Neutral Citation Number: [2018] EWHC 2465 (Admin)

Case No: CO/5288/2017

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

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 21/09/2018

**Before** :
**MRS JUSTICE WHIPPLE DBE**
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**Between :**

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| **BAYER PLC** | **First Claimant** |
| **- and -** | |
| **(1) NHS DARLINGTON CCG**<br>**(2) NHS DURHAM DALES, EASINGTON & SEDGEFIELD CCG**<br>**(3) NHS HAMBLETON, RICHMONDSHIRE & WHITBY CCG**<br>**(4) NHS HARTLEPOOL & STOCKTON CCG**<br>**(5) NHS NEWCASTLE GATESHEAD CCG**<br>**(6) NHS NORTH CUMBRIA CCG**<br>**(7) NHS DURHAM CCG**<br>**(8) NHS NORTHUMBERLAND CCG**<br>**(9) NHS NORTH TYNESIDE CCG**<br>**(10) NHS SOUTH TEES CCG**<br>**(11) NHS SOUTH TYNESIDE CCG**<br>**(12) NHS SUNDERLAND CCG** | **Defendants** |
| **-and-** | |
| **(1) NOVARTIS PHARMACEUTICALS UK LIMITED**<br>**(2) ROCHE PRODUCTS LIMITED**<br>**(3) THE SECRETARY OF STATE FOR HEALTH**<br>**(4) NHS ENGLAND** | **First Interested Parties** |

Case No: CO/5357/2017

**Between:**

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| **NOVARTIS PHARMACEUTICALS UK LIMITED** | **Second Claimant** |
| **-and-** | |
| **(1) NHS DARLINGTON CCG**<br>**(2) NHS DURHAM DALES, EASINGTON & SEDGEFIELD CCG**<br>**(3) NHS HAMBLETON, RICHMONDSHIRE & WHITBY CCG**<br>**(4) NHS HARTLEPOOL & STOCKTON CCG**<br>**(5) NHS NEWCASTLE GATESHEAD CCG**<br>**(6) NHS NORTH CUMBRIA CCG**<br>**(7) NHS DURHAM CCG**<br>**(8) NHS NORTHUMBERLAND CCG**<br>**(9) NHS NORTH TYNESIDE CCG**<br>**(10) NHS SOUTH TEES CCG**<br>**(11) NHS SOUTH TYNESIDE CCG**<br>**(12) NHS SUNDERLAND CCG** | **Defendants** |
| **-and-** | |
| **(1) THE SECRETARY OF STATE FOR HEALTH (ACTING BY HIS EXECUTIVE AGENCY THE MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY)**<br>**(2) NHS ENGLAND**<br>**(3) THE GENERAL PHARMACEUTICAL COUNCIL**<br>**(4) BAYER PLC**<br>**(5) ROCHE PRODUCTS LIMITED** | **Second Interested Parties** |

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**Jemima Stratford QC and Emily MacKenzie** (instructed by **Arnold and Porter**) for the **First Claimant**
**Tom de la Mere QC and Eesvan Krishnan** (instructed by **Covington & Burling LLP**) for the **Second Claimant**
**David Lock QC and David Blundell** (instructed by **Mills and Reeve**) for the **Defendants**
**Martin Chamberlain QC** (instructed by **Fieldfisher**) for **Roche Products Limited**

Hearing dates: 10, 11, 13 and 16 July 2018

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# Approved Judgment

**Mrs Justice Whipple:**

## A. INTRODUCTION

1. By this action, Bayer Plc ("Bayer") and Novartis Pharmaceuticals UK Ltd ("Novartis") challenge the lawfulness of a policy adopted by the twelve Clinical Commissioning Groups ("CCGs") who are Defendants to this action. The policy is headed "Treatment for Age-related Macular Degeneration" and it refers to three different drugs for treating patients with the neovascular form of that condition, which is known as "wet AMD". The three medicines named are (1) Eylea (whose INN, or international non-proprietary name, is aflibercept) for which Bayer holds a marketing authorisation which is specific to ophthalmic use; (2) Lucentis (INN ranibizumab) for which Novartis holds a marketing authorisation which is specific to ophthalmic use; and (3) Avastin (INN bevacumizab) for which Roche holds a marketing authorisation for various uses not including ophthalmic use. All three of these drugs are anti-vascular endothelial growth factor ("anti-VEGF") agents.

2. The policy states that Avastin will be offered to certain patients with wet AMD "*as the preferred treatment option"*.

3. The CCGs have adopted this policy because of the significant difference in price between Avastin and the other two medicines. When compounded (a term I shall explain below), Avastin costs around £28 per injection; Eylea costs around £816 per injection; Lucentis costs around £551 per injection. The actual prices will vary depending on a number of factors, including whether any confidential discount on price has been negotiated with the relevant pharmaceutical company.

4. The Defendant CCGs are from the North of England. Together they form the Northern Clinical Commissioning Group Joint Forum, which is an association without separate legal status; it is for that reason that each CCG within the Joint Forum has taken a decision, independently and separately, to adopt the policy.

5. The Claimants challenge the policy on four grounds:

    i) it is premised on an error of law, namely that there is a lawful basis for the supply of Avastin to treat wet AMD patients;

    ii) it fundamentally undermines the objective of Directive 2001/83/EC on the Community code relating to medicinal products for human use (the "Directive") and constitutes a breach of the duty of sincere cooperation in Article 4(3) of the Treaty of the European Union ("TEU");

    iii) it undermines patients' rights of access to NICE recommended treatments;

    iv) it introduces information for the patients (by means of a Q&A document and a Patient Information Leaflet which accompany the policy) which are misleading and inaccurate in material respects.

6. There is extensive material to set out by way of background. But in the end, the challenge pivots on a handful of key issues which I shall resolve, before coming to my

conclusion on the four grounds advanced. Regrettably, this will be a long judgment. I hope that this index will assist in its navigation:

## B. BACKGROUND

### Wet AMD

7. Age-related Macular Degeneration is known as "AMD". AMD has traditionally been classified as early, intermediate or late according to the stage of disease progression. Late AMD can be further classified as either 'wet' AMD (neovascular) or 'dry' AMD (advanced geographic atrophy). Wet AMD can rapidly lead to severe loss of central vision but can be treated if people at risk are identified early; in people with untreated wet AMD, over half will become visually impaired or blind within 3 years.

8. Currently, the exact cause of AMD is not known but factors such as age, family origin (prevalence is higher in people of white and Chinese family origin), diet and nutrition, genetics and smoking are thought to affect the risk of developing the disease. Socioeconomic factors also may result in later presentation and poorer outcomes.

9. So far as wet AMD is concerned, the loss of vision is caused by the abnormal growth of new blood vessels beneath the macula of the retina. That growth is stimulated by a protein known as vascular endothelial growth factor ("VEGF"). Wet AMD can be treated by products which inhibit VEGF, which are in consequence known as "anti-VEGF" agents or "VEGF inhibitors". The most common primary treatment procedure for wet AMD is injection into the eye (intravitreal injection) of anti-VEGF agents.

### Use of Avastin to treat wet AMD

10. The following paragraphs are adapted from the chronology prepared and agreed by the parties. They provide an overview of events leading to this judicial review.

11. Avastin is a VEGF inhibitor. The intellectual property rights to Avastin are held by a company within the Roche group. On 12 January 2005, the European Medicines Agency ("EMA") granted Avastin a marketing authorisation for treatment of colorectal cancer under the "centralised procedure" under the Directive. That approval has since been extended to other oncology uses. The Summary of Product Characteristics ("SmPC", a document required by Article 11 of the Directive which accompanies any medicine which has a marketing authorisation) was amended in 2012 to emphasise that Avastin is *"not formulated for intravitreal use"*. Roche has never applied for Avastin to be given a marketing authorisation for ophthalmic use.

12. Lucentis is also a VEGF inhibitor. The intellectual property rights to Lucentis are also held by a company within the Roche group. On 22 January 2007, Lucentis was granted a marketing authorisation for the treatment of wet AMD. Thus, Lucentis was the first VEGF inhibitor to be placed on the market specifically authorised for ophthalmic use. Permission to market Lucentis in Europe has been granted by Roche to Novartis.

13. On 27 August 2008, NICE issued technology appraisal guidance (a "TAG", as to which see further below) for Lucentis (this was re-issued in May 2012). The TAG number is TA155.

14. In 2011/12, a group of Southern PCTs adopted a policy favouring the use of Avastin for ophthalmic use. This prompted a judicial review by Novartis against these various PCTs (this is known as the "SHIP JR" to reflect the names of the various PCTs then involved: Southampton, Hampshire, Isle of Wight, and Portsmouth). Permission for judicial review was granted (Thirlwall J), following which the JR was compromised by the PCTs agreeing to alter their policy.

15. The Medicines and Healthcare Products Regulatory Agency ("MHRA") issued guidance in August 2011 stating that bevacizumab for intravitreal use involved manipulation of the medicine to produce multiple aliquots (called "compounding"), and so resulted in an "unlicensed medicine".

16. Eylea is a VEGF inhibitor. The intellectual property rights to Eylea are held by Bayer. On 22 November 2012, Eylea was granted a marketing authorisation for ophthalmic use.

17. On 24 July 2013, NICE issued a TAG for Eylea (TAG number TA294).

18. On 15 December 2014, the Royal College of Ophthalmologists ("RCO") issued a statement on the use of Avastin in wet AMD. The RCO stated that there was no clinically significant difference in the incidence of serious adverse events between Avastin and Lucentis (referring to two trials which had taken place: the "IVAN" trial in 2012 and the "Cochrane" review in 2014). The RCO noted the price differential between the two drugs and that switching to Avastin could save NHS England alone at least £102 million a year. In view of the evidence, it supported both drugs being made available in the UK. But the RCO noted the constraints put on clinicians in 2011 (a reference, presumably, to the MHRA publication). The RCO noted the drain on public resources, the GMC's guidance which states that clinicians must make good use of resources, and NICE guidance that treatment must be cost effective. It

concluded with an urgent call to the UK health regulatory bodies to consider how this unusual situation could be remedied.

19. In February 2015, 120 CCGs wrote to the Secretary of State for Health noting that Lucentis had become the default option for treatment of wet AMD since it had become available on the market and had received positive NICE appraisal, but that it was priced at between 10-20 times as much as Avastin, which had been used prior to the advent of Lucentis. The CCGs referred to the IVAN trial and the Cochrane review, but also to the CATT study in the US in 2012 which had demonstrated comparable effectiveness between Avastin and Lucentis. They also referred to the situation in other EU Member States, the USA, and Guernsey where they asserted Avastin was widely used to treat ophthalmic conditions. The CCGs asked the Secretary of State to take urgent action to facilitate the use of Avastin to save money.

20. The Secretary of State for Health responded in March 2015 saying that under European and domestic law it was illegal to manufacture and supply any unlicensed products unless there was a special need with the meaning of the Medicines Directive (ie Directive 2001/83/EC, to which I shall come). He acknowledged that clinicians could prescribe any treatment, including an unlicensed product or a product not licensed for a particular indication, which they considered to be the best available medicine to meet the patient's needs, subject to funding being available, and subject also to taking MHRA and GMC guidance into account. He noted that NICE was working on the development of a clinical guideline which would refer to Avastin as well as Lucentis for treating AMD. Ministers in the Department of Health have since then written to the CCGs in similar terms.

21. It was against this background that the CCGs adopted the policy on various dates between July and September 2017.

22. In November 2017, Bayer and Novartis issued these judicial review proceedings.

23. On 23 January 2018, NICE issued a guideline on age-related macular degeneration. On the same day, the GMC clarified its approach to clinicians who prescribed Avastin for ophthalmic use. I shall refer to both publications in greater detail below.

24. In February 2018, the CCGs first intimated that they were considering "original vial use", which is where Avastin is not compounded (which I will describe in more detail later, but in simple terms means taking a vial of Avastin and splitting it into separate aliquots or doses, in the manner suggested in the MHRA publication of 2011), but would be used directly from the manufacturer-supplied vial.

25. In April and May 2018, the parties exchanged requests for further information and provided evidence.

26. The case came on for hearing over four days starting on 10 July 2018. After the hearing, the Advocate General promulgated his Opinion in Case C-29/17, *Novartis Farma SpA v Agenzia Italiana del Farmaco ("AIFA")* EU:C:2018:619.

## The Policy

27. The CCGs adopted the policy on various dates between July and September 2017. Each CCG was presented with a document entitled "Report for CCG Governing Bodies" which attached the draft policy at Appendix 1.

28. The report referred to the CATT and IVAN trials, two trials which had considered the clinical effectiveness and safety of using Avastin to treat wet AMD, (at [5]) and to an appraisal by the North of England Treatment Advisory Group (at [6]). It asserted that "*As a range of studies have shown, there is no clinically significant difference between Avastin and Lucentis in terms of safety or effectiveness*" (at [8]). It noted that the main obstacle to making bevacizumab available as a treatment option was likely to be the drug companies themselves (at [10]). It referred to the then-draft NICE guideline which was out to consultation (at [11]-[12]). The recommendation in the report was as follows:

> "23 Given its equivalent safety and effectiveness, and its much reduced cost, the CCG Forum is recommending to CCGs that they adopt the prescribing of bevacizumab (Avastin®) as the first-line treatment option for patients newly diagnosed with wAMD – based on the principle of patient choice, where clinicians are still able to prescribe Lucentis® and Eylea® (see clinical policy attached in Appendix 1).
>
> 24 Our modelling estimates that if 75% of newly diagnosed patients take up Avastin then adopting this policy will yield approximately £43m of cumulative savings over 5 years to the NHS in Cumbria and the North East …"

29. The draft policy was adopted by the CCGs (and from here on I will refer to it as the Policy). After setting out the background, the Policy provides as follows:

> **"Policy: Avastin will be offered to patients with wAMD as the preferred treatment option under the following circumstances:**
>
> - Avastin will be offered to all new patients
>
> AND
>
> - Avastin will be offered to existing patients being treated with Lucentis or Eylea where there is an inadequate clinical response and a treatment switch is being considered
>
> *AND*
>
> - Patients will be given a leaflet with the opportunity to discuss the reasons why Avastin is the preferred treatment option and that they are free to choose one of the NICE approved treatments, ranibizumab (Lucentis) or aflibercept (Eylea).

> **Policy: Ranibizumab (Lucentis) and aflibercept (Eylea) will be offered to patients with wAMD within their marketing authorisation, as options for the treatment of wet age-related macular degeneration if:**
>
> - all of the following circumstances apply in the eye to be treated:
>
>  - the best-corrected visual acuity is between 6/12 and 6/96
>
>  - there is no permanent structural damage to the central fovea
>
>  - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
>
>  - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)
>
> AND
>
> - The manufacturer provides ranibizumab with the discount agreed in the patient access scheme.
>
> - *(The cost of ranibizumab and aflibercept beyond 14 injections in the treated eye is met by the manufacturer)*
>
> - Treatment with Ranibizumab (Lucentis) and aflibercept (Eylea) should be continued only in people who maintain an adequate response to therapy."

30. Appendix 2 to the Report was headed "Q and As for clinicians". Appendix 3 was headed "Information and Advice for patients".

**NICE Guideline NG 82**

31. On 23 January 2018, after the Policy was adopted, NICE produced its guideline NG 82 on the diagnosis and management of AMD. This is a very substantial document. Chapter 10 relates to pharmacological management of AMD. The conclusions in that chapter were based on a review of a wide range of studies summarised at tables 37-39.

32. The introduction to Chapter 10 summarises the background in this way:

> "There are currently licensed treatments for wet AMD and a treatment (bevacizumab) which has been used to treat AMD despite not having a marketing authorisation for such use. It is clear that, without authorisation in the product's SPC, the use of bevacizumab in AMD is off-label. The MHRA view is that the dividing of prepared vials of bevacizumab into smaller

> doses for intraocular use also makes it unlicensed. Doctors are required by the GMC to use licensed medications where available. Moreover, the UK government has previously decided that it will not disregard drug licensing purely to save money on drug costs (see parliamentary written question 227588). However, intraocular bevacizumab is widely used in many other countries, and many UK authorities including the Royal College of Ophthalmologists, have called for it to be made available for NHS practice, in view of the substantial cost savings that would be engendered.
>
> NICE has previously performed technology appraisals, which are incorporated in this guideline, on the licensed anti-VEGF agents. These recommend aflibercept and ranibizumab for late AMD (wet active), and commissioners in England and Wales are bound to fund them as a result. For this guideline, the committee has considered the published evidence on clinical effectiveness and cost effectiveness of all treatments for late AMD (wet active), regardless of license status."

33. It goes on to state, under the heading "Anti-VEGF recommendations":

> "The committee understood that the existing technology appraisal recommendations regarding aflibercept (TA294) and ranibizumab (TA155) would be incorporated into this guideline. The committee agrees that the new model – along with other published economic evidence – showed that treatment with bevacizumab would be unequivocally cost effective when compared with aflibercept and ranibizumab. However, the committee was aware that the use of bevacizumab for the treatment of late AMD (wet active) is judged by the MHRA to represent unlicensed prescribing. The committee therefore agreed that it could not explicitly recommend bevacizumab over the alternative anti-VEGFs, and agreed to make a class-level recommendation that anti-VEGF therapy should be offered for the treatment of late AMD (wet active).
>
> The committee agreed that a class-level recommendation, that anti-VEGF therapy should be offered for the treatment of late AMD (wet active), has the benefit of 'future-proofing' the guidance so that it will remain valid in the event of any changes to the regulatory position."

34. NICE consulted on the guideline before it was published. It received a large number of consultation responses which were summarised, together with NICE's responses to them, in a published document entitled "Stakeholder comments table".

35. A summary of the recommendations made in the Guideline appears at Chapter 4. Those recommendations were also set out, in identical terms, in a separate document published by NICE at the same time, also headed "NICE Guideline" 23 January 2018.

Paragraph 1.5 is headed "Pharmacological management of AMD". Paragraphs 1.5.1 and 1.5.2 state as follows:

> "1.5.1 Offer intravitreal anti-vascular endothelial growth factor (VEGF) treatment[1] for late AMD (wet active) for eyes with visual acuity within the range specified in recommendation 1.5.6.
>
> 1.5.2 Be aware that no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments[2] have been seen in the trials considered by the guideline committee."

The footnotes referred to in that passage state:

> "[1] At the time of publication (January 2018), bevacizumab did not have a UK marketing authorisation for, and is considered by the Medicines and Healthcare products Regulatory Agency (MHRA) to be an unlicensed medication in, this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the prescribing decision. Informed consent would need to be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines, and the MHRA's guidance on the Supply of unlicensed medicinal products (specials), for further information. The guideline may inform any decision on the use of bevacizumab outside its UK marketing authorisation but does not amount to an approval of or a recommendation for such use.
>
> [2] Given the guideline committee's view that there is equivalent clinical effectiveness and safety of different anti-VEGF agents (aflibercept, bevacizumab and ranibizumab), comparable regimens will be more cost effective if the agent has lower net acquisition and monitoring costs."

36. I shall return to the Guideline later in this judgment.

**Clinical Commissioning Groups**

37. CCGs are statutory corporations established under Chapter A2 of Part 2 of the National Health Services Act 2006. CCGs have a statutory responsibility to commission medical and healthcare services, see s 3(1) of the 2006 Act.

38. CCGs do not provide healthcare. Rather, CCGs contract with healthcare providers, such as NHS Trusts and General Practitioners, on standard service conditions. The current version of those conditions is dated May 2018. Important elements of those conditions include: service condition 1, the obligation on the provider to comply with the law and with the NHS Constitution; service condition 2, the obligation on the provider to comply, where applicable, with the registration and regulatory compliance guidance of any relevant regulatory or supervisory body and to respond to applicable

requirements and enforcement actions by such a body; and service condition 4, the obligation placed on the parties to act in good faith towards each other and to co-operate in accordance with law and good practice to facilitate the delivery of services.

39. The following preliminary points must be made:

    i) the relationship between any CCG and a provider is a contractual one; there is no statutory relationship between the parties.

    ii) The Policy, if it is maintained, will apply to providers with whom the CCGs contract via service condition 4: providers will have to pay regard to it in reaching their own treatment decisions, as part of the contractual duty of co-operation owed to the CCG.

    iii) The Policy, if it is maintained, will not be "binding" on the providers. It will simply be taken into account by the providers at the point of provision of healthcare services to patients, alongside other relevant considerations (such as regulatory and practice guidance, therapeutic need, and patient choice).

40. At an operational level, once commissioned, a provider seeks reimbursement from the CCG under a system of payment by results for treatment provided to patients. In that way, the CCGs reimburse the providers with whom they are in a contractual relationship for treating patients with wet AMD.

41. CCGs have a statutory responsibility to ensure that expenditure matches income in any given year, see s 223H National Health Service Act 2006. They are also under a statutory duty to exercise their functions "*effectively, efficiently and economically"* by virtue of section 14Q of the same Act. Careful husbandry of limited public resources is therefore a key part of a CCG's functions.

42. This goal is further reflected in the NHS Constitution, which contains seven key principles which guide the NHS, including:

> "[6] The NHS is committed to providing the best value for taxpayers' money and the most effective, fair and sustainable use of finite resources …".

43. CCGs are entitled to seek to encourage healthcare providers to conserve costs. A good example of a strategy aimed at encouraging healthcare providers to prescribe cheaper drugs is Case C-62/09 *R (Association of the British Pharmaceutical Industry) v Medicines and Healthcare Regulatory Agency* [2011] PTSR 391 (*"ABPI"*) where PCTs introduced schemes which rewarded GPs financially for favouring the prescription of cheaper drugs; the CJEU upheld this as a lawful practice.

44. The domestic courts have recognised that the role of CCGs (or health authorities or PCTs as their statutory predecessors) extends to the assessment of clinical effectiveness as part of their overall function of commissioning healthcare services. It was put in this way in *R v NW Lancashire HA ex p A and Others* [2000] 1 WLR 977:

> "the precise allocation and weighting of priorities is clearly a matter of judgment for each authority, keeping well in mind its statutory

> obligations to meet the reasonable requirements of all those within its area for which it is responsible … in establishing priorities – comparing the respective needs of patients suffering from different illnesses and determining the respective strengths of their claims to treatment – it is vital for an authority … to determine the effectiveness of various forms of treatment…" (per Auld LJ at 991 F – 992 A).

45. In *R (Rogers) v Swindon NHS PCT* [2006] EWCA Civ 392, [2006] 1 WLR 2649, the Court of Appeal held that the PCT was entitled to have a policy of exceptional funding for Herceptin for the treatment of early stage breast cancer even though that use was outside the marketing authorisation for that medicine (ie was "off-label", a term I shall consider later) and was not approved by NICE (noting that in that case the policy was found to be unlawful for other reasons).

46. In *R (AC) v Berkshire West PCT, EHRC intervening* [2011] EWCA Civ 247 the Court of Appeal upheld the PCT's refusal to fund breast augmentation surgery for transsexuals on grounds that the clinical effectiveness of the procedure was uncertain (see [29] and [30], per Hooper LJ).

47. These cases show that a CCG is entitled to take its own view on the clinical effectiveness of a particular medicine or procedure in setting its policies and making commissioning decisions. In so doing, it is bound to take account of guidance of various sorts, including NICE guidance, but it is entitled to come to its own conclusion.

**Other Domestic Healthcare Supervisory or Regulatory Bodies**

48. A number of domestic public bodies and regulators play a part in the operation of the NHS. The following is not a definitive review of the organisation and regulation of the NHS – that would be an enormous task which is not necessary for the resolution of this case – but what follows is an overview of the key players so far as this case is concerned.

*NHS England*

49. NHS England is a statutory corporation established by s 1H of the 2006 Act. NHS England determines applications for the formation of CCGs and variations to their constitution and similar matters. It allots funding to the CCGs, to be applied by the CCGs in the discharge of their functions. Although NHS England is empowered to publish guidance for CCGs pursuant to s 14Z8 of the 2006 Act, it has not in fact published any such guidance relating to the matters which arise in this case, taking the view that these are matters of "some legal controversy" and that other public bodies are better placed to offer guidance, namely NICE, the GMC and the MHRA (see its Observations dated 11 December 2017, at [17]).

50. NHS England was named as an interested party but has not participated in this action, beyond filing written Observations. Its general stance is indicated in the final paragraph of those observations, where it emphasises that:

> "30 … it is essential that [the Defendants and NHS bodies generally] remain free to select (from among the treatments that are lawfully

> available for selection) those that are affordable and cost effective and that the NHS body in question considers necessary to meet the reasonable requirements of those for whom they are responsible".

*National Institute for Health and Care Excellence ("NICE")*

51. NICE was established by s. 232 of the Health and Social Care Act 2012. Section 233 provides that in exercising its functions, NICE must have regard to "*the broad balance between the benefits and costs of the provision of health services or of social care in England".* Here too, therefore, the statute imposes an obligation to have regard to cost.

52. By s. 237, regulations may confer functions on NICE. The relevant regulations are the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013, SI 2013/259 (the "2013 Regulations"). Regulation 5 provides that NICE has the functions of giving advice or guidance, providing information and making recommendations about NHS services, amongst other things.

53. So far as recommendations are concerned, they come in two forms: NICE can make technology appraisal guideline or recommendations, under Regulation 7, which is commonly referred to as a "TAG", with which a relevant health body *must* comply. NICE TAGs are subject to a mandatory funding obligation under the 2013 Regulations. Alternatively, NICE can produce guidelines. These are recommendations on the management of health conditions, including investigations, range of treatments and use of medicines. Guidelines are not mandatory in effect and there is no legal obligation to fund treatment recommended in NICE guidelines. NHS bodies and clinicians are expected to take NICE guidelines into account, although they are not bound to follow them: see *Rogers* noted above, and see also *R (Condliff) v North Staffordshire PCT* [2011] EWCA Civ 910, where the PCT lawfully adopted a local commissioning policy on bariatric surgery which was narrower than the NICE guideline which the PCT considered and rejected in light of competing demands on its resources (see [13]-[14]).

54. Thus, NICE's role extends to considering issues of clinical effectiveness and cost effectiveness. It produces recommendations based on a combination of both factors.

*Medicines and Healthcare products Regulatory Agency ("MHRA")*

55. The MHRA is an executive body of the Department of Health. It was named as an interested party to this litigation but has played no part beyond filing an Acknowledgement of Service.

56. On 1 April 2009, the MHRA published a document on the gov.uk website entitled "Off-label or unlicensed use of medicines: prescribers' responsibilities". This appears to be general guidance, of a fairly informal nature (noting that in the healthcare field, a great deal of guidance is published by a number of different agencies and official bodies, not all of which is of mandatory effect: see, as an example, *Rogers* at [30]). Under the sub-heading "A licensed medicine meets acceptable standards of efficacy, safety and quality" the MHRA said this:

> "A marketing authorisation or product licence defines a medicine's terms of use: its summary of product characteristics (http://emc.medicines.org.uk) outlines, among other things, the indication(s), recommended dose(s), contraindications, and special warnings and precautions for use on which the licence is based, and it is in line with such use that the benefits of the medicine have been judged to outweigh the potential risks. Furthermore, a licensed medicine: has been assessed for efficacy, safety, and quality; has been manufactured to appropriate quality standards; and when placed on the market is accompanied by appropriate product information and labelling."

However, it went on to state, under a new sub-heading "Prescribing in a patient's best interests":

> "However, there are clinical situations when the use of unlicensed medicines or use of medicines outside the terms of the licence (ie, 'off-label') may be judged by the prescriber to be in the best interest of the patient on the basis of available evidence. Such practice is particularly common in certain areas of medicine: for instance, in paediatrics where difficulties in the development of age-appropriate formulations means that many medicines used in children are used off-label or are unlicensed."

The document gave practice guidance for prescribing unlicensed medicines. Then, under the sub-heading "Example of off-label use of medicines", this was stated:

> "Off-label intravitreal use of bevacizumab (Avastin, licensed for treatment of various solid cancers) has been associated with reports of severe eye inflammation and sterile endophthalmitis (http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate /ssLINK/CON041210). The production methods, formulation, and doses for bevacizumab were developed for use in oncology. Its use in the ophthalmology setting has not been authorised."

The next entry is a "clarification" by way of update dated August 2011 (to which I have already referred in general terms above) which stated that the preparation of bevacizumab for intravitreal use results in the creation of an unlicensed medicine.

57. The MHRA published further guidance in 2014 (MHRA Guidance Note 14) and a revision in January 2015 (MHRA Questions and Answers for Specials manufacturers) which address the provision of "specials" – a domestic term referring to medicines prepared under the derogation at Article 5 of the Medicines Directive (to which I shall come). The Defendants do not rely on Article 5. Appendix 2 to Guidance Note 14 stated:

> "**This hierarchy is provided for guidance only and each case should be considered on its individual merit.**

1. An unlicensed product should not be used where a product available and licensed within the UK could be used to meet the patient's special need.

2. Although MHRA does not recommend "off-label" (outside of the licensed indications) use of products, if the UK licensed product can meet the clinical need, even "off-label", it should be used instead of an unlicensed product. Licensed products available in the UK have been assessed for quality safety and efficacy. If used "off-label" some of this assessment may not apply, but much will still be valid. This is better than the use of an un-assessed, unlicensed product. The fact that the intended use is outside of the licensed indications is therefore not a reason to use an unlicensed product. It should be understood that the prescriber's responsibility and potential liability are increased when prescribing off-label."

*General Medical Council ("GMC")*

58. By s 1 of the Medical Act 1983, the GMC has the function of promoting and maintaining proper professional standards and conduct for members of the medical profession. It publishes guidance for medical practitioners, much of which is contained in "Good Medical Practice" (or "GMP"). The March 2013 version of that document provides guidance on good practice in prescribing and managing medicines and devices. It states that doctors should take account of the clinical guidelines published by NICE as well as other bodies (paragraph 11) and that doctors should reach agreement with the patient on the proposed treatment, explaining benefits, risks and burdens (paragraph 24). Under the heading "Prescribing unlicensed medicines", GMP provides:

> "68 You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient.
>
> 69 Prescribing unlicensed medicines may be necessary where:
>
> a There is no suitably licensed medicine that will meet the patient's need. Examples include (but are not limited to), for example, where:
>
> i there is no licensed medicine applicable to the particular patient. For example, if the patient is a child and a medicine licensed only for adult patients would meet the needs of the child; or

ii a medicine licensed to treat a condition or symptom would nonetheless not meet the specific assessed needs of the particular child patient, but a medicine licensed for the same condition or symptom in adults would do so; or

iii the dosage specified for a licensed medicine would not meet the patient's need; or

iv the patient needs a medicine in a formulation that is not specified in an applicable licence.

b Or where a suitably licensed medicine that would meet the patient's need is not available. This may arise where, for example, there is a temporary shortage in supply; or

c The prescribing forms part of a properly approved research project.

70 When prescribing an unlicensed medicine you must:

a be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy

b take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so

c make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine."

59. In a different document entitled "Leadership and management for all doctors" published by the GMC in January 2012, with effect from 12 March 2012, the GMC advised that the terms "must" and "should" meant different things:

- "'You must' is used for an overriding duty or principle.
- 'You should' is used when we are providing an explanation of how you will meet the overriding duty.
- 'You should' is also used where the duty or principle will not apply in all situations or circumstances, or where there

> are factors outside your control that affect whether or how you can follow this guidance."

60. It also stated that the primary duty of all doctors is for the care and safety of patients, and that "*Whatever their role, doctors must do the following… (g) use resources efficiently for the benefit of patients and the public".* This criterion was further explained under the heading "allocating resources" as follows:

> "84 All doctors must make the care of patients their first concern. However, the treatment options that can be offered to patients may be affected by limits on resources.
>
> **All doctors**
>
> 85 If you make decisions about access to treatments on a case by case basis, without referring to agreed policy or guidelines, you risk introducing elements of unfair discrimination or may fail to consider properly the patient's other legal rights. When making decisions about using resources, you must do the following.
>
> a Provide the best service possible within the resources available taking account of your responsibilities towards your patients and the wider population.
>
> b Be familiar with any local and national policies that set out agreed criteria for access to a particular treatment.
>
> c Make sure that decisions about setting priorities that affect patients are fair and based on clinical need and the likely effectiveness of treatments, and are not based on factors that may introduce discriminatory access to care.
>
> d Be open and honest with patients and the rest of the healthcare team about the decision-making process and the criteria for setting priorities in individual cases.
>
> 86 You should involve colleagues, including other healthcare professionals, in discussions about how to allocate wider resources. If issues or disputes about allocating resources arise, you should try to sort them out by discussing options with, for example, patients, the healthcare team, other colleagues (including other health and social care professionals) and managers. You should be open and honest with patients when

> resource constraints may affect the treatment options available."

61. The GMC thus recognises that there are duties on doctors to consider resources when considering treatment options for patients.

62. This is further illustrated by the guidance issued by the GMC in January 2018 in response to NICE guideline NG 82. That response states as follows:

> "The **guidance** (https://www.nice.org.uk/guidance/NG82) clarifies that there are no clinically significant differences in the effectiveness and safety of anti-VEGF medications that are licensed for treating AMD and those that are not licensed, such as Avastin. Doctors have expressed concerns that prescribing the licensed versions costs significantly more than the unlicensed version, Avastin.
>
> In light of NICE's new guidance our Chief Executive, Charlie Massey, has clarified what doctors need to consider when prescribing Avastin for the treatment of AMD.
>
> Charlie Massey, Chief Executive of the General Medical Council said:
>
> 'In an ideal world a licensing solution for using Avastin would be found as the rigours of the licensing regime provide important assurances of patient safety. However, in the absence of this and given the clinical support for using Avastin, including from the Royal College of Ophthalmologists, we want to reassure doctors that this prescribing decision alone would not raise fitness to practise concerns, providing doctors are applying the broader principles of our guidance.
>
> 'We expect doctors to make good use of the resources available to them and sympathise with the concerns of ophthalmologists making decisions between using a cheaper product outside the terms of its license or a more expensive licensed alternative. We cannot of course give specific clinical or legal advice. But we can say that where doctors are working in partnership with patients, following clinical guidance and making prescribing decisions in good faith on the basis of evidence and experience, the use of Avastin would not cause us any concerns.'
>
> **GMC prescribing guidance**
>
> Our prescribing guidance states that doctors should usually prescribe licensed medicines in accordance with the terms of their licence. The use of the words 'should' and 'usually' are significant and indicate that we expect doctors to use their judgment to apply the principles in the guidance to the specific situations they face. We say that when prescribing an

> unlicensed medicine or using a product 'off-label' (beyond the terms of its license) doctors must be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy. We are also clear that doctors 'must give patients (or their parents or carers) sufficient information about the medicines you propose to prescribe to allow them to make an informed decision.'"

63. I shall return to the GMC's guidance later in this judgment.

*General Pharmaceutical Council ("GPC")*

64. The GPC is the regulator for pharmacists, pharmacy technicians and registered pharmacies in England, Scotland and Wales. (It is not the regulator for hospital pharmacies, which are separately regulated by the Care Quality Commission, or CQC.)

65. In May 2014 the GPC issued guidance for registered pharmacies preparing unlicensed medicines. It states:

> "In general, when a prescriber issues a prescription they will prescribe a medicine that is licensed and indicated for the condition to be treated. European and UK law sets out the circumstances under which prescribers can prescribe an unlicensed medicine for supply to a patient. You can find more information on the prescribing of an unlicensed medicine by reading the General Medical Council's (GMC's) *Good practice in prescribing and managing medicines and devices* on their website.
>
> […]
>
> A patient has every right to expect that when an unlicensed medicine is prepared by, or under the supervision of, a pharmacist in a registered pharmacy, it is of an equivalent quality to any licensed medicine they will receive (such as those produced by a regulated and licensed manufacturer). As certain high-profile past cases have shown, preparing an unlicensed medicine in a pharmacy is an activity that can pose a significant risk to patients and have potentially serious consequences when risks and processes are not managed properly.
>
> When a patient is supplied with an unlicensed medicine, it is important that the unlicensed medicine is safe and appropriate. Pharmacists making supplies must also consider their individual professional standards and their responsibilities to the patient. There is also a general legal duty that all medicines supplied to patients are of the nature and quality requested or prescribed."

*Royal College of Ophthalmologists ("RCO")*

66. I have already referred to the statement issued by the RCO on 15 December 2014 to the effect that Avastin and Lucentis were equally effective, but noting that Lucentis was significantly more expensive. It stated that: *"... in view of the evidence that is now available* [the RCO] *would be supportive of both drugs being made available in the UK".*

## LAW

### EU Law – the Treaties

#### *TEU*

67. Article 4 of the TEU provides, so far as is relevant, as follows:

> "1. In accordance with Article 5, competences not conferred upon the Union in the Treaties remain with the Member States.
>
> …
> 3. Pursuant to the principle of sincere cooperation, the Union and the Member States shall, in full mutual respect, assist each other in carrying out tasks which flow from the Treaties."

68. Art 5 provides, so far as relevant:

> "2. Under the principle of conferral, the Union shall act only within the limits of the competences conferred upon it by the Member States in the Treaties to attain the objectives set out therein. Competences not conferred upon the Union in the Treaties remain with the Member States."

#### *TFEU*

69. The Treaty on the Functioning of the European Union ("TFEU") provides, so far as is relevant, as follows, at Article 2:

> "5. In certain areas and under the conditions laid down in the Treaties, the Union shall have competence to carry out actions to support, coordinate or supplement the actions of the Member States, without thereby superseding their competence in these areas."

70. Art 4.2 provides:

> "2. Shared competence between the Union and the Member States applies in the following principal areas:
>
> […]
>
> (k) common safety concerns in public health matters, for the aspects defined in this Treaty."

71. Article 6 provides:

> "The Union shall have competence to carry out actions to support, coordinate or supplement the actions of the Member States. The areas of such action shall, at European level, be:
>
> (a) protection and improvement of human health; …"

72. Art 168.1 provides:

> "1. A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities."

73. Article 168.7 provides:

> "Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care. The responsibilities of the Member States shall include the management of health services and medical care and the allocation of the resources assigned to them. The measures referred to in paragraph 4(a) shall not affect national provisions on the donation or medical use of organs and blood."

**EU law - Directive 2001/83/EC (the "Directive")**

74. The recitals to the Directive (which is also commonly referred to as the Medicines Directive) record that the aim of "any rules governing the production, distribution and use of medicinal products" must be to safeguard public health (recital 3), that the conditions governing the supply of medicinal products to the public should be harmonised (recital 29), that it is appropriate "as an initial step" to harmonise the basic principles applicable to the classification for the supply of medicinal products in the Community (recital 32), but that the provisions dealing with the classification of medicinal products for the purpose of supply should not infringe the national social security arrangements for reimbursement or payment for medicinal products on prescription (recital 33); that it is necessary to exercise control over the whole chain of distribution of medicinal products from their manufacture or import into the Community through to their supply to the public to guarantee that such products are stored, transported and handled in suitable conditions (recital 35), and that consistent pharmaco-vigilance systems should be in place for authorised medical products and holders of marketing authorisations should be proactively responsible for pharmaco-vigilance of those products (recitals 57 and 58).

75. Articles 2 to 5 appear under Title II of the Directive, which is headed "Scope". Article 2 provides as follows:

> "1. This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process."

76. Article 4.3 provides as follows:

> "The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of the national health insurance schemes, or on the basis of health, economic and social conditions."

77. Within this Title, there are two derogating provisions, which, in accordance with the standard approach to the interpretation of derogating provisions, are to be interpreted strictly (see Case C-185/10 *Commission v Poland* EU:C:2012:181 at [31]).

78. The first derogation is Article 3 which provides, so far as is relevant, as follows:

> "This Directive shall not apply to:
>
> 1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).
>
> 2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula)."

79. This is known as the "compounding exception". There are two limbs to the compounding exception, the first exempting supplies prepared in a pharmacy in accordance with a medical prescription for an individual patient (known as the magistral formula), the second exempting supplies prepared in a pharmacy in accordance with the prescriptions of a pharmacopeia and intended to be supplied directly to the patients served by the pharmacy in question (known as the officinal formula).

80. In Case C-544/13 and C/545/13 *Abcur AB v Apoteket Farmaci AB and another* EU:C:2015:481 the CJEU clarified the requirements of Article 3. The Court emphasised the narrowness of those exemptions ([54]). The Court held that the question whether an exemption applied depended on the relevant set of conditions in relation to each exemption being met ([58]), noting that those conditions were cumulative in relation to each exemption ([59]). The conditions for the first limb (magistral formula) were stated to be as follows:

    i) There must be a prior medical prescription, issued by a qualified professional ([60]).

    ii) That prescription must be for an individual patient, who must be identified in advance ([61]).

    iii) The medicine must be produced specifically for that patient, after the prescription in that patient's name has been issued ([61] and [64]). That means that Article 3 cannot apply to a "subscription" supply system where the drug is

> delivered to non-hospital pharmacies where the product is supplied in advance to meet likely need ([63]-[64]).

81. The conditions for the second limb (officinal formula) were set out at [66], including that the medicine must be prepared in accordance with the prescriptions of a pharmacopeia. That limb is not in issue in this case, and I need say no more about it.

82. The Court said it was for the referring court to ascertain if the conditions were met ([65] and [70]). The Court indicated that the preparation of the particular drug in issue, Noradrenalin APL, could not come within Article 3 because it was prepared on the basis of orders placed before any particular patient had been identified, and not for an individual patient identified in advance ([65]).

83. The second derogation is at Article 5 which provides, so far as is relevant, as follows:

> "1. A Member State may, in accordance with the legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility."

84. This is known as the "named patient exception". The Defendants do not suggest that Article 5 has any relevance to the facts of this case or the way in which the Policy might be met by the NHS Trusts. But Article 5 is discussed in some of the cases, in particular *Commission v Poland*, where the Court confirmed that financial considerations cannot in themselves be used to justify a "special" medicine within Article 5, and further that Article 5 cannot be used to prescribe an unlicensed medicine if a licensed alternative is available ([36]-[38]).

85. The next title, Title III, is headed "Placing on the Market". It starts with Article 6 which provides as follows:

> "1. No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive […]."

86. In order to obtain a marketing authorisation, the manufacturer must provide an extensive dossier of material to the relevant body. The Directive only applies directly to applications for a marketing authorisation made to the competent authority of the Member State (in the UK, that is the MHRA). However, in specified cases, an application can or must be made to the European Medicines Agency ("EMA") via the "centralised procedure". The centralised procedure is governed by Regulation (EC) 726/2004. The EMA will consider the application dossier and make a recommendation to the Commission as to whether a marketing authorisation should be granted. When operating the centralised procedure, the EMA is required to apply the criteria set out in Article 8 of the Directive in order to assess and determine whether to recommend that a particular product should be granted a marketing authorisation.

87. Certain products may only be authorised under the centralised procedure, including products derived from biotechnology (known as "biological medicines"). Avastin, Lucentis and Eylea fall into that category. The marketing authorisation for each of them was issued by the commission on recommendation from the EMA. The EMA has an ongoing role in supervising the phamacovigilance requirements in relation to products which benefit from a marketing authorisation issued by the Commission on recommendation from the EMA.

88. Where a product has been granted a marketing authorisation, a separate marketing authorisation or a variation of the existing marketing authorisation may be required, pursuant to the second paragraph of Article 6(1) of the Directive:

> "When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1)"

89. Commission Regulation (EC) 1234/2008 governs the variation of marketing authorisations (it is known as the "Variation Regulation"). It classifies variations into two categories. Some more fundamental changes are extensions which must be evaluated in accordance with the same procedure as the initial marketing authorisation to which they relate (see Article 19 of the Variation Regulation). Other changes are variations which can be minor or major (see Article 2(2) and 2(3) of the Regulation).

90. Title IV of the Directive is headed "Manufacture and Importation", and commences with Article 40, which provides as follows:

> 1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required notwithstanding that the medicinal products manufactured are intended for export.
>
> 2. The authorization referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.
>
> However, such authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.

91. The requirement for a manufacturing authorisation is separate from the requirement for a marketing authorisation. This case is concerned with the latter, but some of the cases refer to both types of authorisation.

## Domestic Law

92. The legislation is contained in s.10 of the Medicines Act 1968 and the Human Medicines Regulations 2012 (2012/1916).

93. Section 10 of the 1968 Act is headed "Exemptions for Pharmacists" and contains a number of exemptions for things done in a registered pharmacy, a hospital or a care home service or a health centre. Sections 10(1) and 10(3) include exemptions for medicines prepared in accordance with a prescription by a practitioner or a specification.

94. As to the regulations, regulation 17 is headed "Manufacturing of medicinal products" and provides:

> "(1) A person may not except in accordance with a licence (a "manufacturer's licence") -
>
> (a) manufacture, assemble or import from a state other than an EEA State any medicinal product; or
>
> (b) possess a medicinal product for the purpose of any activity in sub-paragraph (a).
>
> …"

95. Regulation 46 is headed "Requirement for authorisation" and provides as follows:

> "(1) A person may not sell or supply, or offer to sell or supply, an unauthorised medicinal product.
>
> (2) A person may not sell or supply, or offer to sell or supply, a medicinal product otherwise than in accordance with the terms of—
>
> (a) a marketing authorisation;
>
> …
>
> (3) A person may not possess an unauthorised medicinal product if the person knows or has reasonable cause to believe that the product is intended to be sold or supplied to another person within the European Economic Area.
>
> (4) A person may not in the circumstances mentioned in paragraph (5)—
>
> (a) manufacture or assemble a medicinal product; or
>
> (b) procure the sale, supply, manufacture or assembly of a medicinal product.

> (5) Those circumstances are that the person knows or has reasonable cause to believe that the medicinal product has been or is intended to be sold or supplied contrary to paragraph (1).
>
> (6) For the purposes of this regulation a medicinal product is unauthorised if none of the following is in force for the product -
>
> (a) a marketing authorisation;
>
> …
>
> "

96. By Regulation 47, a breach of regulation 46 is a criminal offence.

97. Part 10 of the Regulations contains exceptions to the requirement for marketing authorisations. Regulation 167 is headed "Supply to fulfil special patient needs" and contains an exception to Regulation 46 in relation to a "special medicinal product" if certain conditions are met.

98. It is not easy to match up the domestic legislation with the Directive (possibly because the Act predates the Directive and has required amendment in light of it). Mr de la Mare argues (correctly, in my view) that any domestic provisions which are designed to implement the Directive must be read in the light of and construed consistently – so far as is possible – with the Directive, under the *Marleasing* principle. It is my understanding that, broadly speaking, the key provisions of the Directive find expression in the domestic law in the following way: Article 6 is implemented by Regulation 46 of the 2012 Regulations; Article 3 is implemented by s 10(1) and (3) of the 1968 Act; Article 5 is implemented by Regulation 167 and Article 40 is implemented by Regulation 17 of the 2012 Regulations.

**The boundary between EU law and domestic law**

99. It is important to identify where the line is drawn between the EU harmonised regime resulting from powers conferred by Member States on the EU (cf Article 5 of the TEU), which is within the competence of the EU; and the area of competence reserved to Member States in relation to health policy, the organisation and delivery of health services and medical care which is reserved to Member States (expressly recognised by Article 168(7) of theTFEU).

100. That boundary is illustrated by a number of judgments of the CJEU (or its predecessor, the ECJ), where the Court has considered the lawfulness of domestic healthcare measures aimed at saving cost. The first is Case 238/82 *Duphar BV v Netherlands* [1985] 1 CMLR 256, where the Court upheld the Dutch authority's right to refuse to reimburse the cost of certain drugs, on the basis that the domestic measure related to the consumption of medicines and was intended to promote the financial stability of the public healthcare scheme (see [16]). The Court recognised that the measure might affect the market and might even result in certain drugs being eliminated from the domestic market altogether (see [18] and [19]) but held that the measure was lawful.

101. The second case is Joined Cases C-352/07 to C-356/07, C-365/07 to C-367/07 and C-400/07 *Menarini Industrie Farmaceutiche Riunite Srl and Others v Ministero della Salute and Agenzia Italiana del Farmaco (AIFA)* [2009] ECR-I 2495 where the Court held that a measure reducing the price for medicines to be paid by the Italian national health service was lawful, being a provision "*intended to govern the consumption of pharmaceutical products in order to promote the financial stability of their health-care insurance schemes*" (; at [19]).

102. In 2010, the Court confirmed in *ABPI* that a national scheme to reward medical practitioners financially for favouring certain named medicines over others, on grounds of cost, was permissible. The particular challenge in that case related to Article 94 of the Directive which prohibits gifts or money being given in order to promote particular products. The Court confirmed that the prohibition in Article 94 did not extend to national public health authorities which are, amongst other things, responsible for defining public health policy priorities and rationalising public expenditure allocated to public health ([32]); it recognised that those public authorities are "*in charge of evaluating the therapeutic value of the medicinal products which they authorise to be marketed"* ([34]); it noted that Article 168(7) TFEU expressly recognises the power of Member States to organise their social security systems and to adopt measures intended to govern the consumption of pharmaceutical products in order to promote the financial stability of their domestic healthcare systems ([36]). The Court stated:

> "35. ... it is permissible for those authorities, in the exercise of the responsibilities which they assume, to determine, on the basis of evaluations of the therapeutic qualities of medicinal products by reference to their cost for the public budget, whether, in order to treat certain conditions, certain medicinal products containing a given active substance are, from the point of view of public finances, preferable to other medicinal products containing a different active substance, but falling within the same therapeutic class."

103. The Court recognised that a prescribing doctor is required not to prescribe any medicine which is not fitting for the therapeutic treatment of his patient ([40]), but that in any event, doctors practice under the supervision of the public health authorities of the member state, which appoint professional organisations to carry out that role, which is the GMC in the United Kingdom:

> "41 … In performing their task of supervising and monitoring the activity of doctors, the public authorities or delegated professional organisations are authorised to provide doctors with recommendations relating to the prescription of medical products…"

104. AG Jääskinen had also confirmed the independence of the doctor in making prescribing decisions:

> "64. For the sake of clarity, it has to be emphasised that it is not against medical ethics for a doctor to pay attention to the price of a medicinal product when choosing which medicines to prescribe. This may be in the specific interest of the patient concerned in those countries where

> the patient has to bear, either entirely or partly, the cost of the medicine. … It also cannot be ruled out that practitioners take into consideration requirements of social justice and cost efficiency which require that the scarce resources available for health care are used rationally and economically, taking into account the interests of all patients. Medical ethics, however, require that a doctor's discretion in the context of prescribing decisions is not constrained by any inappropriate self-regarding financial motives."

105. The fourth case is Case C-185/10 *Commission v Poland.* In that case, the Commission brought infraction proceedings against Poland in relation to a national law which permitted medicinal products to be placed on the Polish market without the need to obtain a marketing authorisation. The Court held that this was a breach of Article 6: see [26] and [27]. There was no question of Article 5 applying because that exception only applied in exceptional cases (see [32]) where the specific needs of the patient required it (see [33] and [34]); financial considerations alone could not justify reliance on Article 5(1) (see [38] and [48]). Poland's argument that this was a measure aimed at ensuring the financial stability of the national social security system was rejected (at [46]), with the Court holding that Member States must still comply with EU law when they exercise their power to organise their social security systems and to adopt cost-saving measures (see [47]).

106. My reading of this case is as follows: the domestic measure adopted by Poland was aimed at reducing costs by permitting unlicensed and cheaper drugs to be imported. The problem was that the domestic measure simply swept away the requirement for a marketing authorisation for these imports, with the consequence that unlicensed medicines were being placed "on the market". This was directly contrary to Article 6 of the Directive. The measure could not be saved by Article 5 because it was plainly beyond the scope of that narrow derogation. The measure was unlawful.

107. I derive the following propositions from these four cases:

i) Member States are permitted to adopt measures which are aimed at saving costs, in order to ensure the financial stability of their domestic healthcare system (*Duphar, Menarini*).

ii) But there are limits on what a Member State can do in the pursuit of saving costs, and Member States must abide by EU law in devising cost-saving measures (*Commission v Poland*).

iii) When medicines are put onto the market, the harmonised EU regime applies, and those medicines must have a marketing authorisation or come within one of the derogations within the Directive; Member States may not therefore introduce a national measure which abrogates the requirement for a marketing authorisation (*Commission v Poland*).

iv) But as long as the provisions of the Directive are not breached:

a) the domestic authorities are free to choose which drugs they wish to purchase or offer to patients or reimburse on behalf of patients. In

other words, consumption decisions are for the Member States (*Duphar*, *Menarini*).

b) The Member States remain free to make consumption decisions even if, in consequence of their dominant buying power, those decisions have an influence on the market and affect the availability of drugs on that market (*Duphar*).

v) The cost of medicines can properly be taken into account by the national authorities of a Member State in making recommendations about the clinical effectiveness of particular drugs, and by medical practitioners at the point of prescribing a particular treatment. These are decisions relating to consumption, within the competence of the national authorities of the Member State (*ABPI*).

vi) It is within the competence of Member States, and part of the role of national public health authorities, to evaluate the therapeutic qualities of medicines by reference to cost, amongst other factors (*ABPI*).

108. In February 2017, a report entitled "Study on off-label use of medicinal products in the European Union" was published. It was published in the name of the European Union, but subject to a disclaimer that the views belonged to the authors and not necessarily to the Commission. I shall refer to some of its contents so far as the use of Avastin for ophthalmic use is concerned later in this judgment. Its authors describe the legal framework in the following way:

> "**The legal framework**
>
> It is important to distinguish the regulation of medicinal products from their use in medical practice.
>
> *Regulation of medicinal products*
>
> The EU established legislation to harmonise national legislation in order to safeguard public health and to achieve the goal of a single market for medicinal products. The requirement of a marketing authorisation is a general rule in the legal framework of medicinal products. According to article 6(1) of Directive 2001/83/EC, it is in principle prohibited to market medicinal products without a marketing authorisation. The decision to grant or refuse a marketing authorisation is based on an assessment of the quality, efficacy and safety of the medicinal product and a benefit/risk assessment performed by EMA via its Scientific Committees and by the national competent authorities.
>
> *Use of medicinal products in medical practice*
>
> EU legislation does not regulate the way medicinal products are ultimately used in medical practice. The prescribing of a medicinal product, on-label or off-label, is a decision taken

> within the relationship between a patient and his or her treating healthcare professional (HCP). The way Member States organise their healthcare system and the way HCPs conduct their practice is not a topic that falls within the remit of the EU. The EU has limited competence in the field of public health; the ultimate responsibility for the definition of health policy and the delivery of health services and medical care lies with the Member States (Article 168 (7) TFEU). …

109. This is an accurate and authoritative summary of the legal position. I believe it to be consistent with my propositions drawn from the relevant case law.

**Cases before the CJEU concerning intravitreal use of Avastin**

110. The CJEU has considered the issue of Avastin being used outside its marketing authorisation for the treatment of ocular disease on two occasions. There is a third case raising that issue currently pending before the CJEU.

*Apozyt*

111. The first of those cases is Case C-535/11 *Novartis Pharma GmbH v Apozyt GmbH* EU:C:2013:226. This was a reference to the CJEU by the Landgericht Hamburg. The Court set out the background facts at [18]-[28]. The Court recorded that "*as in other Member States, Avastin continues to be used in ophthalmology because it costs substantially less than Lucentis*" (at [22]). (The Court did not refer to Eylea, the marketing authorisation for which post-dated the reference.)

112. Apozyt prepared syringes of Lucentis and Avastin for intravitreal use:

> "23. Apozyt prepares, using the content of the medicinal products Lucentis and Avastin, syringes which contain only the dose necessary for an injection on the basis of the dose prescribed by a doctor. The prepared syringes are filled in a sterile environment in a production unit with an isolation chamber. The pre-filled syringes are dispatched and delivered to the pharmacy which has ordered them. According to Apozyt, pharmacies only place orders when patients produce prescriptions to this effect. The decanting into the syringes carried out in that way allows the content of the vials of Lucentis and Avastin to be used for a number of injections, so that the final price of an injection is considerably lower than the price that would be paid for an injection using solely the medicinal products as they are marketed."

113. Novartis sought an order prohibiting Apozyt from conducting this activity, arguing that Apozyt required a marketing authorisation which it did not have, so that its activity was unlawful. The particular debate before the referring Court was whether Apozyt's activities resulted in products being "developed" for the purposes of Regulation No 726/2004, but the Court recast that question:

> "33. By its question, the referring court asks, in essence, whether activities such as those at main issue in the main proceedings require a marketing authorisation under Article 3(1) of Regulation No 726/2004 and, if not, whether those activities remain subject to Directive 2001/83."

Article 3(1) of Regulation 726/2004 is analogous in effect to Article 6(1) of the Directive. The question was whether Apozyt required a marketing authorisation.

114. The answer given by the Court was as follows:

> "41. When it prepares ready-to-use syringes in order to respond to orders placed by pharmacies in which patients have handed in prescriptions for such syringes, a company such as Apozyt does not use any of the biotechnical processes listed in point 1 of the Annex to the Regulation No 726/2004; nor, moreover, does it supply anything to those pharmacies in advance, either directly or indirectly through wholesalers. Furthermore, it is apparent from the order for reference, and in particular from the wording of the question raised, first, that the Landgericht Hamburg proceeds on the basis that the composition of the medicinal product is not modified. Second, the content of the syringes that have been pre-filled in that way is administered to the patient by the prescribing doctor who has thus himself decided to treat his patient using such syringes.
>
> 42. In such circumstances, provided that the referring court does in fact find that the processes in question do not result in any modification of the medicinal product and that they are carried out solely on the basis of individual prescriptions making provision for them, there is no ground for considering that the activity thus carried out can be equated with a new placing on the market of a medicinal product included in point 1 of the Annex to Regulation No 726/2004; accordingly, the company concerned is, in that respect, not subject to the obligation to hold a marketing authorisation granted by the Community pursuant to Article 3(1) of the regulation."

115. The Court concluded that Apozyt's activity occurred "after the medicinal products at issue in the main proceedings have been placed on the market" [43] and then explained, in the same paragraph:

> "[…] the drawing off of liquid medicinal products from the original vials, and the transfer into ready-to-use syringes of the portions so drawn off, without any modification of those products, is in reality analogous to actions which, in the absence of Apozyt's activities, could otherwise be, or have been, carried out, under their responsibility, by doctors prescribing the treatment or by pharmacies themselves in their dispensaries, or else in hospitals."

116. The Court did not consider such an activity required a marketing authorisation (see [42] again), a conclusion underlined by the opening words of [44]:

> "However, … even if the service provided by … Apozyt … does not in itself amount to a placing on the market requiring a marketing authorisation…".

117. There was still a question as to whether that activity required a manufacturing authorisation pursuant to Article 40 of the Directive ([44]). The German Government argued that the supplies fell outside the Directive relying on Article 5 [45]. The Court rejected that argument so far as compounded Lucentis was concerned ([47]) but accepted it, in principle and subject to meeting various requirements imposed by Article 5, for compounded Avastin ([48]). So far as Lucentis was concerned ([50]), the question then remained whether a manufacturing licence was required, which the Court resolved by reference to 40(2):

> "52. … such authorisation is not required for, inter alia, dividing up and changes in packaging where those processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes."

It was for the referring Court to ascertain whether those conditions were met [53].

118. Two important points emerge from that case. First, the Court did not consider that the process of dividing up the medicines into smaller doses amounted to a "modification of the medicinal product" ([41] and [42]). It followed that there was no "new placing" of either product when supplied and no new marketing authorisation was required ([42]).

119. Secondly, the Court referred to "individual prescriptions" at [42] without stating whether the existence of prescriptions was necessary to its conclusion that the product did not need a marketing authorisation. On this point, the parties offered starkly divergent submissions. The Claimants argued that the gateway to off-label use cannot be wider than the derogations under the Directive, if the coherence of the scheme overall is to be preserved; and that the Court was here confirming that the Article 5 conditions (which include a requirement for a prescription) apply indirectly or by analogy to off-label use. The Defendants disagreed with that analysis, arguing that the presence of individual prescriptions in this case formed part of the background facts and was not important to the Court's conclusion that no marketing authorisation was required, that conclusion being predicated on the Court's acceptance that the medicine was not altered and thus there was no "new placing" on the market (see, again, [42]).

120. Having considered the issue at some length, I conclude that the Defendants are correct, and the analysis in [42] is not dependent on the existence of individual prescriptions. I reach that conclusion for the following reasons:

i) The issue being addressed at [42] is whether the medicines have been modified in such a way that a fresh marketing authorisation is required. The existence

(or not) of a prescription is not logically relevant to the question whether the product has been modified.

ii) There is no stated requirement within the Directive for a prescription to be in place before medicines can be supplied for off-label use.

iii) The CJEU does not suggest at [42] or elsewhere in its judgment that it is intending to read such a condition into the anticipated off-label use of Avastin. If it had so intended, then it would have said so clearly, not least because that would be a matter of considerable significance with wide-reaching effects.

iv) Medicines which are intended for off-label use will, in many circumstances, be requested on prescription, simply because they are not available "off the shelf" for use in the manner intended. This is not a universal or defining condition of off-label use. It is just an incident of fact.

v) In *Apozyt*, the German Government relied on Article 5 (and its domestic implementation into German law). Article 5 requires, in terms, that the medicine is supplied on prescription (ie in response to the "specification of an authorised health-care professional"). That provides a satisfactory explanation for the fact that individual prescriptions were provided in this case.

121. Some support for the Defendants' analysis can now be derived from the AGO in *AIFA* where he suggests at [61] that the Court's approach in *Apozyt* was underpinned by the idea that the medicinal substance was not itself altered, and that the changes to the dosage, packaging and method of administering Avastin (as he says, for off-label use) do not result in the creation of a "distinct medicinal product"; and at [67] that if, by contrast, the medicine had been modified, then it would be considered "a new medicinal product" and Article 3 would have to be considered. He appeared to welcome this analysis because it meant that the Directive, including its pharmacovigilance requirements, continued to apply and control the entire chain of distribution, from manufacture to delivery to the public, was retained (see [55] and [63]) (by contrast with any analysis which took the supply outside the Directive altogether, by derogation or otherwise).

122. I conclude that there is little in *Apozyt* to support the Claimants' case. It is not, in and of itself, determinative against the Claimants because it was based on different facts. But it does call into serious question the Claimants' basic propositions that (i) compounded bevacizumab prepared for treating wet AMD patients is a new product which requires a marketing authorisation (as opposed to an off-label use of a product which already has a marketing authorisation); and that (ii) any form of mass supply of compounded bevacizumab necessarily falls outside the scope of the derogations in the Directive.

*AGCM*

123. The CJEU (Grand Chamber) has considered the use of Avastin to treat wet AMD in a recent competition case: C-179/16 *Hoffman-La Roche v Autorita Garante Della Concorrenza E Del Mercato* [2018] 4 CMLR 13 (I shall refer to this case as "*AGCM"*). The Italian competition authority fined Roche and Novartis for engaging in a cartel contrary to Article 101(1) TFEU by agreeing to try to manipulate the

perception of the risks of using Avastin in the field of ophthalmology in order to create public concern and so shift demand towards Lucentis (the background facts are at [32] and [33] of the Judgment). Roche and Novartis appealed the fine, and the Italian Consiglio di Stato referred questions to the CJEU asking, in essence, whether Avastin could be seen as a relevant competitor to Lucentis, given that the marketing authorisation for Avastin did not extend to ophthalmic use.

124. The Court confirmed that pharmaceutical products which are manufactured or sold illegally cannot be regarded as substitutable for or interchangeable with legally manufactured or sold equivalents ([52]), and that it would be unlawful to place a product on the market without a marketing authorisation ([53]), but in this case Avastin did have a marketing authorisation albeit for the treatment of cancer ([54]). The Court said this:

> "55 The dispute in the main proceedings concerns the use of Avastin for the treatment of eye diseases which were not covered by that MA. The referring court thus asks, in essence, whether the AGCM could include that off-label use of Avastin in the relevant market, even in the event that it failed to comply with the requirements laid down by the EU rules on pharmaceutical products. Indeed, Roche argues on that point that a significant proportion, the majority even, of the Avastin intended for off-label use in Italy was serially repackaged without manufacturing authorisation and was sold to healthcare providers in advance, before the submission of individual prescriptions.
>
> 56 In that respect, it should be noted that Directive 2001/83 does not prohibit the use of medicinal products for therapeutic indications not covered by their MA. Article 5(1) of Directive 2001/83 in fact provides that a Member State may, in order to fulfil special needs, exclude from the provisions of that directive medicinal products supplied in response to a bona fide unsolicited order, prepared in accordance with the specifications of an authorised healthcare professional for use by an individual patient under his direct personal responsibility.
>
> 57 On that point, the Court has held that it is apparent from all conditions set out in that provision, read in the light of the fundamental objectives of that directive, and in particular the objective of seeking to safeguard public health, that the exception provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market (judgments of 29 March 2012, *European Commission v Poland (C-185/10)* at [36], and of 16 July 2015, *Abcur AB v Apoteket Farmaci (C-544/13 and C-545/13)* at [56]).

> 58 In addition, the EU rules on pharmaceutical matters govern the condition under which a medicinal product such as Avastin may be repackaged so as to allow its intravitral injection. Thus, according to art.40 of Directive 2001/83, the manufacture of a medicinal product is subject to authorisation, except for repackaging carried out for retail supply by healthcare professionals (judgment of 28 June 2012, *Criminal Proceedings against Caronna (C-7/11)* at [35]). The repackaging of Avastin with a view to its use in ophthalmology therefore requires an authorisation, as a rule, unless it is carried out solely for the purposes of retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States (judgment of 11 April 2013, *Novartis Pharma GmbH v Apozyt GmbH (C-535/11)* at [52]).
>
> 59 It follows that the EU rules on pharmaceutical products prohibit neither the off-label prescription of a medicinal product nor its repackaging for such use but do require that they comply with the conditions laid down in those rules.
>
> 60 Furthermore, as the Advocate General pointed out in point 88 of his Opinion, it is not for the national competition authorities to verify compliance with EU law of the conditions under which a medicinal product such as Avastin is prescribed by doctors, on the demand side, and repackaged, on the supply side, with a view to its off-label use. Such verification can be carried out comprehensively only by the authorities with jurisdiction to ensure compliance with the rules governing pharmaceutical matters, or by the national courts."

125. The Court rejected Roche's submission that the whole supply chain, involving the repackaging of Avastin for use in treating wet AMD was unlawful, see [62]: "*There is nothing in the case file to suggest that … any unlawfulness of the conditions under which Avastin was repackaged and prescribed with a view to off-label use…".* The Court held that it was open to AGCM to conclude that Avastin belonged to the same market as Lucentis ([64]).

126. There are a number of important points which emerge from this case. The first is that the Court repeatedly stated that the use of Avastin for the treatment of ocular disease was "off-label" use. This is consistent with the approach taken by the Court in *Apozyt.* (It is, of course, inconsistent with the approach taken by the MHRA in 2011 in the domestic regulatory context, and with the Claimants' case.)

127. As to what "off-label" means, the Advocate General (AG Saugmandsgaard Øe, who subsequently gave the opinion in *AIFA*) said this:

> "AG47 The off-label use of medicinal products is a medical practice which varies in extent depending on the therapeutic field and the Member State concerned. [10] EU law acknowledges this reality and lays down certain provisions, upstream and downstream of off-label use, which restrict the possibilities for

> placing medicinal products intended for such use on the market and impose on MA holders certain pharmacovigilance obligations in relation to off-label use.
>
> AG48 On the other hand, EU law does not govern the prescribing of medicinal products for off-label use. [13] That practice falls within the scope of the therapeutic freedom of medical practitioners, subject to any restrictions imposed on that freedom by the Member States in the exercise of their power to define their health policies. [14] Equally, the decision to approve a medicine used off-label for reimbursement by the social security systems lies, in principle with the Member States. [15]"

Footnote 13 contains a reference to *CTRS.* Footnote 14 contains a reference to Article 167(8) TFEU and to the AGO in *Apozyt.* Footnote 15 contains a reference to Article 4(3) of the Directive, *ABPI* and *Menarini.*

128. Secondly, the Court acknowledged that the Directive does not prohibit the use of medicinal products for therapeutic indications not covered by their marketing authorisation ([56]). It did not suggest that Article 5 should be read in or applied by implication in such cases although the Court did acknowledge that Article 5 provided one route to lawful use outside a marketing authorisation. But if that was so, "in addition" (opening words of [58]) the manufacturing process might well fall within Article 40(2) so that no manufacturing licence was needed; this was to repeat the point made in *Apozyt* at [52]-[53].

129. Thirdly, the Court did not suggest that the use of Avastin for wet AMD patients was in any way unlawful. To the contrary, the Court accepted that Avastin legitimately competed in the same market as Lucentis. Here too, the Court seems to envisage, as it did in *Apozyt*, that there may exist circumstances where the supplier needs neither a marketing nor a manufacturing licence to carry out its business of supplying Avastin on a commercial basis for intravitreal use, in competition with Lucentis.

130. There is little, if anything, in *AGCM* to support the Claimants' challenge.

*AIFA*

131. On 19 January 2017, the Consiglio di Stato in Italy lodged a request for a preliminary ruling in a case brought by Novartis against AIFA, the Italian Medicines Agency. The background was AIFA's wish to reimburse Avastin for ophthalmic use, against resistance to that course by Novartis.

132. On 25 July 2018, after the hearing in this case, AG Saugmandsgaard Øe delivered his opinion in *AIFA* (the "AGO"). I was sent an unofficial translation of the opinion, originally given in French (there is no official translation into English yet available). I received further submissions from the Claimants and the Defendants based on the AGO. The judgment of the full Court is expected at the end of this year, at earliest.

133. The background to the case is this: Novartis challenged AIFA's decision 622/2014 to include Avastin for ophthalmic use on "List 648", a list of those medicines which

AIFA would reimburse from public funds. AIFA also imposed specific conditions on the use of Avastin for ophthalmic use: the process of compounding was permitted to be undertaken only by hospital pharmacies which were subject to supervision by the relevant national authorities, on receipt of a digitised medical prescription in standard form, and the medicine could only be administered at highly specialised designated hospitals. Provision was made for AIFA to monitor the use of Avastin in this way. The pharmacies prepared the medicine in a "serial, repeated manner" not tailored to the individual patient. (For the facts, see [27]- [31] of the AGO.)

134. Novartis argued that this breached EU law by permitting the use of unlicensed medicines even though there were licensed alternatives available ([34]), that Avastin for ophthalmic use was a new medicine which required its own marketing authorisation ([35]), and that AIFA was encroaching on the competency of the EMA which was responsible for pharmacovigilance ([36]). AIFA argued that the preparation was not prepared industrially and was a magistral formula exempted from a marketing authorisation under Article 3, that alternatively Article 5 applied, that in any event this was "off-label" use so that the only issue related to Article 40 and the need for a manufacturing licence but that was resolved by Article 40(2), and that AIFA was not interfering in any way with the competence of the EMA ([37]).

135. The AG rejected Novartis' proposition that AIFA could not reimburse Avastin used for ophthalmic purposes. He said that this was not contrary to EU law, even if such off-label use was encouraged by AIFA ([48]). He went on to consider whether the provision of Avastin for ophthalmic use was within the Directive at all, and concluded that despite the changes to dosage, packaging and method of administration, the product remained the same and in consequence it was not distinct from Avastin ([58]); for that reason, the medicine remained subject to the Directive and to the EMA's role in pharmacovigilance ([61]). Even though the AG accepted that this was off-label use of Avastin, he rejected the proposition that a fresh marketing authorisation was required. Further, he confirmed that this could fall within Article 3 notwithstanding the serial preparation according to a protocol, see [67], [69] and [74]. Moreover, this activity, in the manner envisaged, did not require a manufacturing authorisation ([84]). The AG was unmoved by Novartis' complaint that this activity was being undertaken not just by hospital pharmacies but by "public" pharmacies on a broad scale and without a specific prescription, which Novartis argued was in breach of both EU and Italian law; the AG said that that was a matter for the Italian authorities to sanction, and did not affect the validity of AIFA's decision ([85]-[86]). Article 5 could not avail AIFA because that exemption was only available where there was no licensed alternative available ([98], relying on *Commission v Poland*). Finally, Novartis was wrong to suggest that AIFA could not undertake the monitoring of Avastin used ophthalmically, because the EMA's competence only related to the issuance by the Commission of a marketing authorisation for a medicine; AIFA's monitoring had nothing to do with that function ([104]).

136. In submissions dated 10 August 2018, the Claimants argue that the AGO confirms the necessity of a prescription in order for any supply of Avastin for ophthalmic use to be lawful, and that AIFA imposed specific safeguards to protect patients, which safeguards are not present in the Policy. They further argue that the AG's conclusion that this was off-licence use was confined to the particular facts of the case, which are not replicated here. They rely on his conclusion that Article 5 was not applicable and

note that he did not address the larger arguments advanced by the Claimants under Ground 2.

137. In responding submissions dated 3 September 2018, the Defendants argue that the key message to take from the AGO, if his approach is adopted by the full Court, is that AIFA was acting lawfully in including Avastin for ophthalmic use in its list of reimbursable medicines. Further, they argue that the AGO confirms that doctors have freedom to decide what drugs to prescribe to their patients within the area of national competence. They say that the AGO confirms – as the two previous CJEU cases did - that this is off-label use and not a new medicinal product, that the AGO envisages compounding being undertaken outside the particular hospital where the Avastin is to be used and thereby sanctions supply by one hospital pharmacy to another, that he confirmed that large scale supply in a serial, repeated manner is not inconsistent with Article 3, and confirmed that the EMA did not have exclusive competence in this area. (I received a further round of submissions, but it is not necessary to detail the further points made which were repetitions, anyway.)

138. I agree with the Defendants. The AGO does not favour the Claimants' arguments. There is now a consistent line of CJEU authority, of which this AGO now forms a part, which confirms that the large-scale compounding of Avastin, whether by commercial compounders (*Apozyt*) or hospital pharmacies (*AIFA*), is compatible, at least potentially, with EU law; further, that Avastin for ophthalmic use competes, legitimately, with Lucentis and Eylea which are specifically licensed for that use (*AGCM*). The Claimants' arguments do not sit easily with these conclusions.

## KEY ISSUES

139. In order to resolve this challenge, it is necessary to determine six issues which lie at the heart of the case:

i) Does the EMA have exclusive competence to determine whether Avastin is effective and/or clinically effective for ophthalmic use?

ii) Can treating clinicians lawfully choose Avastin on grounds of cost?

iii) Is Avastin safe for ophthalmic use?

iv) Is there a mature and established market in compounded bevacizumab prepared for ophthalmic use?

v) Is compounded bevacizumab an unlicensed medicine or an off-label use of a licensed medicine?

vi) What is the relevant test by which the lawfulness of the Policy is to be judged, in domestic law?

### i) Exclusive Competence of EMA

140. The Claimants argue that the EMA has exclusive competence to determine the safety, clinical efficacy and quality of medicines available to the public. That means that only the EMA (in this case, given that Avastin is a biological medicine) has competence to determine whether it is safe and clinically effective for ophthalmic use.

(See, for example, at [12], [24], [140.3] of the Claimants' skeleton.) In oral submissions, Ms Stratford contended that the EMA was exclusively competent to determine efficacy of a particular medicine (ie the extent to which an intervention is effective), whereas NICE had competence to determine issues of clinical effectiveness (the extent to which a medicine produces an overall health benefit).

141. The Claimants mount this argument based on their construction of the Directive, and on the asserted paramountcy of the need to protect human health, which they argue will be jeopardised if the mass supply of an unlicensed medicine is permitted.

142. The Defendants submit that this argument is misguided. The EMA does not have exclusive competence in this area. The Defendants' reasons for resisting this central tenet of the Claimants' case are set out at [55]-[57] of the Defendants' skeleton.

143. In short, I agree with the Defendants' case on this point. It is perfectly clear that domestic authorities, specifically (in this case) NICE and the CCGs, have competence to assess whether Avastin is an effective drug in treating wet AMD, to assess its overall clinical effectiveness for that purpose taking account of safety and cost, and to conduct that assessment by comparing it to the other medicines available to treat wet AMD.

144. My reasons for so concluding are as follows:

i) The EMA is established by the Directive and its role is limited by the Directive. The EMA (and its domestic counterpart, the MHRA) have exclusive competence to determine whether to recommend that a medicine should be granted a marketing authorisation for any particular therapeutic purpose for which the manufacturer seeks such an authorisation. That function is integral to the harmonised system in the Directive. When presented with an application for a marketing authorisation, the EMA assesses the efficacy and safety of the medicine for the proposed use, based on the information provided to the EMA by the applicant. The EMA conducts no wider enquiry into the efficacy of that medicine for treating other conditions, or the relative efficacy of that medicine when compared with other medicines which are available for the same use.

ii) Roche, the manufacturer of Avastin, has not asked for a marketing authorisation to extend to ophthalmic use. The decision not to seek a marketing authorisation for ophthalmic use is Roche's to make. But the fact that Roche has not chosen to seek a marketing authorisation for ophthalmic use demonstrates the limits of the EMA's role. The EMA is simply not involved in the wider consideration of Avastin for ophthalmic use; nor could it be, unless and until Roche asks it to be.

iii) The consequence of that is not, as the Claimants seek to argue, that the national healthcare authorities are prohibited from considering the efficacy or safety of Avastin to treat wet AMD. That seems to me to be an absurd proposition. It would give unbounded power to the pharmaceutical companies to decide which medicines to make available for which purposes. That is not what the Directive envisages or provides; and that would be seriously detrimental to the wider public interest in maintaining a cost-effective public

health system. To the contrary, in my judgment, it *is* for the national healthcare authorities – exclusively, in this case - to assess the efficacy, risk and overall clinical effectiveness (including issues of cost and safety) of a medicine like Avastin which is proposed for use outside its marketing authorisation. This is not a unique situation. The domestic authorities find themselves "alone" in the assessment of any medicine which is proposed for use outside of its marketing authorisation. This is commonplace, for example, in paediatric medicine where medicines are often, necessarily, used outside of their marketing authorisation.

iv) The role of the national authorities in assessing clinical effectiveness is recognised in the domestic statutory framework establishing NICE and the CCGs. It is recognised in the domestic case law (the line of authority from *ex p A* onwards, see above), and it is recognised in the case law of the CJEU (the *Duphar* line of authority, *ABPI* in particular). It is fundamental to the operation of a rational and effective public health system.

v) In carrying out that role, the national authorities are entitled to look at all and any evidence available to them in relation to the efficacy, cost and risk associated with the use of that medicine for the therapeutic purpose envisaged. The review is not limited, as the EMA's would be, to the material provided by the manufacturer; nor is the review limited to determining questions of efficacy and safety of that medicine, alone. The national authorities are at liberty to assess the comparative clinical effectiveness (including value for money) of any medicine.

145. In summary, I reject the Claimants' proposition that the national authorities are acting beyond their competence in assessing the clinical effectiveness (including risk and cost) of Avastin for ophthalmic use, relative to Lucentis or Eylea. Such an assessment has in fact been undertaken by NICE in Guideline NG 82. NICE concluded that there were no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments. The Claimants did not suggest that NICE exceeded its statutory powers in comparing the three treatments and reaching that conclusion, rightly.

146. The CCGs were, in my judgment, also entitled to conclude that the three anti-VEGF agents were of equivalent effectiveness and safety. The CCGs were entitled to take cost into account in reaching that conclusion. These actions fall within the area of national competence recognised in the Directive. They do not usurp the role of the EMA.

147. If further support were needed for this conclusion, it is provided by the AGO in *AIFA*: see [102] to [105].

**ii) Taking cost into account at the point of prescribing an unlicensed medicine**

148. The Claimants also argued that a clinician is not permitted to take account of cost at the point of prescribing. This argument was primarily based on paragraphs 68-70 of the GMC's guidance (GMP) to the effect that a doctor could only prescribe an unlicensed medicine where there were "medical reasons" for so doing, and on the basis that it was "necessary to do so to meet the specific needs of the patient"; that,

Mr de la Mare argued, precluded a doctor from selecting a drug on the basis of cost alone.

149. As the oral hearing progressed, the Claimants came to accept in principle that if a clinician had two (or three) licensed drugs of similar effectiveness to choose from, it was permissible for the clinician to take cost into account as the "tie-breaker". In her oral submissions, Miss Stratford seemed to accept that cost could be the tie-breaker whether or not all the options on the table were licensed medicines (she took the point that the three medicines on the table here were not equivalent because Avastin is not as safe as the other options – I shall deal with that below.) So the Claimants' argument, as I understood it, narrowed to a submission that it was impermissible for a clinician to prescribe an unlicensed drug, on grounds of cost, when a licensed alternative was available.

150. Mr Lock argued against this proposition. He said it was unsupported by any authority or by the GMC guidance, on a proper reading. He argued that in any event, even if a clinician was acting contrary to his professional obligations in so prescribing, that did not mean that the Defendants' policy was unlawful.

151. I prefer Mr Lock's submissions on this point. My reasons are as follows:

i) As a matter of construction, paragraph 68 of GMP does not prohibit a clinician from prescribing an unlicensed drug simply because there are licensed alternatives.

a) That paragraph contains guidance indicating in general terms what a doctor "should usually" do. But the guidance, on its face, admits of exceptions.

b) One such exception is expressed in paragraph 68, namely where a doctor considers the prescription of an unlicensed drug to be necessary on medical grounds. But that cannot be taken to be the *only* possible exception to the general rule. There may be other exceptions too, not spelt out in the guidance.

c) Further, the context in which this case arises is very unusual given the extensive material to show that the cheaper but unlicensed alternative (Avastin) is of equivalent clinical effectiveness and safety as the licenced alternatives. This case is far outside the category of "usual" cases at which paragraph 68 is directed.

ii) Paragraphs 69-70 do not preclude the prescription of unlicensed medicines, simply because there is a licensed alternative available. Specifically, paragraph 69 does not contain a comprehensive list. It is just a list of examples of situations where it "may" be necessary to prescribe an unlicensed medicine. Other situations may exist, which are not on the list.

iii) The GMC guidance, considered overall, positively requires treating clinicians to take cost into account as an element of good medical practice. That obligation does not stop simply because an unlicensed drug is under

consideration. Having regard to resources is an enduring requirement, which touches on every decision which a clinician makes.

152. A treating clinician could reasonably be satisfied that three anti-VEGF inhibitors were of equivalent clinical effect and safety in a given case (such a clinician might base his or her view in part at least on the NICE Guideline 82). In those circumstances, the treating clinician would, as a matter of professional conduct, be free to choose whichever medicine he or she considers to be most suitable, taking account of his or her obligations to the patient, and to patients more generally. The latter consideration would include the allocation of resources: cost would and should be taken into account at this point. That conclusion is supported by the GMC announcement dated January 2018.

153. I make two further observations:

i) In my judgment, the Claimants exaggerate the reach of the Directive when they suggest that the Directive precludes a clinician from prescribing an unlicensed medicine, simply because there is a licensed alternative available. Such a submission strays over the line which separates the EU's competence from that which is reserved to Member States: see Article 168(7), and the CJEU cases considered above (see *ABPI* in particular).

ii) Professional misconduct is not the same as unlawfulness. If a clinician were to be in breach of the GMC's guidance by prescribing Avastin for ophthalmic use in any given case, that clinician might have to face disciplinary proceedings brought by his or her professional regulator but would not have broken the law, simply by breaching professional guidance.

**iii) Is Avastin safe for ophthalmic use?**

154. The Claimants' case is largely based on the proposition that Avastin is not safe, or not as safe as either of Lucentis or Eylea, when used for ophthalmic purposes. That proposition finds a home most neatly under Ground 2, on the basis (so it is said) that treating wet AMD patients with Avastin would expose those patients to risk and would thereby undermine the harmonised system which is aimed at protecting patients (Ms Stratford told me that the harmonised system was created in response to the thalidomide tragedy; so, she argued, patient safety lay at the heart of the harmonised system and at the heart of this challenge). The "safety" argument featured in different ways on different occasions, and the Claimants' reliance on it was not limited to Ground 2. I shall address it as a free-standing argument here, and return to it as necessary when I come to the grounds.

155. The Claimants seek to rely on expert evidence from Mr Kelly (consultant ophthalmic surgeon at Bolton Hospitals NHS Foundation Trust) and Professor Winfried Amoaku (Clinical Associate Professor and Reader in Opthalmology and Visual Sciences at the University of Nottingham and Honorary Consultant Ophthalmologist at the Nottingham University Hospital). Both reports raise concerns about the safety of Avastin for ophthalmic use by intravitreal injection. Both reports pre-date NICE Guideline NG 82 but I was not told how either expert responds to NICE's conclusion that Avastin is as safe as Lucentis or Eylea.

156. The points made by Bayer's experts, repeated in submissions by Mr de la Mare, are that Avastin carries risk when used for ophthalmic purposes (by intravitreal injection), for a number of reasons. The main risks are that Avastin has a different molecular size and structure from the two licensed medicines and is not designed for use in the eye, that the compounding process (which involves opening a vial and dividing it into aliquots) raises issues of shelf life and stability which have not been assessed, that the compounding process also carries a risk of contamination if sterile conditions are not maintained, that the repackaging as a result of compounding brings the medicine into contact with different materials which gives rise to a further risk of migration of substances into the medicine, that more injections of Avastin are needed to achieve the same result as either of the licensed alternatives, that a patient given Avastin for wet AMD is subject to greater monitoring requirements which some NHS departments do not have capacity to undertake, and that medicines intended for ophthalmic use are manufactured to a different standard which involves a lower concentration of particulate matter than is permitted for solutions intended for intravenous use (as Avastin is, when used for treating cancer). In addition, the fact that Avastin is not authorised for ophthalmic use means that it is not subject to pharmacovigilance for that use.

157. The Defendants have maintained throughout that it is not for this Court to determine issues of safety, but in order to answer the Claimants' case, they produced an expert report of Professor Andrew Lotery, Professor of Ophthalmology at the University of Southampton. Professor Lotery's report post-dates NICE Guideline NG 82 (although he does not refer to it). Broadly speaking he asserts that Avastin is just as safe as Lucentis and Eylea. He disputes the Claimants' case that ophthalmic use of Avastin involves increased risk: he points to a number of studies which demonstrated similar efficacy, he suggests that the risk of contamination or infection could be mitigated by appropriate oversight of the compounding process, and he thinks that capacity concerns (frequency of injections and monitoring, etc) could be mitigated. He refers to extensive research to support his conclusions.

158. Both Bayer and the Defendants seek permission to rely on expert evidence (although the Defendants' application is responsive only, their primary case being that this Court should not give permission for any expert evidence because it is irrelevant to the issues before the Court).

159. The challenge brought by the Claimants is to the Policy. That Policy was based on the CCGs' Report which concluded that Avastin was of equivalent safety and effectiveness to Lucentis and Eylea. There is no rationality challenge to that Report. I have already dismissed the Claimants' arguments that the EMA has exclusive competence to assess the safety of Avastin for ophthalmic use, accepting that this is an issue which the CCGs are entitled to consider and determine for themselves. I conclude that the issue of safety, and the expert evidence related to it, is simply irrelevant to this claim for judicial review. If the CCGs were not acting irrationally in concluding that Avastin was safe, the Claimants cannot complain that the Policy, which is based on that conclusion, is unlawful because it fails to take account of safety issues. That is a circular argument. It is flawed.

160. Further and in any event, whatever might have been the position in 2017 when the Policy was adopted, the fact is that NICE has now issued Guideline NG 82 which concurs with the CCGs' conclusion that Avastin is as safe as the licensed alternatives.

NICE is the public body with responsibility under the statute for giving advice and guidance and making recommendations about NHS services (Reg 5 of the 2013 Regulations, see above). EU law recognises the role of such domestic authorities (see eg *ABPI*). Thus, NICE plainly possesses the institutional competence and expertise to reach a view on the safety of Avastin. I am not persuaded that I can or should go behind the NICE Guideline. In consequence, NICE Guideline NG 82 settles the issue of safety, in my judgement.

161. I proceed on the basis that Avastin is of equivalent effectiveness and safety to either of Lucentis or Eylea, when used to treat wet AMD by intravitreal injection.

162. I refuse Bayer's application dated 14 February 2018 to rely on expert evidence (and the Defendants' responding application dated 3 April 2018). I do not consider that any expert evidence is reasonably required to resolve these proceedings (cf CPR 35.1).

**iv) Is there a mature and established market for Avastin compounded for ophthalmic use?**

163. The Defendants argue that there is a well-established market in compounded bevacizumab, or CB, for ophthalmic use. The Claimants dispute the existence of a market in CB. The issue is relevant in a number of ways, but primarily forms part of the Defendants' response to the Claimants' challenge in relation to the commercial supply of CB to NHS Trusts (mode 4, to be discussed below).

164. There is evidence from a wide range of sources that CB is widely used in treating ophthalmic disease. The CJEU has acknowledged the widespread practice of using Avastin for wet AMD (see *Apozyt* and *AGCM*). The NICE Guideline NG 82 acknowledges the use of Avastin for treating wet AMD and includes a long list of healthcare providers in the public and private sectors who offer Avastin for ophthalmic use.

165. For the Defendants, Dr Hambleton has submitted evidence of Avastin being used to treat patients with wet AMD within the NHS and in private practice in the UK, for a variety of conditions including wet AMD (witness statement dated 4 December 2017). He refers to the Report by the Decision Support Unit on "Bevacizumab in eye conditions: Issues related to quality, use, efficacy and safety" dated August 2012 (known as the "Sheffield Study"), which researched the extent to which bevacizumab was used in treating eye conditions in the UK; it listed its research results in two tables and summarised the position in this way: "there is substantial use of IVB [intravitreal bevacizumab] across the UK NHS…" but that "there is little use of IVB in NHS patients with AMD, mainly as a result of NICE guidance in favour of alternative therapy. In other disease areas, a substantial use of IVB is reported. Use of IVB is even more widespread in private practice, including in patients with AMD".

166. Dr Hambleton also states that bevacizumab is used to treat wet AMD in other parts of the EU, referring to Ireland, Austria, France and Italy. In that connection, I note that the *AGCM* case originated in Italy, as does the *AIFA* reference.

167. In February 2017, the Commission report was published. It addresses Lucentis and Avastin (at [4.4.3.1]), and says this:

> "Reimbursement of the costs of Lucentis® has continuously been a reason for debate. Roche tried to prevent off-label use of Avastin® by warning about safety issues linked to its off-label use; a direct comparison of the effectiveness of Lucentis® and Avastin® was not undertaken. In the end, public research funds were used to prove that the two medicines were indeed similarly safe and effective for this indication. Based on clinical evidence of Bevacizumab and Ranibizumab being equally effective and safe in the treatment of AMD, it is now well accepted by HCPs in The Netherlands that Avastin® is the medicine of first choice. In Italy, in 2014, the competition watchdog fined Novartis and Roche after concluding that the two companies had agreed to portray the cheaper Avastin® as more dangerous than Lucentis®. Similarly, a Spanish consumer group formally asked the country's antitrust watchdog to investigate claims that Roche and Novartis conspired to keep patients from using a cheaper macular degeneration drug in favour of their more expensive Lucentis® product. France and the EU also launched separate investigations to find out whether Roche and Novartis indeed colluded to protect sales of Lucentis®. In June 2014, the Italian medicines agency decided to reimburse Avastin® for AMD. In 2014, France made its move to exclude Lucentis® of drug coverage and replace it with Avastin®. Novartis, Roche, and the European Federation of Pharmaceutical Industries and Associations (EFPIA) were arguing that off-label prescribing decisions should be based on medical need rather than economic pressure. In June 2015, the French ANSM (Agence National de Sécurité du Medicament) published a recommendation for temporary use (RTU) for Avastin® for the treatment of AMD. The Avastin® RTU became effective as of September 1st, 2015 and is valid for a period of 3 years. In its 29th June 2016 decision, the Conseil d'Etat dismissed the applications brought by Les Entreprises du Médicament (LEEM), Roche SAS, Novartis Europharm limited and Novartis Pharma, seeking to revoke the provisions of decree nº 2014-1703 of 30th December 2014 amending rules relating to the preparation of Temporary Use Recommendations (RTU) prepared pursuant to I of article L. 5121-12-1 of the Public Health Code. In its 24th February 2017 decision, the Conseil d'Etat dismissed the applications brought by Roche and Novartis seeking to revoke the 24th of June 2014 decision of the National Agency for Medicines and Health Products safety recommendation to treat patients with neovascular age-related macular degeneration. Thus, France maintains its recommendation for Avastin®."

This passage supports the Defendants' case that Avastin is widely used in the EU for ophthalmic purposes.

168. Avastin also appears on the WHO Model List of Essential Medicines under the category for ophthalmic use. According to correspondence submitted to the Court by Roche, Roche applied to have bevacizumab removed from the list for that indication, but WHO refused that application on the basis that the "current listing of bevacizumab remains appropriate" (see WHO letter dated 26 July 2016). That letter also stated, by reference to the WHO's Technical Reports Series 985 and 994, dated 2013 and 2015 respectively, that "the off-label nature of intravitreal use of bevacizumab is clearly reported".

169. I was shown other evidence, mainly websites and publications by hospitals offering ophthalmic services in the UK, to demonstrate that Avastin is widely offered and used in the UK in the treatment of eye conditions. Some of the healthcare providers were private hospitals, others were NHS hospitals.

170. Against this, the Claimants say that they are not aware of any established market in bevacizumab for ophthalmic use. They say that where they have become aware of proposed use of CB for ophthalmic use, they have taken action to stop it: for example, in the SHIP judicial review. They argue that the Sheffield study and other evidence relied on dates back to the time of the SHIP review and is not current (it was suggested that the market had reduced since then); and that any CB that was being supplied was provided under Article 5, as a "special".

171. The Claimants' evidence on the point is equivocal: Mr Schwerdt for Bayer says that the company has become aware in the past of certain CCGs or NHS Trusts proposing to introduce policies for the use of CB to treat wet AMD and other ophthalmic conditions but in each case Bayer has communicated with the relevant CCG or Trust and "*So far as we are aware the relevant policies have not … been pursued*" (statement dated 6 November 2017 at [82]). He also challenges the Defendants' assertions of widespread use in the domestic private healthcare sector on the basis that Avastin is not suggested to be the preferred medicine in any of the instant cases, and that it is difficult to investigate use of CB for ophthalmic purposes in the private sector (second statement dated 22 December 2017 at [13]-[14]). He says nothing about use elsewhere in the EU.

172. For Novartis, Mr Porter submitted two witness statements but neither deals with the point.

173. Mr Chamberlain for Roche, an interested party, provided short written submissions on the mature market. (I record here that Mr Chamberlain appeared, and Roche filed submissions, in order to assist the Court. Roche neither supported nor resisted the claim.) Roche sells Avastin direct to hospitals and to third party commercial compounders. Around 25% of its sales of Avastin in the last 12 months have been to third party commercial compounders. Roche accepts that Avastin may be compounded for a variety of reasons and accepts on the basis of reports from one of those commercial compounders that some supplies of CB by these compounders have been for intravitreal injection (which would include wet AMD, although it is used to treat other conditions also). Having reviewed all its information and based on assumptions, Roche estimates that about 0.04% of its total UK Avastin sales (by volume) in the last 12 months are likely to have been for intravitreal injection. I am grateful to Mr Chamberlain and his clients for investigating the matter, but I do not consider that the information provided by Roche takes the matter much further

forward. It remains unclear what proportion of the Avastin sold to third party commercial compounders is used for ophthalmic use – Roche's figures are in large part based on untested assumptions. And contrary to what Mr de la Mare argued, even a small percentage of a large market in Avastin could evidence an established and widespread market in CB for ophthalmic use.

174. Dr Hambledon's evidence is consistent with other evidence before me, in the form of the Commission report, the NICE guideline, the CJEU cases, the Sheffield study, and other evidence I was shown demonstrating that CB is openly offered for ophthalmic treatment in the UK. It also fits with the chronology of events: Avastin entered the market in 2005, at which point there was no anti-VEGF agent licensed for ophthalmic use. For that reason, as is widely acknowledged, ophthalmologists opted for Avastin (or CB) as the treatment of choice for certain ophthalmic conditions including wet AMD. It would not be surprising to find that many ophthalmologists who had seen good results when using Avastin continued to use that medicine to treat ophthalmic conditions, even after Lucentis and Eylea entered the market at significantly increased cost.

175. I am satisfied that compounded bevacizumab is widely used, in the UK, the EU and further afield, to treat ophthalmic conditions including wet AMD.

176. From that established fact, the Defendants invite me to draw the inference that bevacizumab is readily available for such use, in its compounded form, in the UK and that there is an established and mature market in CB. There is a lack of direct evidence to support that proposition. The Defendants say that that lack of evidence is, at least in part, a consequence of the fact that those who know about this market are unwilling to speak because they fear being targeted by the MHRA or pharmaceutical companies: see [18]-[20] of Dr Hambleton's second statement dated 11 May 2018. Dr Hambleton says that he understands that the NHS Trusts would not face a significant problem in securing supplies of CB. The Claimants resist this inference being drawn, based on evidence which I have already outlined.

177. I conclude that it is reasonable to draw the inference that CB for ophthalmic use is widely available in the UK. If it were otherwise, CB could not be offered so openly in the private sector in the UK. That inference is supported by the use of CB in other Member States (and elsewhere) for ophthalmic treatment. I do not know how large the market is, or whether it can properly be described as mature (although its inception was likely to have been in 2005 when Avastin started being used to treat ophthalmic disease). I do not know who produces CB for this market, whether the supplies originate in the UK, whether the suppliers are commercial operators (and if so, who regulates their activities) or NHS providers (who may be regulated by the CQC, as I understand it). I do not know whether the relevant regulators or other domestic authorities have taken steps to prevent this production, and if they have not, why they have not; or if they have, what the consequence and effect of that action has been. None of these entities are before the Court and none of these points are known. But I am satisfied that there is, in existence, an established market in the supply of CB prepared for intravitreal use.

### v) Is CB an unlicensed medicine or off-label use of a licensed medicine?

178. As the NICE guideline records, views differ as to whether bevacizumab, when compounded for intravitreal use, is an "off-label" use, or an "unlicensed" use. There are two matters to consider: (i) what the process of compounding involves as a matter of fact, and (ii) whether that constitutes off-label use or unlicensed use.

179. As to (i), the Claimants complain that the CCGs have failed to give full disclosure about *how* the CB will be produced to meet the Policy. But the CCGs answer saying that the CB will be purchased by the NHS Trusts, not by the CCGs, and thus the CCGs are not able to state with specificity *how* the CB will be produced or where it will be purchased from – those are matters for the NHS Trusts to determine.

180. I accept the Defendants' arguments on this point. The CCGs are commissioning groups and not healthcare providers or clinicians; accordingly, they cannot say with certainty how CB might be supplied in any given case. The CCGs have managed to identify four potential and generic ways in which CB might be acquired for use (these are the four modes, discussed below). This is a reasonable answer to the Claimants' questions about *how* the Policy will be implemented.

181. Although the Claimants suggested that the compounding process was subject to a number of possible variants and could not readily be described, the process does not seem to me to be particularly complex or difficult to describe. One description of it was given by Mr Schwerdt (replicated at [95] of the Claimants' skeleton). Another was given by the MHRA which described it as "*manipulation of the authorised medicine to produce multiple aliquots, usually in plastic syringes*". The AGO has recently described it. As I understand matters, Avastin is supplied in 4ml and 16ml vials for intravenous infusion; intravitreal injections require much smaller doses, usually of 0.05 ml; the process of compounding involves the vials of Avastin being aseptically aliquoted (ie repackaged) into smaller doses, usually into plastic syringes, which are then chilled or frozen before being sent to the eye treatment facility.

182. As to (ii), the issue remains whether this process exceeds what is permissible for a given use to be "off-label" – in other words, whether the process creates a new product which requires its own marketing authorisation, in the absence of which the product is an unlicensed medicine, or not. The distinction between unlicensed and off-label use appears to depend on a judgement as to the extent of any modification (recalling the AG in *AGCM* who stated that the meaning of "off-label" varies in extent "*depending on the therapeutic field and the Member State concerned*").

183. The Claimants say that CB is plainly a new medicine and the use is unlicensed. They argue that the manipulations involved result in up to six variations from Avastin's SmPC:

i) Changes to the packaging (plastic syringes rather than glass vials);

ii) Changes to dosage (from 5-15mg/kg of body weight to a much smaller dose of 0.05ml);

iii) Changes to the posology (undiluted for ophthalmic use whereas for cancer patients Avastin is diluted with saline);

iv) Changes to the route of administration (intravitreal administration rather than infusion – indeed, the SmPC for Avastin says that it is not formulated for intravitreal use);

v) Possible changes to the shelf life (from 2 years down to, possibly, 14 days); and

vi) Changes to the special precautions for storage (Avastin is to be kept refrigerated and the vial must be kept in the outer carton to protect from light, whereas the storage precautions for CB are not known).

184. The Claimants find support for their contention in the MHRA's guidance of 2011, and in the correspondence and statements by and on behalf of the Secretary of State for Health, all of which confirm that CB is an unlicensed medicine. They note that NICE Guideline NG 82 refers to, and does not contradict, the MHRA's guidance.

185. The Defendants invite me to depart from the MHRA's guidance, on the basis that it is just that – guidance – and has no binding quality. Further, they say that the picture has changed in light of the two CJEU judgments which treat intravitreal injection of Avastin as "off-label" use, and now they draw further support from the AGO.

186. The position is highly unsatisfactory. The MHRA initially referred to CB as "off-label", in the original version of its guidance dated 2009; it then changed its view in the clarification dated August 2011. It is not clear to me why the MHRA changed its view at this time and whether the change of view was in any way connected with the alteration to Avastin's SmPC, which alteration was, at least according to the Italian authorities (in a decision which the CJEU has considered), the consequence of unlawful collusion between Roche and Novartis (see [32] of *AGCM*).

187. The CJEU has now, in two cases, accepted the description of CB for ophthalmic use as "off-label" and has stated in terms that the compounding process does not give rise to a new medicine. The CJEU has acknowledged the widespread use of CB in the treatment of wet AMD and has not suggested that there are safety concerns connected with that practice. The AGO has now supported the CJEU's analysis in a third case. The important point made in each of those cases is that the medicine is not altered in its composition when used for ophthalmic use.

188. NICE has independently concluded that CB is just as clinically effective and safe as either of the licensed alternatives. NICE's view was based on the very substantial body of evidence relating to ophthalmic use of bevacizumab which largely post-dates 2011, when the MHRA's guidance on this issue was published.

189. The GMC has supported NICE's revised view and has removed the possibility that any doctor who prescribes Avastin for ophthalmic treatment will be charged with professional misconduct.

190. There is extensive evidence that CB is being used by private hospitals and some NHS providers for ophthalmic use in the UK already; and it appears that the private sector offers CB for the precise condition for which NICE maintains its TAGs for each of Lucentis and Eylea (in other words, in the private sector, CB does compete with Lucentis and Eylea, openly). This raises a significant issue of fairness to individual

patients and to the public purse more generally, if a cheaper alternative is available in the private sector, but not in the public sector in large part (so it seems) because the MHRA maintains an unexplained classification from 7 years ago to the effect that CB is an unlicensed medicine.

191. It is time the MHRA reviewed its position. I invite it to do so.

192. For the purposes of this judgment, I accept the MHRA's view as last expressed in 2011 to the effect that CB is an unlicensed medicine. I do so for these reasons: (i) the MHRA is the competent domestic body responsible for producing guidance such as that given in 2011; (ii) I have not heard from the MHRA; and (iii) for reasons I shall come to, whether CB is an off-label or unlicensed medicine is not, in the end, important to my conclusion about the lawfulness of the Policy. If it had been, I would have considered requiring the MHRA to attend and make submissions.

**(vi) The relevant test in domestic law**

193. I turn next to consider the legal test to be applied in determining whether the Policy is lawful. Mr de la Mare argues that the Court should assess the lawfulness of the Policy on the basis that what it envisages and intends is a large-scale commercial supply of an unlicensed drug. His case is that such supplies would be unlawful, and so, he says, the Policy is itself unlawful. He relies on *Gillick v West Norfolk and Wisbech HA and Anor* [1986] 2 AC 112 where the lawfulness of the policy under challenge stood or fell with the lawfulness (or not) of the actions envisaged by the policy. He also relies on *R (Letts) v Lord Chancellor (EHRC intervening)* [2015] EWHC 402 (Admin), [2015] 1 WLR 4497, where Green J reviewed the relevant authorities including *Gillick* and then formulated the test in this way:

> "118. The test is hence: Would the Guidance if followed (i) lead to unlawful acts (ii) permit unlawful acts or (iii) encourage such unlawful acts?"

194. Mr de la Mare argues that it is not open to the Defendants to suggest that there are a variety of means by which the Policy might lead to CB being purchased by NHS Trusts because the reality is that the Policy is aimed at promoting the widespread use of CB in preference to the licensed alternatives, which is itself unlawful. As a related point, he argues that the Defendants are not entitled to argue that it is up to the individual NHS Trusts to adopt a lawful method of implementation, because the CCGs are on notice, by these proceedings, that the underlying supplies and purpose of the Policy would be unlawful (he relies on *R (Sharon Shoesmith) v Ofsted and Ors* [2011] EWCA Civ 642 for that proposition). He argues that this Policy will lead to unlawful acts and is designed to encourage those unlawful acts, and reminds me of Regulation 46(4) and the domestic prohibition on procuring unlawful supplies.

195. Mr Lock's case is that the Policy is lawful if it is *capable* of implementation in a manner which is lawful. He relies on those passages in *Gillick* where the Court said that a policy is lawful if it can "in any circumstances" be fulfilled in a manner which is lawful (see Lord Fraser at p 165, Lord Scarman at p 181 and Lord Bridge at p 194). He cites *R (Tabbakh) v Staffordshire and West Midlands Probation Trust and Anor* [2014] EWCA Civ 827, [2014] 1 WLR 4620 at [35] to support his argument that in cases where there are a variety of possible outcomes – assuming that some at least are

lawful - the challenge should not be to the policy (which is, after all, capable of lawful implementation) but to individual decisions pursuant to that policy, which decisions may or may not be lawful. He does not seek to challenge Green J's formulation in *Letts* but rather to emphasise that the Policy in this case is different from that at issue in *Letts* because this Policy is merely advisory, it is not prescriptive as to whether CB should be offered to patients at all, or, if CB is offered and prescribed, how it should be sourced for the patient. Finally, Mr Lock took me to *R (West Berkshire DC) v Secretary of State for Communities and Local Government* [2016] EWCA Civ 441, [2016] 1 WLR 3923 for the proposition that a policy-maker is entitled to assume that the decision-maker in any given case will implement the policy in a manner which is lawful.

196. I am, broadly, with Mr Lock. The correct approach in a case like this must be to ask whether the Policy is capable of lawful implementation. This is subject to one rider, in recognition of Mr de la Mare's submissions, namely that the CCGs cannot seek to hide behind a fig leaf, and the Policy would not be lawful if the only method(s) of lawful implementation is/are unrealistic or would constitute only a tiny part of the anticipated supply of CB to the NHS Trusts; but if, on the other hand, there are realistic methods by which the Policy can be lawfully implemented, then the Policy is not itself unlawful. Individual decisions made pursuant to it may be capable of challenge in due course.

197. My reasons for so concluding are as follows:

i) The Policy relates to future healthcare provision by NHS Trusts (not the CCGs who promulgate the Policy). Further, the Policy itself is merely advisory in nature, and it is up to the NHS Trusts to decide whether to implement the Policy, and if so, how to do so. There is a degree of separation between the Policy and any decision made pursuant to it. As such, this case is very different on its facts from *Letts,* where the relevant policy relating to exceptional public funding applied with mandatory effect to guide decisions by caseworkers.

ii) Further, the Policy could be met in a wide range of ways, which makes this case different on its facts from *Gillick* where there was a single (allegedly unlawful) act to which the policy might lead, namely the prescription of contraception for a girl under 16 without parental consent.

iii) The shape of this Policy, with its variety of possible outcomes, is much more like *Tabbakh* (where the MAPPA process was challenged, unsuccessfully) and *R (Refugee Legal Centre) v Secretary of State for the Home Department* [2004] EWCA Civ 1481; [2005] 1 WLR 2219 (where the fast track scheme for adjudication of asylum claims was challenged unsuccessfully). I acknowledge that those cases turned on issues of procedural fairness which are not present in this case. But in each, the issue was whether the scheme was *inherently* flawed, in which case the Court accepted that the scheme itself would be unlawful, or not, in which case the scheme itself would be lawful although individual decisions made pursuant to it might still be challenged. The Court put it this way in *Refugee Legal Centre* at [7] (per Sedley LJ):

> "Potential unfairness is susceptible to one of two forms of control which the law provides. One is access, retrospectively, to judicial review if due process has been violated. The other, of which this case is put forward an as example, is appropriate relief, following judicial intervention to obviate in advance a proven risk of injustice which goes beyond aberrant interviews or decisions and inheres in the system itself. In other words it will not necessarily be the answer, where a system is inherently unfair, that judicial review can be sought to correct its effects. …".

The Court concluded that the fast track scheme fell within the former category and was lawful, even though individual cases decided within that scheme might still be justiciable by the courts ([22]-[24]).

iv) Mr de la Mare's submissions depend in large part on his submission that by the Policy, the Defendants intend to procure the bulk supply of CB to NHS Trusts in advance of any prescription (he provided a note listing the instances where he said the Defendants had so asserted and relied on that note to press his case that that intention lay at the heart of the Policy). But I do not accept that characterisation of the Defendants' case or the Policy: the Defendants put forward four possible modes by which the Policy might be fulfilled, accepting that each of those modes might itself have a number of variants; the Defendants do not rule out the possibility that prescriptions might be in place in advance, or that some supplies might not be on a bulk scale; they say that they do not know how the NHS Trusts might seek to meet the Policy. Therefore, to meet the Defendants' case, I must consider each of the possible modes and the range of ways in which the Policy might (realistically) be met by the NHS Trusts. I may or may not agree with the Claimants' submissions about them at the end of the day; but this is not, or at least not necessarily, a case where the Policy, if pursued, would (even might) lead to a single identifiable outcome. The Defendants' case is more complicated than that.

v) Further, I accept that the Defendants are entitled to argue that they do not know how the NHS Trusts will procure CB for use in their hospitals, if they choose to offer CB to their wet AMD patients at all. They are entitled to rely on the presumption that the NHS Trusts will act lawfully in the manner in which they choose to implement the Policy (per *West Berkshire*), if there is a choice between lawful and unlawful methods of implementation, at the point that a decision falls to be made by an NHS Trust or an individual clinician within such a Trust.

198. In summary, the issue for the Court is whether this Policy is realistically capable of lawful implementation. If it is, then the Policy would be lawful. If the actual implementation in any given case was unlawful, the possibility of challenge to that decision would remain. This is not to gainsay Green J's formulation in *Letts*, but to modify it to fit the facts of this case. I would formulate the test, as it applies in this case, as follows: is the Policy realistically capable of implementation by the NHS Trusts in a way which does not lead to, permit or encourage unlawful acts?

## THE FOUR MODES

### Preliminaries

199. The crux of the Claimants' case is that the policy is intended to encourage large scale production of compounded bevacizumab for treating wet AMD. The Defendants say that there are four broad ways, or "modes" in which the CB could be sourced by NHS Trusts: (1) Original vial use; (2) Compounded "in house" by the hospital's own pharmacy; (3) Compounded by another NHS hospital pharmacy; and (4) Compounded by a commercial entity which stands outside the NHS.

*Preliminary Issue (1): scope of the arguments*

200. The Claimants suggested that the Defendants had disavowed any reliance on either of the derogations in the Directive (see, for example, [112], [113] and [115] of the Claimants' skeleton). The Claimants are right to note that the Defendants do not seek to rely on Article 5 (see eg Detailed Grounds at [105]). But the Defendants make no wider concession, or positive submission, about how the NHS Trusts might go about purchasing or procuring Avastin for ophthalmic use: that is, they say, up to the Trusts. Therefore, Article 3 is still relevant on the Defendants' case (see, for example, [28d] and [29] of the Defendants' written submissions for day 4 of the hearing), although their case is by no means limited to Article 3. I reject the Claimants' characterisation of the Defendants' case: all options for supply remain open.

201. Secondly, I was addressed by Mr de la Mare and Mr Lock on the domestic legislation, and whether domestic pharmacies of two sorts (registered pharmacies on the one hand, and hospital pharmacies on the other) could avail themselves of various provisions within s 10 of the Act. I do not consider it necessary or desirable to undertake an analysis of domestic law or to deal with those arguments in this judgment. This is an EU law challenge, and if the modes, any or all, are permissible under EU law, I would expect the result to follow that they are permissible in domestic law also; on that basis, the domestic legislation does not require separate consideration. But further, the domestic provisions are complex and I believe that they are better considered (and applied) by reference to actual, concrete supplies, rather than in the abstract.

202. Third, to state the obvious, the exercise upon which I am about to embark is hypothetical. No supplies of CB to any NHS Trust or patient served by any NHS Trust have to date been made. I undertake the exercise in order to test the lawfulness of the Policy, and not to determine whether any particular supply which might or might not in the future be made, between parties who are not present in this Court and have had no opportunity to address the Court, is lawful.

*Preliminary Issue (2) – late introduction of mode (1)*

203. The Claimants raise a preliminary objection to the Defendants' suggestion that there are four possible modes. They point to correspondence between individuals employed at the CCGs, at around the time the policy was drafted and subsequently implemented, in which the Policy is described as directed at the use of compounded bevacizumab; to the Detailed Grounds of Defence which propose only modes (2), (3) and (4) (as they are now known); and to the Defendants' witness evidence which

confirms that original vial use (mode (1)) was first considered in February 2018, after the Policy was adopted by the CCGs. They argue that the introduction of mode (1) post-dates the Policy and would, if the Defendants seriously intend to deploy it, require a new policy to be adopted and published. Thus, the Claimants argue that mode (1) should form no part of my review.

204. I am not persuaded that I should limit my analysis to modes (2), (3) and (4). That is for a number of reasons. First, the Policy was not prescriptive as to *how* it should be fulfilled. Thus the Policy has always been open to being fulfilled in a number of different ways, whether the policy-makers had thought of them or not at the time the Policy was implemented. Secondly, I cannot see that the Policy would require any amendment to encompass mode (1) – it is not prescriptive, as I have said. The Claimants are not right to suggest that a new policy would be required if mode (1) were envisaged. Thirdly, I am not persuaded that correspondence passing between individuals who were involved in the development of the policy should be used to interpret the Policy; interpretation of the Policy is a matter for the Court. Fourthly, and in any event, I have now heard full argument on the legal merits of each of the proposed modes and it would not be in the interests of justice for me simply to deal with some but not all modes. The parties need to know the answer to the overarching question, which is whether the Policy is lawful, and that requires me to consider each of the modes in which the Defendants say it could, realistically, be met.

*Preliminary Issue (3): is it open to the Claimants to challenge modes (3) and (4) as unlawful, now?*

205. The Defendants argue that the Claimants have known for a long time who are the likely providers of CB to the NHS Trusts pursuant to the Policy: the names of the NHS Trusts with capacity to manufacture CB in large quantities in their "in-house" pharmacies are known (mode (3)), as are the identities of the commercial organisations which supply CB to the established and mature market (as I have found it to be, mode (4)). Moreover, the Defendants point to the existence of the mature and established domestic market in CB and argue that it is too late now to suggest that to access that market would constitute a breach of EU law, when the Claimants have not taken any action before now to challenge the activities of suppliers of CB. They argue that the correct parties are not before the Court, but further, that as a matter of law, the Claimants have, in effect, "missed the boat" when it comes to arguing that EU law prevents NHS healthcare providers from purchasing CB for ophthalmic use in their hospitals. In this connection, the Defendants rely on *Shoesmith* to suggest that a party is obliged to resolve an underlying dispute of which that party has notice where the lawfulness of a second decision depends on the outcome of that dispute.

206. The Claimants resist this suggestion. They say that they have taken action to prevent what they consider to be breaches of EU law when they have been made aware of them (noting their challenge in the SHIP judicial review). But more specifically, they dispute the assertion that they have "missed the boat", questioning the basis on which that assertion, based it seems on an analogy with estoppel or prescription in private law, is advanced. They say the Defendants have got their law wrong.

207. I am with the Claimants on this point. I am not persuaded that the Claimants are now barred from arguing within this judicial review that third party supplies of CB would be unlawful:

i) I do not accept the Defendants' analysis based on *Shoesmith.* In that case, the Secretary of State had made a decision, which turned out to be unlawful on grounds of procedural unfairness, but on which Haringey had in the meanwhile relied in reaching its own decision to dismiss. The sequence here is entirely different: the CCGs have promulgated the Policy in the hope of influencing future decisions made by the NHS Trusts. The CCGs have an expectation that the NHS Trusts *will* act lawfully, but there is no past decision by the NHS Trusts on which the CCGs have based their Policy. There is no equivalent here to the past decision of the Secretary of State in *Shoesmith.*

ii) In any event, the Claimants' complaint is that future supplies of CB to NHS Trusts in response to the Policy will be unlawful as a matter of EU law and domestic criminal law (citing Regulation 47). I do not agree that the Claimants have "missed the boat" so far as this judicial review is concerned, by failing to challenge past supplies of CB by third parties to others who are not even parties to these proceedings. There is no general principle of estoppel which prevents a party from complaining that a breach of EU law or domestic common law is occurring or will occur, even if that party failed to challenge similar activity between different persons in the past.

iii) In light of those conclusions, it is not necessary for me to make any finding on the Claimants' factual case that they have challenged infringements in the past, when they have become aware of them.

*Preliminary Issue (4): the CJEU cases*

208. Before embarking on an analysis of the four modes, I repeat a point made above: the CJEU has considered the use of Avastin, on a large scale, for ophthalmic purposes, on two occasions (with the AGO having given a view in relation to a third case). The CJEU has not suggested that such use is unlawful. Models which mirror those examined in *Apozyt* and, if the AGO is upheld, *AIFA*, are lawful under EU law.

209. On one view, that would be sufficient to resolve this case in the Defendants' favour, assuming that such models were realistic (I have no reason to think they are not – if they could work in Germany and Italy, why should they not work here?).

210. But that does not provide a complete answer to this case, because the Court has not yet spoken in the *AIFA* case, there is a point of distinction here because CB is an unlicensed medicine according to the MHRA, and anyway I have been invited to consider other arguments beyond those addressed by the CJEU and AGO. Accordingly, I turn to the four modes identified by the Defendants.

**Mode 1: Original Vial Use**

211. Dr Hambleton describes single vial use in his second witness statement, dated 11 May 2018 at [17]. It involves drawing a small amount of Avastin (0.05-0.1 ml) directly from the vial for injection directly into the eye; the balance of the drug remaining in the vial would be discarded (assuming a 4ml vial, the wastage would be substantial). There would be no compounding process.

212. This method of using Avastin was not considered by the MHRA, and I do not consider the MHRA's guidance of 2011 extends to use in this way.

213. Although the point was not formally conceded, I am satisfied that such a use would be properly classified as "off-label". It would involve using the medicine direct from the manufacturer's vial by the clinician at the bedside (or in the operating theatre) without that medicine having been subjected to any form of compounding process at all.

214. The Claimants argue in their skeleton that such a mode of using Avastin for treating wet AMD would be unlawful. They make three points:

i) The scope for the systematic encouragement of off-label use cannot be wider than the gateway for the use of unlicensed medicines, so that the two exemptions (Articles 3 and 5) must be "read in" to any proposed off-label use, to permit it only where it is justified on clinical grounds for a specific patient. *Apozyt* is relied on, at [42] in particular.

ii) To do otherwise would contravene the wider objects of the Directive, including the duty of sincere cooperation under Art 4(3) TEU. In this context, the Claimants rely on Case T-452/14 *Laboratoires CTRS v Commission* EU:T:2015:373, where the General Court annulled the decision of the Commission granting a marketing authorisation for a drug called Kolbam, in circumstances where that authorisation included use for certain therapeutic indications which were already within the marketing authorisation for a different drug, called Orphacol. So, it is said, it is clear that the harmonised system envisages some exclusivity for medicines which have a marketing authorisation and that to permit extensive off-label use would undermine the wider purposes of that system. Patient safety is in jeopardy if the system is not respected in this way.

iii) Original vial use is in clear breach of MHRA and GMC guidance. Reliance is placed on extracts from the MHRA guidance on specials and on the GMC guidance contained in GMP.

215. The Defendants argue that regulation of off-label prescribing is a matter for the domestic authorities. It is not within EU law at all. They rely on Article 4(3) of the TEU and Article 168(7) of theTFEU, and the long line of cases referred to above which confirm that the use of medicines off-label is indeed a matter for the national authorities. Further, they argue that *Apozyt* provides no support for the Claimants' arguments in this respect because [42] of the Judgment does not mean, and cannot sensibly be understood to mean, that Article 5 of the Directive applies even where the use is off-label. They say that *CTRS* is of no assistance either: that case concerned a different part of the EU regime, which relates to "orphan" medicines, in relation to which EU law contains a system of incentives to encourage pharmaceutical companies to invest in research, development and bringing to the market of medicinal products intended to treat rare medical conditions; one of the incentives is a period of market exclusivity of 10 years. They say that *CTRS* supports the Defendants' case by confirming that off-label prescribing falls outside the scope of EU law:

> "79 … off-label prescribing is not prohibited, or even regulated, by EU law. There is no provision which prevents

> doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted."

216. I agree with the Defendants. For reasons given earlier in this judgment, I am not persuaded that [42] of *Apozyt* should be read as the Claimants suggest. Off-label use is not subject to limitations which are to be "read in" by analogy with Articles 3 and/or 5. I agree with Mr Lock that *CTRS* is a different case dealing with a different part of the EU regime and has no relevance here.

217. The Claimants raise the safety argument in the context of original vial use. But I have already concluded that there is no safety issue so far as Avastin for ophthalmic use is concerned (see above in light of NICE Guideline NG 82), and that in any event, given that the use is off-label, safety issues are for the authorities of the member state to address.

218. I have already noted that the MHRA's 2011 guidance did not consider this mode of use, and that its 2014 guidance relates to "specials", a domestic name for items provided under the derogation in Article 5, which is of no relevance.

219. I have also already addressed the GMC guidance, and have concluded that that guidance is compatible with the prescription of CB on costs grounds even where there are licensed alternatives available.

220. Original vial use would not, in my judgment, require a fresh marketing authorisation and would not be prohibited by EU law. It would be an example of "off-label" use. Regulation and oversight would be a matter for the domestic authorities. I do not consider it to be a fanciful method of use: although it is an inefficient and consequently expensive way to use Avastin, it would still represent a considerable saving of public funds when compared with using Lucentis or Eylea. (The Claimants' evidence is that Avastin used by this method would cost around £291 per injection.)

**Mode 2: Compounded Bevacizumab supplied by a hospital's own pharmacy**

221. Modes (2), (3) and (4) involve compounding, and they fall within the scope of the MHRA's 2011 guidance which requires me to approach these modes on the basis that CB is an unlicensed medicine; if the MHRA were to change its view and to accept that CB is off-label use, the analysis for these modes would be simpler and more closely aligned with mode (1).

222. So far as mode (2) is concerned (production in a hospital pharmacy), Mr Lock argues that the Directive has no application at all, because the CB is not being placed "on the market" (within Article 2(1) of the Directive). Rather it is being supplied "in house" by the hospital pharmacy to the hospital's own clinicians. Mr Lock says that a hospital pharmacy supply would be within the NHS and within the area of national competence, and the supply would be an internal consumption choice for the NHS Trusts, and thus permitted under EU law. He acknowledges that there may still be issues as to whether a manufacturing licence is required, but he notes the likely applicability of article 40(2) to resolve that complication (by analogy with *Apozyt*), and that the Claimants take no issue in relation to the absence or otherwise of a manufacturing licence in relation to any of the modes of delivery.

223. Mr Lock draws further support from The Law and Regulation of Medicines by Dr Peter Feldschreiber (2008) OUP at para 2-36, which states as follows:

> "2.36 Article 6(1) contains the key requirement that no medicinal product may be placed on the market unless it has a marketing authorization. The term 'placed on the market' is not defined in the Directive, although it is a concept used in many different Community instruments relating to the free movement of goods (eg medical devices). In the light of those definitions, the preferable interpretation is that a medicinal product is placed on the market in a Member State the first time it enters the supply chain in that state. Subsequent supplies do not constitute placing on the market – otherwise each wholesale supplier or retailer would require a marketing authorization."

224. He argues that this analysis tallies, to some extent at least, with the "downstream" analysis adopted by the AG in *AGCM* at [47] and the Court's suggestion at [43] of *Apozyt* that compounding by hospital doctors and pharmacies does not amount to putting a product on the market.

225. In answer, Mr de la Mare and Miss Stratford argue that the EU medicines regime remains applicable, even if the proposed supply is by a hospital's own pharmacy. They say that in-hospital supply is not really what the Policy intends, in any event.

226. I conclude that supplies of CB by a hospital's own pharmacy would not be within the reach of the Directive:

i) As a matter of ordinary language, it is a stretch to suggest that the hospital pharmacist is putting CB "on the market" in the UK. The pharmacist will be preparing the CB for despatch to a different part of the same hospital, for use by hospital staff, in the treatment of patients at that hospital. This is an entirely "in-house" operation.

ii) Such an in-house operation would be the paradigm example of "downstream" activity, identified by the AG in *AGCM* and reflecting the approach of the CJEU at [43] of *Apozyt*. This is within the domestic area of competence, and consistent with the CJEU authorities which have examined where the boundary lies (see above).

227. I conclude that a hospital pharmacy would not require a marketing authorisation before supplying the CB to clinicians in the same hospital or Trust.

228. If the hospital pharmacy was to adopt the practice of supplying only in response to a prescription then the NHS Trust could, additionally or alternatively, rely on Article 3 (cf *Apozyt* and *AIFA* at [67]).

229. The Defendants advance an alternative argument in relation to mode (2), which is that CB is not, or is not likely to be, prepared industrially when it is prepared by a hospital pharmacy, noting that by the language of Article 2(1), a marketing authorisation is only required if the product is "prepared industrially or manufactured by a method involving an industrial process". They rely on Case C-276/15 *Hecht-Pharma GmbH*

*v Hohenzollern Apotheke* EU:C:2016:801 to argue that it is at least possible that the process deployed by a supplier of CB will be non-industrial. In that case, the Court held that incense capsules manufactured by HA, a pharmacy, and marketed as food supplements, in competition with a similar product manufactured on an industrial scale by Hecht-Pharma, did not require a marketing authorisation because they were not prepared industrially. The Court acknowledged that having regard to the objective of protection of public health pursued by EU rules on medicinal products, the terms "prepared industrially" and "manufactured by a method involving an industrial process" should not be narrowly interpreted (see [31]), but said that an industrial process differs from an artisanal process and, citing *Abcur,* it held that "*an industrial process is characterised in general by a succession of operations, which may, in particular, be mechanical or chemical, in order to obtain a significant quantity of a standardised product*" [32]. The Court was satisfied that in the present case, the capsules were not produced industrially by an entity operating on a large scale but in small quantities by artisanal methods (the quantities produced were 213 packages in a year, [34]; German law set the threshold for non-industrial production at 100 packages per day). The Court said:

> "35 It follows that a medical product for human use, such as that at issue in the main proceedings, does not appear to be prepared on an industrial basis or manufactured according to a method involving an industrial process within the meaning of that provision and, consequently, does not appear to come within the scope of that directive. However, it is for the national court to determine whether that is the case."

230. The Claimants' response is that the proposed supply of CB to the CCGs pursuant to the Policy is a world away from the artisanal production of food supplements as was at issue in *Hecht,* and so that case is not relevant. Further, the Claimants point to *Abcur* where, in relation to the meaning of industrial process, the Court held this:

> "49 Furthermore, recital 35 in the preamble to Directive 2001/83 refers to the necessity of exercising control over the entire chain of distribution of medicinal products, from their manufacture or import into the EU through the supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions.
>
> 50 Having regard to the objective of protection of public health pursued by the EU rules on medicinal products for human use and thus recalled, the terms 'prepared industrially' and 'manufactured by a method involving an industrial process' cannot be interpreted narrowly. Those terms must therefore include, at the very least, any preparation or manufacture involving an industrial process. Such a process is characterised in general by a succession of operations, which may, in particular, be mechanical or chemical, in order to obtain a significant quantity of a standardised product.
>
> 51 In those circumstances, the view must be taken that the standardised production of significant quantities of a medicinal

> product to be stocked and sold wholesale and the large-scale or serial production of magistral formulae in batches are characteristic of industrial preparation or manufacture by a method involving an industrial process."

The Court held that products such as those at issue in the main proceedings did fall within the scope of the Directive, see [52].

231. On the basis of these authorities, I conclude that it is at least possible that supplies of CB to one of the NHS Trusts might be "non-industrial". That is more likely the closer the supply is to the point of consumption, and so more likely in an NHS supply setting and more likely still if the supply is by the hospital's own pharmacy. I cannot be more categoric: the answer in any given case will depend on the facts.

**Mode 4: CB supplied by a commercial entity**

232. Mr de la Mare argues that CB provided by a commercial entity is being put on the market, such that a marketing authorisation is required. At this point, the fact that there is an established and mature market becomes relevant: (i) it means that there are third party commercial compounders, who participate and contribute CB to this market, who are not before the Court and who are not parties to this litigation; I do not know what arguments they might wish to advance to defend themselves from the challenge to the lawfulness of their supplies; (ii) in any event, even if that market is built on repeated breaches of EU law as the Claimants assert, I am not persuaded that an NHS Trust would necessarily be in breach of EU law in taking advantage of it to purchase CB for ophthalmic use. It could be said that the NHS Trust was not encouraging or procuring such a supply (recalling the test in *Letts* and the terms of regulation 46(4)) given that the product is already in circulation. I heard no argument on this point.

233. Alternatively, it may be that commercial providers would prepare CB on receipt of a prescription as did the commercial provider in *Apozyt*, and now see *AIFA.*

234. In the further alternative, the batches could be produced in quantities which were not industrial, which, relying on *Hecht,* might open another lawful means of supply.

235. For all these reasons I am not persuaded that supplies by commercial providers are necessarily unlawful.

**Mode 3: CB supplied by another NHS pharmacy**

236. I come to this mode last, because the analysis will either be the same as mode (2) (supply by an NHS pharmacy), as Mr Lock argues it should be, or mode (4) (commercial supply). I cannot determine on which side of the line a supply by another NHS pharmacy would fall in a factual vacuum: I would need some facts, an actual supply, in order to decide whether that supply was in reality a commercial supply or an in-house supply. It all depends.

237. In any event, I have already decided that each of modes (2) and (4) is potentially lawful. So it does not matter, for the purposes of this judicial review, whether a category (3) supply falls to be analysed as a commercial supply, or not.

## Summary on Modes

238. For different reasons, I conclude that each of the proposed modes at least *might* be lawful. The position for modes (1) and (2) is stronger. Mode (4) might be lawful: even if the commercial providers were acting in breach of EU law, I am not persuaded that it would necessarily be unlawful for the NHS Trusts to purchase CB from them. Mode (3) is a hybrid, capable, hypothetically, and depending on the facts, of being categorised either as an "in-house" supply within the NHS (mode (2)) or a commercial supply by a third party supplier (mode (4)).

## RESPONSE TO THE GROUNDS OF CHALLENGE

### Ground 1

239. Finally, I turn to answer the Claimants' grounds. I am not persuaded that the Directive prohibits the supply of Avastin, whether compounded or not, to NHS Trusts, in any one of the ways advanced (let alone in *all* of the four modes suggested, which is the case advanced by the Claimants). Each mode provides a means by which the Policy might realistically be implemented. Ground 1 therefore fails.

### Ground 2

240. The Claimants argue that the policy will undermine the coherence of the EU regime overall in two ways: (i) patient safety will be jeopardised; and (ii) the coherence of the system, including the protection afforded to pharmaceutical companies in relation to their products, will be damaged. They rely on Article 4(3) TEU, the role of the EMA, and the risk to public health if the Policy is permitted (see [12] of the Claimants' skeleton).

241. So far as safety is concerned, I have addressed this already. The CCGs are competent to assess clinical effectiveness, including issues of safety and cost; and in light of the NICE Guideline NG 82 I am not persuaded that there is any safety deficit.

242. So far as the coherence of the system is concerned, I conclude that the Claimants significantly overstate the protection afforded to pharmaceutical companies by the Directive. The high point of their argument is *CTRS*, but that was a case concerned with a different part of the Directive. Avastin is not an orphan drug, and it is no surprise that it does not benefit from the same level of protection.

243. The CJEU has not supported the pharmaceutical companies' various challenges in either of the two cases on Avastin it has considered; and the AGO does not support Novartis in *AIFA.* This larger argument was available in each case but found no support.

244. The answer to the Claimants' complaint that the floodgates would open and pharmaceutical companies would be at liberty to make alterations to medicines at will, without obtaining marketing authorisations to reflect those alterations, is provided by the Directive: the pharmaceutical companies would be bound by Article 6(1) to seek a new marketing authorisation if the medicine had been altered in any of the ways there specified (or possibly to seek authority to amend the SmPC if the alterations were modest). The authorities of Member States (and indeed individual

prescribers) are not subject to the same regime, they are acting within their area of national competence when they choose an unlicensed or off-label alternative. Thus, the Claimants are wrong to complain that the effect of the Policy is to achieve by the back door what cannot be achieved by the front door: this is to conflate the two different areas of competence recognised by the Directive, and wrongly to suggest that the rules designed for the regulation of the market, which rules apply to pharmaceutical companies, also govern national healthcare choices; they do not.

245. In any event, I cannot accept that the scheme and purpose of the Directive should extend to protecting the commercial interests of the pharmaceutical companies in a case such as this, where the facts are unusual and the jeopardy to the public purse is enormous. That would upset the careful balances in the Directive, between the commercial interests of pharmaceutical companies on the one hand and the public benefit safeguarded by the State on the other, and between the centralised competence of the EMA on the one hand and the competence conferred on national authorities on the other.

246. Ground 2 fails.

**Ground 3**

247. The Claimants contend that the Policy undermines NICE, which has issued TAGs recommending Lucentis and Eylea for the treatment of wet AMD. The specific complaint is that the Policy restricts access to products recommended in this way by NICE, alternatively it frustrates the NICE recommendations and so pursues an improper purpose.

248. The Defendants answer that the TAGs merely provide options for prescribing clinicians. The CCGs comply with the TAGs and with Guideline NG 82 by making both Lucentis and Eylea available, as options. The Policy recognises that Lucentis and Eylea are both available and funded, within the specific parameters identified by their TAGs. Therefore, it cannot be said that the Policy breaches patients' rights of access to NICE-approved medicines, because it expressly offers them that option.

249. I accept the Defendants' answer to Ground 3. The effect of the Policy is not to undermine NICE. The patient can still choose Lucentis or Eylea, if that patient's wet AMD is within the parameters specified in the TAGs for those two medicines. Patients have that option, and NICE is not undermined.

250. Ground 3 fails.

**Ground 4**

251. The Claimants' final ground of challenge is that the Patient Information Leaflet and the Q and A document, attached as appendices to the Report considered by the CCGs when they adopted the Policy, contains materially misleading statements. The alleged flaws in the Leaflet are:

    i) The statement that the patient will be treated with Avastin, when in fact the patient will be treated with CB.

ii) The failure to point out that the patient will have no recourse to Roche if there is a product liability issue.

iii) The failure to explain that the CCGs are not legally competent to undertake a safety and efficacy assessment, that role lying with MHRA which maintains guidance recording reports of severe adverse reactions.

iv) Suggesting that the main difference between Eylea and Lucentis, and Avastin, is cost, when there are other differences too (including different molecular size, structure, binding affinity to the VEGF protein, differences in manufacturing standards, that Avastin has not been through the rigorous procedure to obtain a marketing authorisation from the EMA, increased risk of infection, and more injections required with Avastin).

v) Not clarifying to the patient that the patient can choose Lucentis or Eylea if they prefer, notwithstanding cost, if they come within certain parameters, and that Lucentis and Eylea are considered to be "cost-effective" by NICE.

252. The Q and A is said to be defective in the following ways:

i) It describes the treatment as off-label, not unlicensed.

ii) It fails to explain the restrictive terms of the GMC guidance and in any event misrepresents that guidance.

iii) It underplays the risk of challenge to the CCGs.

253. It is said that these defects render the Information Leaflet and Clinician Q and A unlawful, improper or irrational; the mis-statements are calculated to influence prescribing choices, and are thus potentially unethical interferences with a clinician's objectivity; further, it is a legal requirement that full and accurate information is given to the patient.

254. In resisting this ground, the Defendants raise certain preliminary issues: the patient information leaflet is not issued by the CCGs, but by the NHS Trusts, if they choose to, in language which the NHS Trusts will determine in due course; both documents are in draft, neither has in fact yet been issued, thus there is no "decision" for the Claimants to challenge; in any event, the CCGs have a broad discretion about what information to recommend is passed on to patients, and are under no legal obligation to provide any such information at all. On the substance, the Defendants deny that the documents contain misleading statements or omit important information.

255. So far as the patient information leaflet is concerned, I accept the Defendants' submission that this is a draft document which has not in fact been published at all, so there is no decision to challenge. Further, the Defendants are right to point out that the document, if it is published at all, will be published and relied on by the NHS Trusts in providing information to their patients; the NHS Trusts, not the CCGs, will be responsible for the final language and content of the document. That document is therefore not open to challenge by the Claimants in this action.

256. So far as the clinician Q and A is concerned, this too is a document in draft. But it is, as I understand it, a document for which the CCGs will be responsible by contrast with the patient information leaflet. But none of the points made by the Claimants about this document has any substance: the description of "off-label" is understandable given the recent decisions of the CJEU and the confusion which attaches to the meaning of that term; it is not an error of law which vitiates the document. GMC guidance is publicly available and known to clinicians already, it does not need to be extensively repeated in the Q and A (and anyway, I have rejected the Claimants' submissions on what that guidance requires or means). The reference to a risk of challenge is not inaccurate, and is anyway prophetic: the CCGs have been challenged. In summary, there is no substance to the Claimants' case that this document is unlawful.

257. Ground 4 fails.

## CONCLUSION

258. My conclusions on the key issues can be summarised as follows:

i) The EMA does not have exclusive competence to determine whether Avastin is clinically effective and safe for ophthalmic use. NICE and the CCGs also have competence in that arena.

ii) Treating clinicians can lawfully choose Avastin for ophthalmic use on grounds of cost.

iii) The Claimants' argument that Avastin is not safe when used for ophthalmic purposes does not arise for determination in the context of this challenge to the Policy; but in any event and even if it did, NICE has concluded that Avastin so used is safe, and that settles the issue. Expert evidence is not necessary and permission to rely on it is refused.

iv) There is an established market in CB prepared for ophthalmic use.

v) Based on the MHRA's 2011 guidance, CB is an unlicensed medicine and not an off-label use. But it is time the MHRA reviewed its position.

vi) The relevant test by which the lawfulness of the Policy is to be judged in domestic law is this: is the Policy realistically capable of implementation by the NHS Trusts in a way which does not lead to, permit or encourage unlawful acts?

259. My conclusion on each of the four modes of supply is as follows:

i) Original vial use (mode (1)) would be a form of off-label use, which would not require a marketing authorisation. It is a realistic method of meeting the Policy.

ii) The supply of CB by a hospital's own pharmacy (mode (2)) would not be off-label use, but it would not necessarily require a marketing authorisation under EU law, because the supply is "in-house" and so within the area of domestic competence, alternatively it could come within Article 3 if the conditions were

met, further alternatively it might not be prepared industrially. It is not possible to be definitive because much would depend on the facts of any given supply.

iii) The commercial supply of CB by a third party supplier (mode (4)) would not be off-label use, and it is more likely that such supplies should be subject to a marketing authorisation, but it is not established that an NHS Trust would be acting unlawfully in purchasing such supplies given the existence of an established market in CB; alternatively, it is possible that Article 3 could be relied on; alternatively, it is possible that the supplies would not be prepared industrially. It is not possible to be definitive because much would depend on the facts of any given supply.

iv) The supply by one NHS pharmacy to another NHS hospital (mode (3)) would, on analysis, be the same as (2) or (4). It is not possible to be definitive because much would depend on the facts of any given supply.

260. In light of those conclusions, I reject all four grounds of challenge. In consequence, this application for judicial review is dismissed.

261. I wish to thank all counsel and legal teams involved in this case. I have received a great deal of assistance from them. Each team presented their client's case with care and skill.