg/m^2 each intravenous bolus or infusion]), followed by surgery, and continued therapy with Herceptin intravenous formulation or Herceptin subcutaneous formulation as originally randomized for 10 additional cycles for a total of one year of treatment.

The analysis of the efficacy co-primary endpoint, pCR, defined as absence of invasive neoplastic cells in the breast, resulted in rates of 40.7 % (95 % CI: 34.7, 46.9) in the Herceptin intravenous arm and 45.4 % (95 % CI: 39.2 %, 51.7 %) in the Herceptin subcutaneous arm, a difference of 4.7 percentage points in favour of the Herceptin subcutaneous arm. The lower boundary of the one-sided 97.5 % confidence interval for the difference in pCR rates was -4.0, implying non-inferiority of the Herceptin subcutaneous formulation compared to the Herceptin intravenous formulation. For the PK co-primary endpoint refer to section 5.2. For the comparative safety profile see section 4.8.

39. Halozyme said that this showed that recombinant human hyaluronidase had a positive treatment effect of its own on the breast cancer patients enrolled in the study, who were being treated with Herceptin, and that it could be inferred that this was not just a function of the recombinant human hyaluronidase helping the Herceptin to do its job. The logic was as follows:

    a. The study compares intravenous Herceptin with subcutaneous.

    b. The intravenous route is the best possible route of administration because the drug goes straight into the circulation.

    c. By contrast, with subcutaneous administration the Herceptin has to diffuse from the injection site so it might work less well.

    d. However, in the study the subcutaneous arm did *better*. This cannot be explained by the recombinant human hyaluronidase in the subcutaneous formulation helping the Herceptin to do its job (it was not present in the IV formulation), because if that was what was going on the subcutaneous arm could, at best, do *as well*. The *improved* results could only be because the recombinant human hyaluronidase was actually treating the cancer.

40. Thus, Halozyme said, the Hearing Officer was in error at paragraphs 111 and 112 where he said that a metabolic effect (which may indeed be shown in the clinical trial) was not enough and there had to be a treatment effect on the cancer concerned. Similarly, it said he was in error at paragraph 120 where he concluded that the results were seen because recombinant human hyaluronidase made it easier for the Herceptin to circulate.

41. The fatal error with all this is that the clinical trial was not intended to show and does not show that the subcutaneous formulation was better than the

intravenous. It explicitly says that it was to show non-inferiority. And although the "headline" numbers cited are 40.7% for subcutaneous and 45.4% for intravenous (with lower being better because they are percentages of patients who are breast cancer-free), the confidence intervals overlap so it is not safe to conclude, and it was not intended by the writer of the SmPC that one should be able to conclude, that the subcutaneous formulation was better.

42. I do not think Mr Mitcheson had any answer to this during the oral submissions before me. I can see the general shape of the logic (speaking for myself I would have been very slow to accept it without an expert to support it but I can understand the Hearing Officer relying on his own expertise to assess it) but it all founders when the factual premise that the subcutaneous formulation was better is not made out.

43. So again, I think that the Hearing Officer had a proper basis for his conclusion (and again, although it is not necessary, I would have reached the same one). It might conceivably be said that he should not have used the word "better" in the second-last line of paragraph 120 given that the trial was only about non-inferiority but he did say "*appears* to work better" (emphasis added) and I expect that he had in mind the headline numbers referred to above. In any event, it is a trivial point and does not undermine the overall logic.

44. The other point on which Halozyme fastened was paragraph 133 of the Decision where the Hearing Officer referred to the recombinant human hyaluronidase just acting as an excipient "breaking down GAGs at the injection site". Halozyme submitted that that was a clear error: the recombinant human hyaluronidase was recognised to break down GAGs at the tumour, not the injection site. I have to say that initially I thought it was a potentially promising point, and it seemed to provide some extra leverage or credibility to the clinical trial point. Mr Baran for the Comptroller at first felt he had to accept that it was an error and an inconsistency but argued that it did not undermine the Decision in relation to the clinical trials, or the logic of it generally.

45. In fact, however, the proposition that recombinant human hyaluronidase acts at the injection site in this way is explicitly stated in the EPAR at section 2.3.1. So the Hearing Officer was perfectly fair in what he said at paragraph 133. Not only that, but the relevant part of section 2.3.1 was actually referenced in Halozyme's skeleton for the appeal before me (for another proposition). I am entirely confident that Halozyme's representatives did not notice this contradiction in its position, and that the criticism of paragraph 133 of the Decision was made *bona fide*, but this is a graphic illustration of the risks of "island hopping", dotting around the materials looking for isolated problems without the fact-finding tribunal's appreciation of all the materials.

46. I recognise that doing the clinical trial may well have caused delay in the time to market, but it was common ground before me that that is not in itself the test.

47. Since I reject Halozyme's attack on the Hearing Officer's factual assessment on the basis of all the materials that Halozyme argues ought to be considered, this appeal fails. Recombinant human hyaluronidase is not an active ingredient.

48. I therefore do not need to consider the Respondent's Notice or the Hearing Officer's view that materials such as the basic patent and scientific literature could not properly be considered in the absence of a starting point in the MA. Mr Baran submitted that the Comptroller would welcome guidance on these matters. I do not think this is the right case to go into those matters, and Mr Baran did not suggest that there are a large number of SPC applications that turn on them, or that it is urgent. I think it is better that the question is looked at when a suitable case arises after the result of the CJEU reference referred to above is known and with fuller argument. For example, I was uncomfortable that I did not have the full picture about the effect on an unsuccessful SPC applicant's right to appeal if the regulator's decision on the active ingredient/excipient characterisation led to an automatic rejection by the UKIPO, and I was not at all confident that I knew whether the regulator asks the same question as the *Forsgren* test requires when it considers what is an excipient.

49. The appeal is dismissed.