Neutral Citation Number: [2020] EWCA Civ 449

Case No: C1/2018/2744
C1/2018/2746

IN THE COURT OF APPEAL (CIVIL DIVISION)
On appeal from
THE HIGH COURT OF JUSTICE, QUEEN'S BENCH DIVISION
ADMINISTRATIVE COURT
Mrs Justice Whipple

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 25/03/2020

Before:

LORD JUSTICE UNDERHILL
(Vice-President of the Court of Appeal, Civil Division)
LORD JUSTICE FLOYD
and
LADY JUSTICE ROSE

- -

Between:

(1) BAYER PLC
(2) NOVARTIS PHARMACEUTICALS UK LIMITED **Appellants**

- and -

(1) NHS DARLINGTON CCG
(2) NHS DURHAM DALES, EASINGTON & SEDGEFIELD CCG
(3) NHS HAMBLETON, RICHMONDSHIRE & WHITBY CCG
(4) NHS HARTLEPOOL & STOCKTON CCG
(5) NHS NEWCASTLE GATESHEAD CCG
(6) NHS NORTH CUMBRIA CCG
(7) NHS NORTH DURHAM CCG
(8) NHS NORTHUMBERLAND CCG
(9) NHS NORTH TYNESIDE CCG
(10) NHS SOUTH TEES CCG
(11) NHS SOUTH TYNESIDE CCG
(12) NHS SUNDERLAND CCG **Respondents**

- and –

(1) ROCHE PRODUCTS LIMITED
(2) THE SECRETARY OF STATE FOR HEALTH AND SOCIAL CARE
(3) THE ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY
(4) NHS ENGLAND **Interested**
(5) GENERAL PHARMACEUTICAL COUNCIL **Parties**

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Ms Jemima Stratford QC and **Ms Emily MacKenzie** (instructed by **Arnold & Porter Kaye Scholer LLP**) for the **First Appellant**
Mr Thomas de la Mare QC and **Mr Eesvan Krishnan** (instructed by **Covington & Burling LLP**) for the **Second Appellant**
Mr David Lock QC and **Mr David Blundell** (instructed by **Mills & Reeve LLP**) for the **Respondents**
Ms Victoria Wakefield QC (instructed by **Fieldfisher LLP**) for the **First Interested Party**
Mr George Peretz QC (instructed by **the Treasury Solicitor**) for the **Second Interested Party**
Ms Monica Carss-Frisk QC (instructed by **CMS Cameron McKenna Nabarro Olswang LLP**) for the **Third Interested Party**

The other Interested Parties were not represented and did not appear

Hearing dates: 19th–22nd November 2019
Written submissions: 25th and 27th November 2019

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Approved Judgment

Lord Justice Underhill:

INTRODUCTION

1. This is an appeal against a judgment of Whipple J, handed down on 21 September 2018, dismissing an application for judicial review brought by the two Appellant pharmaceutical companies. The Appellants' challenge was to a policy ("the Policy") adopted by the Respondent Clinical Commissioning Groups ("CCGs") that the NHS Trusts from which they commission services should use a drug called Avastin as the preferred treatment option for an eye disease generally referred to as wet age-related macular degeneration ("WAMD"). I will start by setting out a bare outline of the facts which give rise to the claim. In doing so I will refer to aspects of the EU drug licensing regime, and some other factual matters, that I will need to explain more fully at a later stage; but more detail generally can be found in Whipple J's comprehensive judgment.

2. *CCGs and NHS Trusts*. The relevant constitutional arrangements within the NHS are clearly set out by Whipple J at paras. 37-47 of her judgment. For present purposes I need only note the following. CCGs are statutory corporations established under Chapter A2 of Part 2 of the National Health Services Act 2006. They have a statutory responsibility to commission medical and healthcare services: see section 3 (1). Typically they do so from NHS Trusts, which are separate legal entities. The relationship between CCGs and NHS Trusts in commissioning services is contractual. There are standard conditions of service governing such contracts. One (service condition 4) requires the parties to co-operate with one another to facilitate the delivery of services. It is common ground that as a result of that duty NHS Trusts from whom the Respondents commission treatment of patients with WAMD will have to take the Policy into account in making their decisions about which drug to use. The Policy is thus not as such binding on the Trusts, but the CCGs' intention and no doubt expectation is that it will be followed.

3. *Treatment of WAMD*. WAMD is a very common disease worldwide, mainly (as the name indicates) among older people. It is now generally treated by the injection into the eye ("intravitreal injection") of so-called "anti-VEGF agents", which inhibit the over-production of the protein which causes the condition.

4. *Avastin and its licensing*. The first anti-VEGF agent to be used in this way was a drug produced by Roche[1] (the First Interested Party) marketed as Avastin, of which the active ingredient is bevacizumab. Avastin was originally developed for the treatment of colorectal cancer. It was approved for that purpose by the US Food and Drug Administration in 2004, and subsequently for treatments of other cancers, and it is now widely licensed for such purposes internationally. It was licensed by the European Commission on the recommendation of the European Medicines Agency ("the EMA") for such use in the EU in January 2005. The use of Avastin for the wholly different purpose of treating WAMD was initially experimental but soon became widespread, principally in the US and in developing countries but also to some extent in Europe, including the UK. At the root of the issues in this case is the

[1] It is not necessary, and I will not attempt, to distinguish between the specific companies in the three pharmaceutical groups with which we are concerned – Roche, Bayer and Novartis.

fact that Roche has never applied, whether to the FDA or by way of an EU marketing authorisation, to vary the licence for Avastin to cover its use for the treatment of WAMD; indeed its formal "Summary of Product Characteristics" ("SMPC") says in terms that it is "not formulated for intravitreal use". Use of a medicine otherwise than for the purposes, or under the conditions, specified in its licence is generally described as "off-label". Off-label use of a drug is not necessarily unsafe or otherwise inappropriate, provided that the clinician takes full responsibility for the decision to use it.

5. *Compounding.* Avastin is supplied in glass vials containing 4 ml of fluid. For the oncological uses for which it is licensed the contents of the vial are diluted before administration. The amount required for intravitreal use is no more than 0.1 ml per injection (undiluted). Typically, therefore, the contents of each 4ml vial are divided for such use between a large number of syringes. That process was referred to before Whipple J as "compounding"[2], and Avastin which has been divided in that way as "compounded bevacizumab" ("CB"); likewise, businesses or institutions which compound Avastin have been referred to as "compounders". Whipple J herself also used the term "aliquoting", which refers to the division of a larger quantity of a drug into equal (typically dose- or sample-size) quantities. As we shall see, in some of the EU case-law compounding is described as "repackaging": that too is rather odd language, because it seems awkward to describe a syringe as a "package", but, as we will see, the terminology appears to have been chosen in order to reflect the language of the applicable legislation.

6. *Lucentis and Eylea.* Meanwhile other anti-VEGF agents have been developed and, unlike Avastin, have received EU marketing authorisations specifically for intra-ocular use to treat WAMD. The two which are in widespread use in this country are:

   – Lucentis (active ingredient ranibizumab), which was developed by Roche but which is licensed in Europe to Novartis. Lucentis received its EU marketing authorisation in 2007. It was originally supplied in glass vials containing 0.23 ml, together with a syringe into which the clinician would draw off the contents of the vial: thus both vial and syringe would be for single use only. Latterly, after (we were told) considerable regulatory effort, its marketing authorisation was extended to cover the supply of Lucentis in a pre-filled single-use syringe.

   – Eylea (active ingredient aflibercept), which was developed by Bayer and which received its EU marketing authorisation in 2012. It is supplied in a single-use glass vial, from which the clinician will need to draw the requisite dose into a syringe.

7. *Cost differential.* The circumstance which has led to these proceedings is that the cost of treating WAMD using Lucentis or Eylea is enormously greater than that of using Avastin (that is, CB). At published prices Lucentis costs about £550 per injection and Eylea about £800, although NHS Trusts are likely to be able to negotiate a substantial discount. CB, by contrast, can apparently be purchased from compounders for about £28 per injection. Typically, treatment for WAMD will involve a course of ten

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[2] This seems to be almost the opposite of the normal meaning of the verb "compound", given that no new ingredient is added to the bevacizumab; but this specialist usage is apparently well understood.

injections over a period of rather more than a year. It appears from the evidence before us that some health authorities and clinicians suspect that the reason why Roche has not applied for a licence for the use of Avastin to treat WAMD is that that would destroy the very lucrative market for Lucentis. Roche lodged a witness statement from Mr Robert Ferraro, the Vice-Director of its Group Legal Department, setting out what he said were legitimate reasons why it had not applied for such a licence. Whipple J made no finding on that question, and it is not necessary for us to do so either.

8. *The move for clinicians to prefer Avastin.* In view of that price differential it is unsurprising that once Lucentis and Eylea became available on the UK market considerable interest developed in whether clinicians, particularly in the NHS, should be encouraged to use CB in preference. There were, however, regulatory and other concerns, some of which we will have to consider in this appeal, about promoting the use of Avastin in circumstances where its marketing authorisation did not cover its intra-ocular use. The question was addressed in an editorial in the *British Medical Journal* in November 2014 urging the government "to remove the hurdles" to the use of Avastin for the treatment of WAMD. In December 2014 the Royal College of Ophthalmologists ("the RCO") issued a statement to essentially the same effect, saying that Avastin was as safe and effective as Lucentis and Eylea. On 23 February 2015 the Chairs of all or most of the CCGs in England wrote to the Secretary of State for Health urging him, *inter alia*, to authorise the National Institute for Health and Clinical Excellence ("NICE")[3] to review the comparative cost-effectiveness of Avastin, Lucentis and Eylea, evidently with a view to opening the way to the greater use of CB.

9. *The NICE Guideline.* In January 2018 NICE published its Guideline NG82 on "The Diagnosis and Management of Age-Related Macular Degeneration". Chapter 10 of the Guideline reviewed the use of CB, Lucentis and Eylea in the treatment of WAMD. Its recommendation 22 was that "no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments have been seen in the trials considered by the guideline committee" and included a footnote pointing out that, that being so, "comparable regimens will be more cost effective if the agent has lower net acquisition, administration and monitoring costs". That is somewhat coyly expressed (for reasons explained in the introduction to chapter 10 – see para. 33 of the judgment of Whipple J), but it makes it clear that there were no safety or effectiveness grounds for not preferring Avastin if it was indeed cheaper in real terms.

10. *The MHRA review.* The regulatory status of CB as a treatment for WAMD has been considered on more than one occasion by the Medicines and Healthcare Products Regulatory Agency ("the MHRA"), which is the government agency responsible for ensuring the safety and efficacy of medicines. At the time of the hearing before Whipple J its position was that, whereas Avastin was licensed, CB should be regarded as a distinct and unlicensed product. Whipple J was prepared to proceed on that basis but she noted some inconsistencies in how the MHRA had expressed itself on other occasions, and she was not convinced that its stance before her was correct and that the use of CB to treat WAMD should not be treated as off-label use of Avastin; she accordingly encouraged the MHRA to review its position. It has since done so. The

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[3] The relevant statutory responsibilities of NICE are set out at paras. 51-54 of Whipple J's judgment.

review, published in July 2019, gives a full and careful account of the background, including a review of the literature about the safety of CB and an explanation of the compounding process: I shall have to return to some aspects of that later. Its conclusion is that the compounding of Avastin does not in itself produce a distinct "unlicensed product" but that if and to the extent that CB is "placed on the market" for intravitreal use it would require a distinct marketing authorisation covering that use. It acknowledges that the question whether or in what circumstances CB is indeed "placed on the market" depends on the outcome of this appeal.

11. *The Policy: Decision.* The Northern Clinical Commissioning Group Joint Forum, which comprises the twelve Respondent CCGs, decided to investigate how they could make savings by promoting the use of Avastin for the treatment of WAMD in preference to Lucentis and Eylea. It identified a potential source of supplies of CB. It also took legal advice. In or about July 2017 it issued a Report addressed to the Governing Bodies of its constituent CCGs which explained the cost-savings that were likely to be achieved from the use of Avastin in preference to Lucentis and said that the evidence showed that there was no clinically significant difference between Avastin and Lucentis[4] in terms of safety or effectiveness: it referred in particular to the NICE Guideline, which had already been published in draft. The Report attached a draft policy ("the Policy") which the CCGs were asked to adopt, whereby Avastin would be offered as "the preferred treatment option" to patients with WAMD. The Policy was accompanied by drafts of a Q&A sheet addressed to clinicians and a sheet headed "Information and Advice for Patients". The latter makes it clear to patients that while Avastin is the preferred treatment on cost grounds they can choose to be treated with Lucentis or Eylea.

12. *The Policy: Content.* The introductory section of the Policy, headed "Background", reads as follows:

> "Neovascular (wet) age-related macular degeneration (wAMD) is a common condition that affects people aged 50 years and older, and causes severe impairment of central vision. There are approximately 20,000 new cases per year in England and 1,379 for the North East and Cumbria. Projections suggest that the number of prevalent cases of wAMD will increase steadily due to population ageing.
>
> Ranibizumab (Lucentis) and aflibercept (Eylea) are licensed for the treatment of AMD. Both treatments have been approved by NICE for use in the NHS if the companies provide the drug with the discount agreed in the patient access scheme. Lucentis is priced at £742 per injection[5] and Eylea is priced at £816 per injection. The discount agreed in the patient access scheme is confidential but widely acknowledged to be about [___][6] per injection.

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4 There is no explicit reference to Eylea.

5 We were told that the figure for Lucentis was inaccurate, but nothing turns on that for our purposes.

6 The figure is redacted in the version produced to the Court.

> Bevacizumab (Avastin) is licensed for the treatment of certain cancers. Avastin is also widely used to treat AMD outside of the terms of its licence (commonly referred to as 'off-label') particularly in the private sector and in other parts of the world including the USA. Avastin is priced at £28 per injection. Studies have shown that there is no clinically significant difference between Avastin and Lucentis in terms of safety or effectiveness. There is no comparative study comparing Avastin and Eylea in the treatment of wAMD, but there is evidence that there is no clinically significant difference in safety between Avastin and Eylea for the treatment of macular edema caused by retinal vein occlusion. The inclusion of Avastin as a treatment option for wAMD therefore represents a significant saving to the NHS with no reduction in the quality of care."

There then follow two sections headed "Policy", the first relating to the use of Avastin and the second to the use of Lucentis and Eylea. I need only set out the former, which reads:

> "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)."

The Policy concludes by setting out the criteria for discontinuation of treatment, which are not relevant for our purposes.

13. *The Policy: Implementation.* As explained above, the Respondents could not themselves implement the Policy. It would take effect by the Trusts from which they commission treatment for patients with WAMD implementing in their own treatment decisions; but, as I have said, it was the intention and no doubt the expectation that they would do so. The Trusts in question are City Hospitals Sunderland NHS Foundation Trust, County Durham and Darlington NHS Foundation Trust, North Cumbria University Hospitals Trust, South Tees Hospitals NHS Foundation Trust and Newcastle upon Tyne Hospitals NHS Foundation Trust ("the Trusts").

14. *The Policy: sourcing of CB.* Although the clear implication of the Report and the Policy is that supplies of CB would be available – and, apparently, available forthwith – they give no details. There is nothing in either document about the practicalities of

obtaining CB, nor is there any consideration of any associated legal or regulatory issues. The Respondents' evidence before Whipple J was that there were at least four NHS Trust hospital pharmacies in England which had the capacity to compound and supply substantial quantities of Avastin for intravitreal use and had done so in the past, and at least one commercial supplier.[7] A contemporary letter, to which I refer at para. 144 below, appears to show that the Respondents at some point identified a particular manufacturer, but there is no evidence as to who that was. The absence of evidence on that point gives rise to one of the principal difficulties of the case: it is necessary to consider the lawfulness or otherwise of the supply of CB in the abstract.[8]

15. It is that Policy (including the accompanying documents) which is the subject of the Appellants' challenge in the present proceedings. I will explain the detailed grounds of challenge later. It is sufficient to say at this point that it is a central part of the Appellants' case that the implementation of the Policy would lead to breaches by the Trusts, and possibly others, of the EU legislation which regulates the marketing and manufacture of medicines, and the domestic implementing legislation.[9] It is important to appreciate that, subject to one self-contained point ("issue 3E"), that is the only basis of challenge with which we are now concerned. It is not suggested that there was anything objectionable on public law grounds in the Respondents taking cost into account in formulating the Policy or in their forming a view about the clinical effectiveness or safety of CB. At para. 43 of her judgment, Whipple J said:

> "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."

At para. 47, having referred to *R v NW Lancashire HA ex p A* [2000] 1 WLR 977 and *R (Rogers) v Swindon NHS PCT* [2006] EWCA Civ 392, [2006] 1 WLR 2649, and *R (AC) v Berkshire West PCT* [2011] EWCA Civ 247 she said:

> "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

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7 The hospitals identified were the Queen Alexandra Hospital, Portsmouth, the Royal Liverpool Hospital, the Royal Free in London, and the Wirral University Teaching Hospital: the Royal Liverpool was mentioned several times in the course of argument before us, but apparently only by way of example. The commercial supplier was named as ITH Pharma.

8 There was some debate in the skeleton arguments about how it came about that the issues had to be resolved in such a factual vacuum, but it was not developed in oral submissions, and it would not be useful for us to seek to attribute blame.

9 At the time that the Policy was promulgated the UK was of course still a member of the EU. Even since its withdrawal on 31 January the relevant legislation remains in effect at least until the end of this year: see section 1A of the European Union (Withdrawal) Act 2018 (as amended by the European Union (Withdrawal Agreement) Act 2020).

> bound to take account of guidance of various sorts, including NICE guidance, but it is entitled to come to its own conclusion."

Neither proposition was challenged before us.

16. Bayer was represented before us by Ms Jemima Stratford QC, leading Ms Emily MacKenzie; and Novartis by Mr Thomas de la Mare QC, leading Mr Eesvan Krishnan. Ms Stratford and Mr de la Mare sensibly agreed to split responsibility between them for different parts of the Appellants' submissions. The CCGs were represented by Mr David Lock QC, leading Mr David Blundell. All these counsel appeared before Whipple J.

17. A number of Interested Parties were joined in the proceedings. At first instance only Roche appeared. It was also represented before us by Ms Victoria Wakefield QC, but it made no submissions. Two of the other Interested Parties – the Secretary of State for Health and Social Care, represented by Mr George Peretz QC, and the Association of the British Pharmaceutical Industry ("the ABPI"), represented by Ms Monica Carss-Frisk QC, appeared before us, though not below. The interest of the Secretary of State does not simply lie in his responsibility for the NHS generally: more particularly, the MHRA is an executive agency of his Department. Mr Peretz was instructed to explain the position of the MHRA following the 2019 review but also to advance specific submissions on some of the particular issues raised by the appeal.

THE LEGISLATION

(1) THE EU LEGISLATION

Introduction

18. At paras. 99-109 of her judgment Whipple J set out a careful analysis of what she called "the boundary between EU law and domestic law" in the field of health policy, which ultimately derives from article 168 (7) of the TFEU. None of that analysis was challenged before us, and I need not reproduce it in full, but her concluding paragraphs are useful background.

19. At para. 107, having considered the decisions of the CJEU in *Duphar BV v Netherlands* 238/82, [1985] 1 CMLR 256, *Menarini Industrie Farmaceutiche Riunite Srl v Ministero della Salute*, C-352-6/07, C-365-7/07 and C-400/07, [2009] ECR-I 2495, *R (Association of the British Pharmaceutical Industry) v Medicines and Healthcare Regulatory Agency*, C-62/09, [2011] PTSR 391, and *Commission v Poland*, C-185/10, ECLI:EU:C:2012:18, she said, at para. 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*)."

20. At paras. 108-109 she endorsed the following summary contained in a report published by the EU entitled "Study on off-label use of medicinal products in the European Union":

"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)."

The Medicines Directive

21. The full title of the Medicines Directive is "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to Medicinal Products for Human Use". The original Directive has been amended on a number of occasions.

22. The Directive has 61 recitals. The only ones to which I need to refer are:

> "(2) The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.
>
> …
>
> (35) It is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Community through to supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions. The requirements which must be adopted for this purpose will considerably facilitate the withdrawal of defective products from the market and allow more effective efforts against counterfeit products.
>
> …
>
> (40) The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information."

23. The Directive comprises sixteen Titles and two Annexes. Title I contains definitions, to some of which I will refer in due course. The other Titles which are material for our purposes are II-IV, VII and IX. I take them in turn.

Title II

24. Title II is headed "Scope". Article 2 is the primary article defining the scope of the Directive. Paragraph (1) reads:

> "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."

"Medicinal product" is defined in article 1, but nothing turns on the details of the definition for our purposes. There is no definition of the term "placed on the market", which, as will appear, is central also to Title III.

25. Article 3 identifies a number of types of medicinal product which fall outside the scope of the Directive. For our purposes only items 1 and 2 are relevant. They read:

> "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)."

26. Article 5 deals with what are known in the industry as "specials". Paragraph (1) reads:

> "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."

Title III

27. Title III is headed "Placing on the Market". The provisions relevant for our purposes are in Chapter 1, which provides for a system under which medicinal products may only be "placed on the market" if they have a "marketing authorisation". In the cases of some products the marketing authorisation may be granted by the competent authority within a member state; but in the case of "biological" medicines, which include the anti-VEGF agents with which we are concerned, it may only be granted by the European Commission on the recommendation of the EMA: see para. 39 below. The grant of a marketing authorisation is often referred to as "licensing".

28. Article 6 is the primary provision under Chapter 1. It reads (so far as material):

> "(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 or an authorisation has been granted in accordance with [the "EMA Regulation" considered below].
>
> 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. …
>
> (1a)-(2) …"

29. It will be observed that what article 6 regulates is the "placing on the market" of a medicinal product. That is not, as I have said, a defined term. It was common ground before us that it does not refer only to the initial supply by the manufacturer or importer but also covers subsequent steps in the supply chain, but I will have to consider later at what point the process is to be treated as coming to an end. It will also be noted that an additional marketing authorisation is required in any of the circumstances identified in the second sub-paragraph of paragraph (1).

30. Article 8 sets out the procedure for applying for a marketing authorisation. Paragraph (3) provides that an application must be accompanied by the "particulars and documents" which it lists at (a)-(m), which are to be submitted "in accordance with Annex 1". Annex 1 specifies with great particularity the requirements of a "marketing authorisation dossier". Mr de la Mare took us through the requirements of this paragraph (with some reference also to Annex 1) in some detail. They are, as one would expect, extremely rigorous. Among the matters specified are:

> "(d) Description of the manufacturing method.
>
> (e) Therapeutic indications, contra-indications and adverse reactions.
>
> (f) Posology, pharmaceutical form, method and route of administration and expected shelf life.
>
> (g) …
>
> (ha) A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting audits, in accordance with point (f) of Article 46. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice."

(For article 46, referred to in (ha), see para. 34 below.)

31. Article 11 specifies the information which must appear in the SMPC. This covers much the same matters as article 8, including therapeutic indications and shelf life.

Title IV

32. Title IV is headed "Manufacture and Importation". The primary provision is article 40. Paragraphs (1) and (2) read:

> "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."

(The unnumbered second sub-paragraph under paragraph (2) was referred to before us, in accordance with EU practice, as article 40.2 *bis*.)

33. It will be noted that the effect of paragraph (2) is that a manufacturing authorisation is required for the processes of "dividing up, packaging or presentation", which would appear to cover compounding; but that that is subject to the exception relating to such processes when carried out in pharmacies. I shall have to return to this below.

34. The following provisions of Title IV, and in particular article 46, impose various, and stringent, obligations on the holder of a manufacturing authorisation. These include, at article 46 (f), an obligation "to comply with the principles of good manufacturing practice for medicinal products". Those principles are set out in Commission Directive 2003/94/EC. I need not refer to them here, save to note that article 5 requires that:

> "all manufacturing operations for medicinal products subject to a marketing authorisation are carried out in accordance with the information provided in the application for marketing authorisation".

That is a reference to article 8.3 (d): see para. 30 above. In his oral submissions Mr de la Mare submitted that the effect of that provision was that a manufacturing authorisation could not be given for a product that did not have a marketing authorisation, except in the case of what he described as "an investigational medicine for which there is no marketing authorisation but an exemption scheme under the Directive". Accordingly, he submitted, "there is no prospect of any manufacturing licence being obtained to make CB unless and until there is a marketing authorisation for CB". Mr Lock did not respond to that specific submission but I am not at present persuaded that it is correct. However, the point is not determinative of any of the issues which we have to decide.

Title VII

35. Title VII is headed "Wholesale Distribution and Brokering of Medicinal Products". The relevant provisions for our purposes are those regulating wholesale distribution, which is defined in article 1.17 as:

> "All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned."

36. The principal provision with which we are concerned is article 77, which requires wholesale distributors of medicinal products to have a "distribution authorisation". The relevant provisions read:

> "(1) Member States shall take all appropriate measures to ensure that the wholesale distribution of medicinal products is subject to the possession of an authorisation to engage in activity as a wholesaler in medicinal products, stating the premises located on their territory for which it is valid.
>
> (2) …
>
> (3) Possession of a manufacturing authorization shall include authorization to distribute by wholesale the medicinal products covered by that authorization. Possession of an authorization to engage in activity as a wholesaler in medicinal products shall not give dispensation from the obligation to possess a manufacturing authorization and to comply with the conditions set out in that respect, even where the manufacturing or import business is secondary.
>
> (4)-(7) …"

37. I should also note that article 76 restricts the distribution of medicinal products to those covered by a marketing authorisation. The relevant provisions read:

> "(1) Without prejudice to Article 6, Member States shall take all appropriate action to ensure that only medicinal products in respect of which a marketing authorization has been granted in accordance with Community law are distributed on their territory.
>
> (2) In the case of wholesale distribution and storage, medicinal products shall be covered by a marketing authorisation[10] granted pursuant to [the EMA regulation] or by the competent authorities of a Member State in accordance with this Directive.

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[10] Spelling pedants will wish to be assured that the alternation between "authorization" and "authorisation" is a feature of the Directive itself (at least as amended) rather than an artifact introduced by me.

(3)-(4) …"

Title IX

38. Title IX is headed "Pharmacovigilance" and requires member states to operate pharmacovigilance systems. Article 101 (1) *bis* reads:

> "The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure."

The EMA Regulation

39. Regulation (EC) 726/2004 of the European Parliament and Council lays down the procedures for authorisation and supervision of medicinal products at the EU level and for that purpose establishes the EMA. I will for convenience refer to it as "the EMA Regulation". Article 3.1 reads:

> "No medicinal product appearing in the Annex may be placed on the market within the Union unless a marketing authorisation has been granted by the Union in accordance with the provisions of this Regulation."

The Annex referred to is Annex I, which is headed "Medicinal Products to be Authorised by the Union". Item I in the list of such products reads:

> "Medicinal products developed by means of one of the following biotechnological processes:
>
> — recombinant DNA technology,
>
> — controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
>
> — hybridoma and monoclonal antibody methods."

It is by virtue of those provisions that, as noted above, the anti-VEGF agents with which we are concerned in this case have their marketing authorisations granted by the EMA rather than by the domestic authorities.

(2) THE DOMESTIC LEGISLATION

40. The requirements of the Medicines Directive are now implemented in domestic law by the Human Medicines Regulations 2012 (to which I will sometimes refer as "the HMR"), which were made by the Secretary of State under (so far as material) the powers conferred by section 2 (2) of the European Communities Act 1972. Among their provisions are extensive amendments to the Medicines Act 1968. I take first the

provisions implementing the parts of the Directive relating to marketing authorisations, manufacturing authorisations and wholesale distribution, and then those which define the scope of the Regulations in accordance with Title II.

Marketing Authorisation

41. The provision intended to implement article 6 of the Directive is regulation 46. I need set out only paragraphs (1) and (6), which read (so far as relevant):

> "(1) A person may not sell or supply, or offer to sell or supply, an unauthorised medicinal product.
>
> …
>
> (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;
>
> (b)-(d) … ."

42. "Marketing authorisation" is defined in regulation 8 (1) as either "a UK marketing authorisation" or "an EU marketing authorisation". The former is defined as a marketing authorisation given by "the licensing authority", which is itself defined by regulation 6 as comprising the Ministers there specified: those Ministers in practice act through the MHRA. The latter is defined as a marketing authorisation granted under the EMA Regulation (see para. 39 above).

Manufacturing Authorisation

43. The provision intended to implement article 40 of the Directive is regulation 17. I need only set out paragraph (1), which reads:

> "(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)."

That prohibition is subject to various exceptions specified in the rest of the regulation, but I need not set them out here.

44. The terms "manufacture" and "assemble" are defined in regulation 8 (1) as follows:

> "'assemble', in relation to a medicinal product or an active substance, includes the various processes of dividing up, packaging and presentation of the product or substance, and 'assembly' has a corresponding meaning"
>
> …

> 'manufacture' in relation to a medicinal product, includes any process carried out in the course of making the product, but does not include dissolving or dispersing the product in, or diluting or mixing it with, a substance used as a vehicle for the purpose of administering it."

45. By regulation 21 the authority to grant a manufacturer's licence is conferred on the licensing authority, i.e. in practice the MHRA (see para. 42 above).

Wholesale Dealer's Licence

46. The provision intended to implement articles 76-77 of the Directive is regulation 18. The relevant parts are as follows:

> "(1) A person may not except in accordance with a licence (a 'wholesale dealer's licence') —
>
> (a) distribute a medicinal product by way of wholesale dealing; or
>
> (b) possess a medicinal product for the purpose of such distribution.
>
> (2) Paragraph (1) —
>
> (a) does not apply —
>
> (i) to anything done in relation to a medicinal product by the holder of a manufacturer's licence in respect of that product,
>
> (ii)-(iii) …
>
> (b)…
>
> (3)…
>
> (4) In these Regulations a reference to distributing a product by way of wholesale dealing is a reference to —
>
> (a) selling or supplying it; or
>
> (b) procuring or holding it or exporting it for the purposes of sale or supply,
>
> to a person who receives it for a purpose within paragraph (5).
>
> (5) Those purposes are —
>
> (a) selling or supplying the product; or
>
> (b) administering it or causing it to be administered to one or more human beings,
>
> in the course of a business carried on by that person.

> (6) A wholesale dealer's licence does not authorise the distribution of a medicinal product by way of wholesale dealing, or possession for the purpose of such distribution, unless a marketing authorisation … is in force in respect of the product [subject to two immaterial exceptions]
>
> (7) …"

47. The term "business", which appears in paragraph (5), is defined in regulation 8 (1) as including:

> "(a) a professional practice;
>
> (b) any activity carried on by a body of persons whether corporate or unincorporated; and
>
> (c) the provision of services by or on behalf of the Secretary of State, the Minister for Health, Social Services and Public Safety, the Welsh Ministers or the Scottish Ministers as the case may be under [the National Health Service Act 2006 and the equivalent legislation governing the NHS in other parts of the UK]."

Scope

48. The restrictions on the scope of the Directive effected by article 3 (see paras. 25 above) are intended to be implemented by regulations 4 of the Regulations. Regulation 4 is headed "Special Provisions for Pharmacies Etc." Paragraph (1) reads:

> "Regulations 17 (1) (manufacturing of medicinal products: requirement for licence) and 46 (requirement for authorisation) do not apply where any provision of section 10 of the Medicines Act 1968 so provides."

49. That requires reference to section 10 of the Medicines Act 1968, which is headed "Exemptions for Pharmacists" and was itself amended by the Regulations. It contains various exemptions, but we were referred only to sub-sections (1) and (3). These read (as amended):

> "(1) The restrictions imposed by regulations 17 (1) (manufacturing of medicinal products) and 46 (requirement for authorisation) of the 2012 Regulations do not apply to anything which is done in a registered pharmacy, a hospital, a care home service or a health centre and is done there by or under the supervision of a pharmacist and consists of —
>
> (a) preparing or dispensing a medicinal product in accordance with a prescription given by a practitioner, or
>
> (b) assembling a medicinal product provided that where the assembling takes place in a registered pharmacy —

> (i) it shall be in a registered pharmacy at which the business in medicinal products carried on is restricted to retail sale or to supply in circumstances corresponding to retail sale and the assembling is done with a view to such sale or supply either at that registered pharmacy or at any other such registered pharmacy forming part of the same retail pharmacy business, and
>
> (ii) the medicinal product has not been the subject of an advertisement;
>
> and those restrictions do not apply to anything done by or under the supervision of a pharmacist which consists of procuring the preparation or dispensing of a medicinal product in accordance with a prescription given by an appropriate practitioner, or of procuring the assembly of a medicinal product.
>
> …
>
> (3) Those restrictions do not apply to the preparation or dispensing in a registered pharmacy of a medicinal product by or under the supervision of a pharmacist in accordance with a specification furnished by the person to whom the product is or is to be sold or supplied, where —
>
> (a) the product is prepared or dispensed for administration to that person or to a person under his care."[11]

(Sub-section (3) covers the case of "specials" and thus reflects article 5.)

THE CJEU CASES ABOUT COMPOUNDED AVASTIN

INTRODUCTION

50. Health providers elsewhere in Europe have been as anxious as the CCGs in the present case to take advantage of the lower cost of Avastin as a treatment for WAMD, notwithstanding the absence of a marketing authorisation for intra-ocular use. The use of CB in, in particular, Germany and Italy has led to legal proceedings which have reached the CJEU on three occasions. The cases are:

(1) *Novartis Pharma GmbH v Apozyt GmbH*, C-535/11, ECLI:EU:C:2013:226 ("*Apozyt*");

(2) *F. Hoffmann-La Roche Ltd v Autorita Garante della Concorrenza e del Mercato*, C-179/16, C-179/16 ECLI:EU:C:2018:25 ("*AGCM*"); and

(3) *Novartis Farma SpA v Agenzia Italiana del Farmaco*, C-29/17, ECLI:EU:C:2018:931 ("*AIFA*").

[11] There was originally a head (b) but it was removed by amendment some years ago.

I should say that the decision of the Court in *AIFA* was not available at the time of Whipple J's decision, though the Opinion of the Advocate General was published in the interval between the oral argument and the promulgation of her judgment and she referred to it.

51. The first of those decisions, *Apozyt*, which is affirmed and in particular respects developed by the other two, holds that in certain circumstances the supply of CB is not caught by the requirement for a marketing authorisation, and also that its preparation does not in specified circumstances require a manufacturing authorisation; this was referred to before us as "the *Apozyt* exemption"[12]. The scope and effect of the *Apozyt* exemption is central to the issues before us, and it is important that I consider it first.

(1) *APOZYT*

Introduction

52. *Apozyt* was a reference by the Landgericht Hamburg. The essential facts are that Apozyt GmbH was a commercial undertaking which was in the business of preparing and supplying single doses of both Avastin and Lucentis[13] in pre-filled syringes to doctors throughout Germany for intra-vitreal injection for the treatment of WAMD: that is, it was a compounder. The compounding was not performed by pharmacists, but the reference proceeded on the basis that Apozyt was "a person legally authorised by [German law] to carry out such processes", within the meaning of the final words of article 40.2 *bis* of the Medicines Directive[14]. It was Apozyt's evidence that the process was carried out "in each case on the instructions of a pharmacy which has a doctor's prescription for each patient" (see para. 37 of the Opinion of Advocate General Sharpston).

53. Novartis, as the licence-holder for Lucentis, brought proceedings asserting that Apozyt's activities constituted a breach of article 6 of the Medicines Directive. The Landgericht referred the following question to the CJEU:

> "Does the term 'developed' in the introductory words of point 1 of the Annex to [Regulation No 726/2004] extend to processes in which portions only of a medicinal product which has been developed and produced on a ready-to-use basis in accordance with the above procedures are drawn off into another container, after being prescribed and ordered at the time concerned by a doctor, if as

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12 The label is not strictly accurate: see para. 91 below.

13 Novartis had not at that point obtained a marketing authorisation for its own pre-filled syringe (see para. 6 above). It is not clear, but does not matter for present purposes, whether Apozyt extracted more than one dose from each vial of Lucentis: it will certainly have done so for Avastin, which comes in much larger vials.

14 There was some debate before us as to whether it had been definitively established that Apozyt had such an authorisation. The Advocate General appears to state that it did, but the Court treated it as a matter which was required to be established when the case returned to the German court. However, nothing turns on this as regards the issues of principle.

> a result of the process the composition of the medicinal product is not modified, and therefore in particular to the production of pre-filled syringes which have been filled with a medicinal product which is authorised under the Regulation?"

54. The Advocate General, accepting a submission by the Commission, considered that the question as formulated was wrong to focus on the language of the EMA Regulation – and in particular on the term "developed" – because "the substantive requirements are set out in the Directive, while the Regulation contains rules that are essentially procedural" (see para. 47 of her Opinion). Accordingly she reformulated the question (at para. 50) as:

> "Where a medicinal product falling within paragraph 1 of the Annex to Regulation No 726/2004 has been developed and produced on a ready-to-use basis and has been granted a marketing authorisation specifying the containers in which the product is to be marketed, can a process which (1) involves portions only of that product being drawn off into another container, after being prescribed and ordered at the time concerned by a doctor, but which (2) does not involve any modification to the composition of the product, be carried out without requiring a separate marketing authorisation, or a variation of the existing marketing authorisation, under the Regulation?"

She conducted her analysis thereafter principally by reference to the terms of the Directive.

55. The Court considered the Commission's submission about the formulation of the question at paras. 36-39 of its Judgment. The passage is somewhat opaque, but it does not seem that it accepted the Advocate General's reformulation, because it treated the requirement for a marketing authorisation as deriving from article 3 (1) of the EMA Regulation rather than from article 6 of the Directive (though it does appear, like her, to regard the Landgericht's focus on the meaning of the term "developed" as unhelpful). For our purposes, however, the debate is not important: the Court's reasoning is equally applicable whichever provision is the formal source of the requirement for a marketing authorisation for Avastin.

56. The Court's formal *dispositif* was as follows:

> "Activities such as those at issue in the main proceedings, provided that they do not result in a modification of the medicinal product concerned and are carried out solely on the basis of individual prescriptions calling for processes of such a kind – a matter which falls to be determined by the referring court – do not require a marketing authorisation under Article 3(1) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, but remain, in any event, subject to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as

> amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010."

57. The effect of the decision therefore was that in the circumstances identified following the words "provided that" a compounder does not require a marketing authorisation. However, in the text of the Judgment, though not in its formal decision, the Court also addressed the question whether Apozyt's activities required a manufacturing authorisation. I take its reasoning on those two questions in turn.

Marketing Authorisation

58. The paragraphs of the Court's reasoning which address this aspect begin with paras. 41-42, which read 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 biotechnological processes listed in point 1 of the Annex to 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."

Although that conclusion is stated by reference to article 3 (1) of the EMA Regulation, it would, as already noted, apply equally to article 6 of the Medicines Directive.

59. At para. 43 the Court addresses Novartis's reliance on its earlier decision in *Aventis Pharma Deutschland GmbH v Kohlpharma GmbH*, C-433/00, [2002] ECR I-7761. In that case there were separate marketing authorisations for Insuman, an insulin product, depending on the pack size: one covered a pack containing ten "cartridges", while the other covered a pack of five. Aventis marketed Insuman in France in packs of five. Parallel importers bought such packs in France and bundled them into a single shrink-wrapped package, with an overall sticker, for marketing in Germany. It

was held that the marketing authorisation for a ten-cartridge pack did not cover a "double pack" of the kind in question. As to that, the Court says:

> "… [T]he circumstances of the present case can be distinguished from those at issue in *Aventis*, which concerned repackaging for the purposes of parallel trading, and the Court observes in particular, concurring with the Portuguese Government, that the activity carried out by a company such as Apozyt occurs after the medicinal products at issue in the main proceedings have been placed on the market. In particular, 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."

60. There was some debate before us as to the basis of the Court's reasoning in those paragraphs, but in my view it is adequately clear. There are essentially two elements.

61. First, it is clear from paras. 41-42 that the Court decided that the process of "placing on the market" came to an end at the point where a clinician prescribes the product in question for a particular patient. Thus any subsequent transfer of the product so prescribed is not part of that process; and that is so even where, as on the facts of *Apozyt*, it involves a supply from an outside provider rather than simply between health professionals (e.g. from hospital pharmacy to clinician). The basis on which the Court distinguishes *Aventis* in para. 43 is consistent with that analysis. The statement that the compounding process occurs "after the medicinal products … have been placed on the market" is potentially confusing, because it might suggest that what matters is the *initial* placing on the market; but I think it is clear that what the Court meant was, in effect, "after the medicinal products have ceased to be on the market". That is apparent not only from the reasoning of the prior paragraphs but from the second half of para. 43 itself: the point there made that Apozyt's activities are "analogous" with what could have been done by a doctor or hospital pharmacy shows that the Court was treating the compounding process as part of what is done with the product by (or at the instance of) the end-user, namely the prescribing doctor. This, therefore, is the basis for the "individual prescription" requirement confirmed in the *dispositif*.

62. Secondly, the Court was concerned to confine the "*Apozyt* exemption" to cases where the compounding consisted simply of a process of aliquoting – that is, mere division or "repackaging"[15] – and to exclude cases which could "be equated with a new placing on the market of a medicinal product" (see para. 42). That is the basis of the "no modification" requirement. It does not spell out its reasoning, but it is not difficult to divine: it is easy to see why the Court will have thought that the

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15 It does not use the term "repackaging" in this part of the Judgment (possibly because it would chime awkwardly with its distinguishing of *Aventis*, which was concerned with re-packaging in a more usual sense). But it does do so when summarising the effect of *Apozyt* at para. 73 of its Judgment in *AIFA* (see para. 82 below), and the term correctly conveys the essential point that there is no change in the substance of the product itself.

protections conferred by article 6 should continue to apply where the compounding process effected a change to the characteristics of the product itself.

63. That analysis, and in particular the first element, differed from that of the Advocate General, whose view had been that each step in the supply of a medicine constitutes a "placing on the market" up to the point where it is administered to the patient (see para. 58 of her Opinion). Mr de la Mare in his oral submissions made it plain that he believed that the analysis of the Advocate General was to be preferred, contrasting its "logical and legal purity" with what he described as the Court making law "on the hoof". That may or may not be a fair criticism, but our task is to identify the Court's reasoning and to apply it; and it is in my view clear that its reasoning was as I have analysed it above.

64. There remain important issues about the effect of both the "individual prescription" and the "no modification" requirements. But I will deal with those later.

Manufacturing Authorisation

65. Having reached its conclusion on whether Apozyt's supply of compounded Lucentis and Avastin required a marketing authorisation, the Court proceeded, at para. 44 of its Judgment, to observe that that was not determinative of the lawfulness of its activities, since there remained a separate question about whether it required a manufacturing authorisation under article 40 of the Medicines Directive. It proceeded to consider that question at paras. 45-53.

66. The first issue that arose in that connection was whether Apozyt's activities fell within the scope of the Directive at all. It was not submitted that article 3 had any application, no doubt because Apozyt was not a pharmacy. But the German Government submitted that Apozyt's activities fell within the terms of article 5 – that is, that it could be regarded as producing "specials". The Court considered that submission at paras. 45-50. It held that article 5 could not apply to the preparation of compounded Lucentis, since it was in substance the same product as that covered by the marketing authorisation: "the injection volumes used are no different from those provided for in the marketing authorisation and nor is the product used for a therapeutic indication not covered by the marketing authorisation" (para. 47). That was not true of Avastin, and the Court acknowledged that there might be circumstances where a doctor took the view that treatment with CB was preferable for a particular patient, in which case its preparation for that purpose would fall within article 5 (para. 48). I need not, however, consider this reasoning further, since no reliance is placed on article 5 in the present appeal.

67. On the basis, therefore, that the compounding of (at least) Lucentis fell within the scope of the Directive, the Court considered the application of article 40 at paras. 51-53 as follows:

> "51. With regard to the requirements applying to an activity such as that carried out by Apozyt, the referring court mentions Article 40 of Directive 2001/83. In that regard, it is indeed the case that, under the first subparagraph of Article 40(2) of the directive, authorisation, as referred to in that provision, is required for that activity in so far as it

> concerns the repackaging of medicinal products which have a marketing authorisation.
>
> 52. However, as Ireland and the Commission submit, under the second subparagraph of Article 40(2) of Directive 2001/83 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.
>
> 53. It will thus fall to the referring court to ascertain, in particular, on the one hand, whether Apozyt is 'legally authorised' in Germany to carry out such processes and, on the other, whether those activities are in fact included within a system for the retail supply of medicinal products by pharmacies. On the latter point, the referring court will in particular have to determine whether the processes in question are carried out only on the basis of individual prescriptions that call for them to be carried out."

68. It is necessarily implicit in those paragraphs that the compounding process can be regarded as constituting "preparation, dividing up, [or] changes in packaging or presentation" within the meaning of article 40.2. That is unsurprising: aliquoting can naturally be regarded as involving the "dividing up" of a product and/or changes in its "packaging" (once one gets over the oddity of referring to a syringe by that term). This is in any event confirmed by para. 58 of the Court's judgment in *AGCM* and para. 77 of its Judgment in *AIFA*: see below. Beyond that, the Court is simply (subject to one important gloss discussed at paras. 102-107 below) re-stating what appears in article 40.2 *bis* itself: the processes must be carried out by pharmacists in dispensing pharmacies (or by other persons legally authorised in the Member States) and solely for "retail supply". I will have to say more about those requirements below.

69. As we have seen the Court does not refer to the need for a manufacturing authorisation in its formal *dispositif*, no doubt because that had not been raised as a question by the referring Court. But that does not make what it says about it any the less authoritative.

The Subsequent Proceedings in Germany

70. As will have appeared, although the Landgericht had made the reference in *Apozyt* on the basis of certain facts, it had not been definitively established whether those facts did actually obtain. That issue was determined in subsequent proceedings in Germany. We were referred to the decision of the Hanseatisches Oberlandesgericht Hamburg, in the course of a judgment dated 18 December 2015, on the issue whether Apozyt's activities "result[ed] in a modification of the medicinal product".

71. The relevant passage is at paras. 208-215 of the Oberlandesgericht's judgment. It began by rejecting a submission by Novartis that it followed from the fact that pre-filled syringes prepared by Apozyt were a deviation from the terms of the marketing authorisations for both Avastin and Lucentis that the product had been "modified" in the relevant sense. It pointed out that that could not have been what the CJEU meant

by "modification". It had of course been well aware that compounding necessarily involved a departure from the terms of the marketing authorisation in many respects; if that in itself constituted modification there would have been no need for any further enquiry. Rather, what it must have intended was that the product should have undergone "a modification in its composition due to the decanting process into pre-filled syringes". As to that, it was clear that Apozyt did not "take anything from, or add anything to, the substance of the decanted product" (para. 212). However, the Oberlandesgericht appears to have accepted that a modification, in the CJEU's sense, would also occur if there were (para. 213)

> "as a result of the decanting process, as, necessarily to be expected, modification in the biological, chemical or physical properties of the product compared with the original physical state of the product … if as a result quality, efficacy and safety … would be significantly impacted."[16]

As to that, it held, in effect, that it had been for Novartis to adduce evidence of modification of that character and it had not done so.

(2) *AGCM*

72. *AGCM* is a competition case and only tangentially relevant to the issues before us. There is in fact only a single passage in the Judgment of the Court to which I need refer, but I will summarise the background in slightly more detail than would otherwise be necessary since it is also relevant to the *AIFA* decision.

73. Avastin was widely used in Italy for the treatment of WAMD and was included by the Agenzia Italiana del Farmaco ("AIFA"), the Italian state medicines agency, among the products for whose intravitreal use clinicians could obtain reimbursement from the national health service, the Servizio Sanitario Nationale ("the SSN"). It was accordingly a serious competitive threat to Lucentis. The Italian competition authority ("AGCM") found that Roche and Novartis had entered into an agreement to seek to promote (unjustified) public concern about the safety of Avastin used intravitreally and that as a result its use had declined steeply, with a corresponding increase in the use of Lucentis at huge cost to the public purse; and that this constituted a breach of article 101 of the TFEU. It imposed penalties accordingly. Roche challenged that decision in the Italian courts.

74. The Consiglio di Stato referred to the CJEU four questions about (in broad outline) whether the off-label use of a medicinal product could ever be regarded as part of the relevant market. The Grand Chamber, following the Opinion of Advocate General Saugmandsgaard Øe, answered those questions essentially in favour of AGCM.[17]

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16 The translation with which we were provided (by Novartis, but without objection from the Respondents) was not professionally prepared and contains some awkwardnesses of expression (though these appear to result from over-literalness, which is a fault in the right direction). However, the overall meaning is clear enough.

17 I should record that Roche's evidence before Whipple J was that the CJEU's decision on the reference was not dispositive of its challenge to the findings of the AGCM, which continues to be disputed in the Italian courts.

75. The only passage in the Judgment of the Court which bears on the issues before us is at paras. 55-59, where it addresses an argument on the part of Roche that the use of Avastin to treat WAMD was not only off-label but in breach of article 40 of the Medicines Directive because much of it:

> "was serially repackaged without manufacturing authorisation and was sold to healthcare providers in advance, before the submission of individual prescriptions".

The Court's response (para. 59) was that the relevant EU rules do not prohibit the off-label prescription of a medicinal product "nor its repackaging for such use", but that they do require compliance with "the conditions laid down". In the latter connection it referred (at para. 58) to *Apozyt*, which it described as having held that:

> "[t]he 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 …".

That is of some value as a short summary of how the Court understood its earlier decision.

(3) *AIFA*

76. As noted above, AIFA had, in effect, authorised the use of Avastin as a treatment for WAMD by including it in the list of products for which clinicians working in the Italian national health service could claim reimbursement. Novartis, as licensee of Lucentis, brought proceedings in the Italian courts claiming that since there was no marketing authorisation for the supply of Avastin for intravitreal use such supply constituted a breach of article 6 of the Medicines Directive. The Consiglio di Stato made a reference to the CJEU.

77. The facts before the Court can be summarised briefly. Para. 24 of the Opinion of Advocate General Saugmandsgaard Øe records that for use in the treatment of WAMD Avastin is

> "… repackaged by taking the medicinal substance out of the original vial and dividing it into several single-use syringes each containing 0.1 ml, for intravitreal injection".

It appears from paras. 27-30 of the Opinion, which are based on the formal administrative decisions under which CB was made reimbursable, that reimbursement is subject to a number of conditions designed to ensure the safety of its preparation and administration (and also the informed consent of the patient). So far as preparation is concerned, the decisions prescribe that, "for the purposes of guaranteeing sterility", compounding must be performed only "by hospital pharmacies satisfying the requirements laid down, in compliance with rules that ensure the doses are properly prepared": point (a) in the decision quoted at para. 27. The "requirements laid down" and the "rules" ensuring proper preparation are not specified, but it seems clear that the reference is to rules prescribed by the relevant

public authority, if not by AIFA itself. There is provision for the maintenance of a "monitoring register" of adverse reactions, which AIFA will itself review: see paras. 27, at (d), and 29. At para. 31 the Advocate General says:

> "The referring court also states that pharmacies prepare Avastin for the purpose of use in eyes on the basis of individual prescriptions. However, those prescriptions are not customised according to the different individual needs of each person, and the preparation in question is therefore produced in equal quantities for each patient, in batches and repeatedly."

78. One factual point on which there is no explicit statement is whether under the Italian system CB prepared in hospital pharmacies can only be supplied to the particular hospital to which that pharmacy is attached. However, the rationale behind the various requirements identified in paras. 60-63 above would not require such a rule, and it seems unlikely that that is the case. I also note that the language of para. 84 of the Advocate General's Opinion, quoted at para. 89 below, refers simply to syringes being "supplied to hospitals".

79. I need not set out in full the questions referred by the Consiglio di Stato. For present purposes we are concerned only with the first and second questions, which the Court took in reverse order.

80. The second question raised by the reference is whether the supply of CB fell outside the scope of the Directive because the compounding process was caught by the terms of article 3.1 of the Directive – the "magistral formula". This question had not arisen in *Apozyt*, because Apozyt was not a pharmacy. The Court held that article 3.1 did not apply, for a number of reasons given at paras. 55-65. I need not quote the entire passage. But I should note that at para. 58 the Court observes:

> "… [T]he processes for repackaging Avastin undertaken in accordance with the national measures at issue in the main proceedings do not significantly change the composition, form or other fundamental characteristics of that medicinal product. Those repackaging processes cannot be regarded as the 'preparation' of a new medicinal product derived from Avastin by means of a magistral formula or an officinal formula."

There might at first sight appear to be a tension between the Court's reasoning on this issue and its reasoning in *Apozyt* on the need for a marketing authorisation. But that is not the case. In both instances the starting-point is that compounding does not (or at least may not) create a fundamentally new product. In *Apozyt* the importance of that is that if the compounded Avastin is not a new product it is not being "put on the market". In *AIFA* the importance is that article 3 is concerned only with the preparation of new products.

81. Given that CB was thus held to fall within the scope of the Directive, the question was whether any of the substantive provisions precluded its use by the Italian health service in the way which AIFA's reimbursement authorisation permitted. As noted, Novartis's challenge had been specifically on the basis of article 6, i.e. because the compounders had no marketing authorisation; and that was the only provision referred

to in question 1 of the reference. But, as in *Apozyt*, the Court believed that it was necessary to consider whether there was a breach of article 40, because of the absence of a manufacturing authorisation. In both respects it essentially adhered to what it had said in *Apozyt*, but the language is not quite identical and it is worth setting out the passages in full. I take the two aspects in turn.

82. As to the need for a marketing authorisation, the Court begins, at paras. 69-71, by recapitulating the effect of article 6, with some reference to the case-law, including *Aventis*.[18] It then turns to the effect of *Apozyt*, as follows:

> "72. In a case similar to that at issue in the main proceedings, the Court held that the repackaging of Avastin for off-label use in the treatment of eye diseases did not require a new [marketing authorisation], provided that that process does not result in any modification of the medicinal product and that it is carried out solely on the basis of individual prescriptions making provision for that process ([*Aventis*], paragraph 42).
>
> 73. The reasoning behind that decision is that, contrary to the facts of [*Aventis*], the process of repackaging Avastin takes place [downstream of] that medicinal product being placed on the market, after a doctor has prescribed its use in such conditions for a patient through an individual prescription.
>
> 74. The Court thus stated that 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 modifications of those products, is in reality analogous to actions which, in the absence of another undertaking'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 ([*Apozyt*], paragraphs 42 and 43).
>
> 75. Subject to factual findings to be made by the referring court, the repackaging of Avastin under the conditions laid down in the national measures at issue in the main proceedings, does not therefore require an MA to be obtained in so far as that process is prescribed by a doctor by means of an individual prescription and undertaken by pharmacists for that medicinal product to be administered in hospitals."

It is important to note that in the official English-language version of the Judgment the phrase "downstream of" which I have square-bracketed in para. 73 appears as "prior to". But it was common ground before us that that was a mistranslation of the

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[18] In *AIFA* the Court does not, as it did in *Apozyt*, frame the issue by reference to article 3.1 of the EMA Regulation. I am not sure why, but for the reasons already given the point does not matter.

original French, where the phrase used is *en aval de*, for which the dictionary definition is "downstream of" or "downhill from"[19].

83. As regards the need for a manufacturing authorisation, the Court summarises, at para. 76, the effect of article 40 and refers to its earlier judgments in *Caronna*, C-7/11, and *Apozyt*. At para. 77 it says:

> "As the Advocate General stated in point 79 of his Opinion, despite the fact that it may be found before the referring court that the pharmacies authorised to divide up and repackage Avastin under the national measures at issue in the main proceedings do not hold the authorisation required under Article 40(1) of Directive 2001/83, those pharmacies could nevertheless fall within the exception under the second subparagraph of Article 40(2) of that directive. Subject to findings of fact to be made by the referring court, it must be held that if it is found that, in accordance with the national measures at issue in the main proceedings, Avastin is, on the basis of an individual prescription, repackaged to be used off-label for the treatment of eye diseases, by a pharmacy lawfully authorised to that effect, for that medicinal product to be administered in hospitals, such a process falls within the exception of the directive and does not require manufacturing authorisation."

That is of course to the same effect as paras. 53-55 of the Judgment in *Apozyt*.

84. Those conclusions, and the reasoning on which they are based, reflect the recommendations of the Advocate General. But there are five passages in his Opinion to which Mr Lock particularly referred us.

85. First, we were referred to para. 45, which reads:

> "It should be noted in that regard that, under Article 168(7) TFEU, the organisation and management of health services and the allocation of the resources assigned to them are the responsibility of the Member States. Article 4(3) of Directive 2001/83 and the second paragraph of Article 1 of Regulation No 726/2004 reaffirm those national powers, stating that the provisions of those instruments are not to affect the powers of Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions."

Mr Lock attached importance to that passage as a reminder that the EU has no general competence in the field of healthcare provision: the lawfulness of the arrangements for the supply of CB as a matter of EU law must be judged entirely by reference to the provisions of the Directive (and the EMA Regulation).

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[19] In Italian, which was the language of the case, the phrase is *a valle dell' …*, which likewise means "below". We were also told that the word in the German text is *erfolgt* – "follows after".

86. Secondly, he referred to paras. 47-48 in the Opinion of the Advocate General, which summarised the approach of EU law to off-label use of medicines. These read:

> "47. 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. 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.
>
> 48. On the other hand, EU law does not govern the prescribing of medicinal products for off-label use. 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. Equally, the decision to approve a medicine used off label for reimbursement by the social security systems lies, in principle with the Member States."

That passage is not directly relevant to the issues before us but is a useful statement of the position about off-label use (cf. paras. 18-20 above), specifically in the context of Avastin.

87. Thirdly, Mr Lock drew our attention to para. 57, where the Advocate General says:

> "I note, in that respect, that preparing Avastin to treat AMD involves modifications relating to the strength, packaging and route of administration of that medicinal product. On the other hand, neither the order for reference nor the case file submitted to the Court indicates that preparing it in that way affects the medicinal substance itself. On the contrary, the AIFA decisions merely allow Avastin to be repackaged in single doses, under conditions intended to ensure sterility."

This is a particularly clear statement of the point made at para. 62 above.

88. Fourthly, Mr Lock asked us to note how the Advocate General explained the "no modification" requirement in *Apozyt* at para. 60 of his Opinion. He said:

> "The premise underlying that approach, it seems to me, was that, provided the medicinal substance itself is not thereby altered, the changes to the strength, packaging and route of administration of Avastin so that it can be used off label do not give rise to the creation of a different medicinal product for the purposes of applying EU pharmaceutical rules."

89. Finally, at paras. 82-84 the Advocate General explains why supply to a hospital for administration to a patient constitutes retail rather than wholesale supply. The passage reads:

> "82. Directive 2001/83 does not define 'retail supply'. The ordinary meaning of that expression is the supply of goods to the public in single units or small quantities. In *Caronna* the Court of Justice construed that concept as opposed to that of 'wholesale distribution'. Article 1(17) of Directive 2001/83 defines 'wholesale distribution' and distinguishes it from, precisely, supplying medicinal products to the public.
>
> 83. As can be seen from [*Apozyt*], complying with that requirement does not require the medicinal products that have been divided up and repackaged to be supplied directly to the patients for whom they are intended. In that case, the individual syringes obtained from a vial of Avastin were in fact supplied to the pharmacies that had placed orders for them. The Court held that that circumstance did not prevent the requirement in question from being satisfied, entailing as it did only that the relevant processes should be included within a system for retail supply by pharmacies. In that respect, the Court attached particular importance to whether or not those processes were carried out on the basis of individual medical prescriptions.
>
> 84. In the present case, it is apparent from the order for reference that the Avastin is divided up and repackaged on production of medical prescriptions. The individual doses prepared in that way are supplied to hospitals where they are subsequently administered to the patients concerned. Incidentally, Avastin is in the class of medicinal products which can only be administered in hospital, and therefore could not be supplied directly to patients. Accordingly, the dividing up and repackaging of Avastin does not, in my view, require a manufacturing authorisation."

ANALYSIS OF THE *APOZYT* EXEMPTION

90. It is necessary to summarise the extent of the *Apozyt* exemption as it appears from that trilogy of cases.

91. I should emphasise by way of preliminary that *AIFA* clearly establishes that CB is not taken outside the scope of the Directive (or of the Regulation) by article 3, because compounding does not create a new "medicinal product": see para. 80 above. Nor are we concerned on this appeal with whether it might in a particular case be taken out of scope by article 5 (though that issue was addressed in *Apozyt* – see para. 66 above). The "*Apozyt* exemption" has nothing to do with Title II but arises from the Court's construction of the language of the substantive articles in Titles III and V. (It is for that reason rather inappropriate to refer to it as an "exemption", but the label is too convenient to do without.)

92. The effect of the *Apozyt* exemption is twofold:

(1) *Marketing Authorisation*. The supply of CB by a compounder to a clinician does not constitute a "placing on the market" within the meaning of article 6 (or the Regulation), and accordingly does not require a marketing authorisation, provided that:

(a) the compounding process does not result in a "modification of the medicinal product concerned" – "the no modification requirement", and

(b) the compounding is carried out "solely on the basis of individual prescriptions" – "the individual prescriptions requirement".

I should say that Whipple J did not accept that the exemption was subject to the individual prescriptions requirement. I respectfully disagree with her about that, but it will be more convenient to give my reasons later.

(2) *Manufacturing authorisation.* The compounding of Avastin does not require a manufacturing licence provided that:

(a) the compounding is carried out either (i) in a "dispensing pharmacy" or (ii) by a person legally authorised to carry it out; and

(b) it is carried out "solely for retail supply".

93. The effect of each of those conditions was to a greater or lesser extent contentious before us. I take them in turn.

(1) MARKETING AUTHORISATION

(a) "Modification"

94. The starting-point is that I agree with the Oberlandesgericht Hamburg that the fact that the "strength, packaging and route of administration" of CB, and indeed the indications for which it is administered, are different from those of Avastin as specified in the marketing authorisation does not in itself mean that it is "modified" in the sense intended by the Court: if it did, the proviso would swallow up the primary conclusion. It is in my view clear that the Court was referring only to modifications to what the Advocate General in *AIFA* (see para. 88 above) described as "the medicinal substance itself". Mr de la Mare referred us to the phrase used by the Court in its judgment in *AIFA* in holding that compounding did not fall within article 3.1 of the Directive – that it did not "significantly change the composition, form or other fundamental characteristics of [the Avastin/Lucentis]" (see para. 80 above). That seems to me to convey essentially the same point. As to what constitutes such a change, I agree with the view of the Oberlandesgericht Hamburg that what the Court must have meant was any change in the state of the product (biological, chemical or physical) which might significantly affect its "quality, efficacy and safety": see para. 213 of its judgment, quoted at para. 71 above. Indeed that was common ground before us.

95. It was also common ground that the Court cannot have intended that the question whether the supply of CB by a compounder to a clinician (whether directly or indirectly) constituted a "placing on the market" should depend on whether the product supplied on any particular occasion was so modified. Rather, the question must be whether the compounding process itself involved such modification: that is what the Oberlandesgericht Hamburg no doubt intended to indicate by its use of the phrase "as necessarily to be expected" (in the German, *zwingend zu erwartende*).

96. As to that, it is clear that the compounding process involves no deliberate modification: it is intended to be, in the language of the CJEU, no more than a "repackaging" of the Avastin, which adds nothing to its "substance". But in his oral submissions in connection with the Appellants' ground 3 (and in particular "issue 3A") Mr de la Mare submitted that that was not the whole question. It was necessary also to consider what he described as "quality" – that is, unintended "modification" arising from failures in the compounding process. By reference in particular to the account of the compounding process given in the MHRA review, he identified various ways in which such modification might occur. There might, for example, be an unanticipated reaction between the Avastin and the materials used in the body of the syringe, or the substance used to lubricate the piston. It might also occur by the Avastin being contaminated in the course of the transfer process: the obvious example would be microbial contamination, but Mr de la Mare referred us to a passage in the MHRA review which mentions the risk, if a proper filter needle were not used, of contamination of the transferred Avastin by "particulates" (e.g. particles created by the puncture of the stopper of the vial with the needle).[20] The references to a limited shelf-life also necessarily implied that the substance would lose quality, efficacy or safety after a certain period.

97. Mr de la Mare contended that the test of modification had to be "geared towards" or "focused on" these risks, because if they eventuated the quality, efficacy or safety of the CB would be liable to be impaired. I understood his submission to be that the compounding process must be treated as modifying the substance of the Avastin unless it was demonstrable that "appropriate quality standards" (a phrase to which he drew our attention in the MHRA review) were adopted – which, to anticipate, he said that the evidence before the Judge did not establish, and as to which she had in any event made no findings.

98. I do not accept those submissions. It is essential to remember that the context for the no modification requirement is the issue of whether the supply of compounded Avastin (or indeed Lucentis) involved a "placing on the market" within the meaning of article 6. As discussed at paras. 60-63 above, the rationale for the *Apozyt* exemption is that the Court regarded what it described as "re-packaging" as part of the use of an existing product by the end-user – that is, by the prescribing doctor or a pharmacy (or other authorised person). I do not see how, logically, that analysis could be affected by whether failures of quality control have led to the product being contaminated (or to a real risk of contamination): questions of that kind can have nothing to do with the point at which the product ceases to be "placed on the market". In my view it is clear that what the Court meant by "modification" was a change in the substance of the Avastin (more technically, in its physical, chemical or biological properties) which is necessarily inherent in the fact of compounding rather than the risk of contamination or other changes as a result of failures of quality control.

99. That does not mean that the Court would not expect that the compounding process would be subject to proper quality control: of course it would. But that does not need

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[20] I should say, to avoid misunderstanding, that the MHRA mentions these risks, and the precautions to be taken against them (such as the use of a filter needle), as part of a general assessment of "quality considerations". It is not part of its purpose to assess the extent of any risk of failures in quality control, though it does in fact observe that the low level of reported serious adverse reactions is "reassuring on the safety of intravitreal [CB]".

to be achieved through the mechanism of the Directive or built in to the definition of article 6. There would be nothing surprising about the Court proceeding on the basis that pharmacies (or other persons with a special authorisation to perform compounding, such as Apozyt) would be subject to professional and regulatory standards that gave proper protection against any risks in the compounding process; indeed in *AIFA* there were clear findings that the reimbursement authorisations incorporated a system designed to ensure quality control (see para. 77 above). After all, other operations performed in pharmacies are explicitly excluded from the scope of the Directive by articles 3 and 5. It is also important to bear in mind that, as Mr Lock reminded us, the EU has no legislative competence as regards matters of medical treatment. It would be consistent with the logic of the *Apozyt* exemption to treat the safety of the compounding process as an aspect of clinical procedures which are under the control of doctors and/or pharmacists.

100. As I have already mentioned, the Appellants did in fact seek to argue before us that there was reason to doubt the adequacy of the systems for ensuring quality control in the English hospital pharmacies that were the likely source of any CB used pursuant to the Policy (see paras. 179-181 below); but any challenge to the lawfulness of the Policy on that basis should be squarely based on that fact rather than shoehorned into a challenge based on the construction of article 6.

101. As Mr de la Mare says, Whipple J did not expressly consider these questions: the shape of the issues as understood by her seems to have been rather different. But she proceeded on the basis that the compounding process did not involve a modification of CB so as to take it outside the scope of the *Apozyt* exemption, and I believe that she was right to do so.

(b) Individual Prescriptions

102. I should start with Whipple J's conclusion, referred to at para. 92 (1) above, that the *Apozyt* exemption was not subject to a proviso about individual prescriptions. At para. 119 of her judgment she says that the reference at para. 42 of the Judgment in *Apozyt* does not state "whether the existence of prescriptions was necessary to its conclusion that the product did not need a marketing authorisation" and at para. 120 she concludes that it was not. She gives her reasons as follows:

> "(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."

103. The Appellants challenge that conclusion as their Ground 2, and they are supported in that regard by the Secretary of State. As I have already said, I believe that the challenge is well-founded. The most obvious problem with the Judge's analysis is simply that it ignores the clear language of both para. 42 of the Court's judgment in *Apozyt* and the *dispositif*, which explicitly identify two distinct provisos to the exemption – "provided that they do not result in a modification of the medicinal product concerned and are carried out solely on the basis of individual prescriptions"[21]. That in itself makes it in my judgment impossible to treat the reference to individual prescriptions as in some way secondary or inessential. But the problem goes beyond the actual language. For the reasons given at para. 61 above, it is in my view clear that the requirement for individual prescriptions reflects an essential element in the Court's justification for the exemption.

104. There is also a wider perspective. I cannot do better than endorse a passage from Mr Peretz's helpful skeleton argument on this point:

> "Perhaps most importantly from the perspective of the Secretary of State, [Whipple J's] reading of *Apozyt* weakens the Directive, and is inconsistent with its overall structure. That reading would mean that any operator could lawfully resell down the distribution chain, without a marketing authorisation other than that for the original product, a medicine repackaged so as to be administered via a different route and for a different therapeutic indication than those considered by the EMA or MHRA when granting the original marketing authorisation. Such an outcome would, in the Secretary of State's submission, be inconsistent with the provisions of the Directive that require that new or varied marketing authorisations be applied for and granted before medicines can be placed on the market for different routes of administration or therapeutic indications than those set out in the original marketing authorisation: see Article 6(1). The Directive's insistence on that point is fundamental to the effective operation of the regime: a new presentation or new therapeutic indication of a medicine requires thorough additional scrutiny of its safety, quality and efficacy: scrutiny additional to the scrutiny it underwent when first authorised in its original presentation or original proposed indication."

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[21] I quote from the *dispositif*, but the relevant words of para. 42 are substantially the same.

105. It follows that I cannot accept Whipple J's points (i) and (iii)-(iv). Point (ii) is true as far as it goes, but it does not really assist: the *Apozyt* exemption is a Court-created gloss on the language of article 6. I do not, with respect, accept point (v): the Court explicitly rejected the German Government's reliance on article 5 (see para. 66 above).

106. In their skeleton argument Mr Lock and Mr Blundell seek to defend Whipple J's conclusion on the basis that the individual prescriptions requirement is not to be found in the express terms of the Directive. That is so, but of course the requirement derives from the way in which the CJEU construes the Directive in formulating the *Apozyt* exemption. They also emphasise that decisions as to what drugs are to be treated as prescription-only is a matter for national law and outside the competence of the EU. They rely in this regard on aspects of the reasoning in *AGCM*. This point was not developed orally, and I can see nothing in it. We cannot go behind what the Court clearly decided in *Apozyt*; but in any event the Court's reasoning does not involve any intrusion on the competence of member states but simply uses the question whether such a prescription is in place as a touchstone of whether CB is being "placed on the market".

107. There remains an issue about precisely what the phrase "on the basis of individual prescriptions" entails. That was, however, argued before us in the context of the requirements of article 40.2 *bis*, and it is more convenient to deal with it when I consider those: see paras. 112-116 below.

(2) MANUFACTURING AUTHORISATION

108. I take in turn the two conditions identified at para. 91 (2) above.

109. As to (c) – the requirement that the compounding be performed either (i) by pharmacists in dispensing pharmacies or (ii) "by persons legally authorised in the Member States to carry out such processes" – this does not require much exposition. We were referred to no UK legislation providing for authorisations of the kind referred to at (ii), although *Apozyt* shows that German legislation does so. No issue was raised before us about the word "dispensing".

110. As to (d) – "solely for retail supply" – the phrase "retail supply" has an odd ring in the context of a drug that can only be administered in a hospital context, but it clearly connotes supply for the purpose of administration to a particular patient. At para. 53 of its Judgment in *Apozyt* the Court expands the language of the Directive by saying that the issue is whether Apozyt's activities "are … included within a system for the retail supply of medicinal products by pharmacies"; but I do not think that that adds anything of substance. What is more important is its statement in the following sentence that it will be necessary to determine whether the compounding is carried out "only on the basis of individual prescriptions". That is plainly because where CB is prepared for a particular patient it is self-evidently being prepared for "retail supply". The existence of a prescription is, in effect, the mark of a retail supply.

111. It follows that the individual prescriptions requirement arises in the context of article 40.2 as much as in the context of article 6, and for essentially the same reason. The Court regards it as justifiable to treat the supply of CB as falling outside the scope of

article 6 and article 40 if, but only if, it forms part of the "retail" process of the treatment of a particular patient under the direction of the treating doctor.

112. As already indicated, there was an issue before us as to the precise content of the individual prescriptions requirement. It was common ground that the compounder need not have an individual prescription in its own hands at the moment that it prepares and/or supplies a particular unit of CB: it was enough that it should have been informed that the prescription exists[22]. Rather, the issue was about the precise stage at which that should occur.

113. As to that, it was the Appellants' case that it was necessary that a prescription should have been written, and its existence communicated to the compounder, at the start of the compounding process. It was the Respondents' case that all that was necessary was that the prescription should exist at the moment of supply. The potential practical difference between the two approaches is that the latter would allow a compounder to prepare batches of CB in anticipation of incoming "orders" (i.e. prescriptions), to be drawn down against prescriptions as notified, whereas on the Appellants' approach production would have to be purely reactive. We were told that a syringe of CB would only have a shelf-life of a week or two, so that the syringe used for any particular injection would have to have been prepared and supplied shortly before. It would not therefore be possible to build up stockpiles covering many weeks' supply.

114. Mr Lock submitted that the issue was of less practical importance than might appear at first sight. Even if the Appellants' approach was correct it should be recalled that each prescription would cover a course of ten monthly injections, and, given that WAMD is a common condition, any compounder supplying multiple hospitals would be preparing syringes for very many patients. In any one week, therefore, there would be prescriptions covering a sufficient number of syringes for them to be prepared in batches on a bulk basis, without the need for precise matching.[23] Nevertheless, he submitted that, to the extent that it mattered, it was the Respondents' approach which was correct. The purpose of a prescription was to ensure that the patient received the right drug. That purpose was satisfied by a prescription being in place at the moment of the supply of the drug to the doctor. To require that it be in place at the earlier stage would simply involve creating an administratively burdensome paper-chase.

115. I do not believe that in those submissions Mr Lock correctly characterises the purpose of the individual prescriptions requirement. It has nothing to do with seeing that the patient gets the right drug: that is, as he himself says, a matter outside the competence of the EU. Rather, it is about drawing the distinction between matters of treatment which occur "downstream" of supply to the end-user (here, the treating hospital) and the "upstream" activities of manufacture and supply which the Directive seeks to regulate. It is, as Mr de la Mare put it, "a proxy for controlled retail supply".

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22 That seems to have been the procedure followed by Apozyt.

23 I should say that I did not understand Mr de la Mare to submit that, where a compounder is preparing CB in response to a number of orders, it should be possible at any stage in the process to point to a particular syringe and identify it as allocated to a particular named patient. That would obviously be futile, given that all the doses are identical. His point was simply that if twenty syringes are being prepared they must be covered from the start by twenty existing prescriptions.

116. Even on that basis, however, I see some attraction in the argument that it should not matter whether the prescription is in place at the moment when the production starts. But the starting-point must be the language used by the CJEU. At para. 42 of its Judgment in *Apozyt* it expresses the requirement as being that the relevant "processes" should be "carried out" on the basis of individual prescriptions. That must refer to the compounding process (not least because in the same sentence it requires that they should not result in a modification of the product). On a natural reading, that means that not only the supply but the compounding itself should not be carried out unless and until a prescription is in existence. No doubt this particular issue was not live before the Court, but there is a conceptual logic in the way it expressed itself, and I am not persuaded that we should disregard its language only because a substantially similar result could be achieved by limiting the requirement to the point of supply. In short, I agree with Mr de la Mare that the individual prescriptions requirement is for *prior* prescriptions.

117. Whichever approach is taken, it is clear that the *Apozyt* exemption is not inconsistent with the preparation and supply of CB in large volumes. Apozyt was clearly a bulk supplier, and it appears that the Italian hospital pharmacies considered in *AIFA* were also producing CB on a large scale.

OVERVIEW

118. The *Apozyt* exemption as I have sought to explain it clearly has a close relationship with the "true" exemptions in Title II, and particularly with article 3, which likewise incorporates an "individual prescriptions" requirement and whose rationale is likewise to exclude (to put it crudely) things that happen under the control of doctors or pharmacists from the requirements of Titles III and IV. Its effect is essentially to extend that exclusion beyond the case covered by article 3 – i.e. where the pharmacist makes changes to the substance of the product, so as to create a new product – to the case where the changes are not to the "substance" but to other features (packaging, mode of delivery etc) which would otherwise be the subject of regulation. It does so on the basis that the compounding of Avastin under the control of a treating doctor in an individual case occurs "downstream" of the point at which the Directive's control of marketing and manufacture ceases: it is to be treated essentially as part of the clinical process. That may be – Mr de la Mare would say that it was – a creative exercise of construction; but the Court's thinking is understandable and it must be respected.

THE JUDGMENT OF WHIPPLE J

119. Whipple J summarised the grounds on which the Appellants challenged the lawfulness of the Policy as follows:

> "(1) 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.
>
> (2) It fundamentally undermines the objective of [the Medicines Directive] and constitutes a breach of the duty of sincere cooperation in Article 4(3) of the Treaty of the European Union.

> (3) It undermines patients' rights of access to NICE recommended treatments.
>
> (4) 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."

120. Not all those grounds are live before us, and even to the extent that they are, the particular issues which we have to consider are in some respects different, or advanced in a different way, than they were below. For that reason I will not attempt a comprehensive summary of the Judge's reasoning. For our purposes the essential points are as follows.

121. First, after explaining the background and carrying out a thorough review of the law, at paras. 139-198 she determined six "key issues". As a result of the way the case has developed before us I need refer only to three.

122. The Judge's key issue (ii) was whether the Policy would involve clinicians acting in breach of Guidance from the General Medical Council ("the GMC") which the Appellants said prohibited them from taking cost into consideration when making prescribing choices. At paras. 148-153 she held that there was no such prohibition.

123. Key issue (iii) was "Is Avastin Safe for Ophthalmic Use?". As to that, her primary conclusion was that it was not open to the Appellants on their pleaded case to challenge the conclusion of the CCGs, embodied in the Policy, that such use was indeed safe: see para. 159. But she also said, at paras. 160-161:

> "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 … . 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."

124. Key issue (vi) concerned the correct formulation of the test to be applied in determining whether the Policy was lawful. Her conclusion, at para. 196, broadly adopting the formulation advanced by Mr Lock, was:

> "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."

At para. 198 she summarised her self-direction as follows:

> "[I]s the Policy realistically capable of implementation by the NHS Trusts in a way which does not lead to, permit or encourage unlawful acts?"

125. Next, the Judge proceeded to identify four "modes" by which the Policy might be implemented by Trusts, subject to the issue of lawfulness. That was necessary because, as I have said, the Policy itself says nothing about the means by which Trusts could or should obtain Avastin for the treatment of WAMD and it was necessary to consider all possibilities. She defined the four modes at para. 199 of her judgment as:

> "(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".

Modes 2-4 are self-explanatory, but I should explain mode 1. It was part of the Respondents' case before the Judge that there would be nothing unlawful in a Trust buying Avastin in its original 4ml vials and a doctor simply drawing off the 0.1ml required for a single injection for a patient and discarding the rest. There would in that case be no compounding at all. No doubt it would be extremely wasteful to be throwing away over 90% of the product, but it would still be only (roughly) half as expensive as buying Lucentis or Eylea.

126. After considering some preliminary points, at paras. 211-237 the Judge considered the lawfulness of each of the modes in turn. I need not give the details here. At para. 238 she summarised her conclusions as follows:

> "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))."

127. Finally, at paras. 239-257, she addressed the pleaded grounds of challenge. I take them in turn.

128. As regards ground 1 – no lawful basis of supply – she says, at para. 239:

> "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."

That effectively follows from para. 238, which I have quoted above.

129. At para. 240 she characterises the essence of ground 2 as being that the Policy would undermine the coherence of the EU regime because (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". In connection with element (ii) the Appellants had relied in particular on the decision of the General Court in *Laboratoires CTRS v Commission* [2015] EUECJ T-452/14 ("*CTRS*"), which concerns a so-called "orphan drug".

130. Element (i) was answered by her finding on "key issue (iii)" (see para. 123 above). Summarising that finding, she says, at para. 241:

> "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."

131. She addresses element (ii) at paras. 242-245, which read as follows:

> "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 [Advocate General's Opinion] 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."

132. I need not summarise the Judge's findings on grounds 3 and 4.

133. It is convenient to note here two elements in the Judge's detailed reasoning on ground 1 which were not adopted by Mr Lock before us.

134. First, she referred to the fact that by virtue of article 2.1 the Directive only applies to medicinal products which are "either prepared industrially or manufactured by a method involving an industrial process" (see para. 24 above) and held that on some possible scenarios the Trusts might be able to implement the Policy using CB which was not so prepared or manufactured. That finding was challenged by the Appellants in their grounds of appeal, and very shortly before the hearing Mr Lock told them that he would not seek to defend that element in the Judge's reasoning, though he did not accept that it invalidated her decision overall.

135. Secondly, the Judge held that if the Trusts were prepared to adhere to a prior prescriptions requirement they could rely on article 3.1 of the Directive to acquire CB from a hospital pharmacy. It is now clear from the decision of the CJEU in *AIFA* that she was wrong about that.

THE ISSUES ON THE APPEAL

136. The Appellants pleaded joint Grounds of Appeal. I need not set them out in their pleaded form because they were helpfully summarised in an "Overview of Grounds" submitted by Ms Stratford and Mr de la Mare at the start of the hearing. That reads:

> "Ground 1: Did the Judge get the test for reviewing the lawfulness of the Policy wrong or wrongly apply the test?
>
> Ground 2: Was the Judge wrong to find that prior prescriptions were not part of the *ratio* in *Apozyt*?

> Ground 3: Was the Judge wrong to find Modes 2 (own-hospital), 3 (intra-NHS) and 4 (commercial) supply were potentially lawful?
> *Issues:*
> - 3A – Is CB a *modification* of Avastin such that, when it is supplied under any of modes 2-4, that is necessarily a new placing on the market?
> - 3B – Is there in any event a placing on the market in relation to modes 2-4 because there is a release into the distribution chain for each of those modes?
> - 3C – …
> - 3D – Does the Policy unlawfully undermine the Directive (including if all supply is done under the Art. 3 compounding exemption?)
> - 3E – Is the Policy contrary to GMC guidance and, if so, does that make it unlawful?
>
> Ground 4: Was the Judge wrong to find that Mode 1 (original-vial use) was potentially lawful?"

(Ground 3C related to the "industrial process" point conceded by Mr Lock.) Grounds 1, 2, 3A, 3B and 4 challenge aspects of the Judge's reasoning on the original ground (1) before her. Ground 3D relates to the original ground (2). As to ground 3E, this challenges her finding on "key issue (ii)" (which, as I understand it, was an aspect of original ground (1)). Ms Stratford advanced the Appellants' oral submissions on grounds 1, 3D, 3E, and 4; and Mr de la Mare on grounds 2, 3A and 3B.

137. It is important to note at this stage that it was an important part of Ms Stratford's case, in particular in relation to ground 1, that even if there were ways in which the Policy could in theory have been lawfully implemented, the Respondents did not at the time envisage proceeding in any of those ways and/or they were not in any event realistically practicable.

138. I am not sure that the Appellants' arrangement of the pleaded grounds represents the most useful framework for the issues which we have to decide, and I do not think it will make sense simply to consider them one-by-one. I propose instead to start by going through each of the four modes, determining both (a) whether, and if so how, they could be followed without breaching the requirements of the Medicines Directive (or the EMA Regulation) or the domestic implementing legislation – "lawfulness"; and (b) Ms Stratford's point identified at para. 137 above – "reality". Once I have gone through that exercise it will be easier to address the specific grounds, which I will take in turn, but leaving ground 1 to the end.

THE FOUR MODES

139. I should note by way of preliminary that although, as noted above, Whipple J carried out a similar exercise, I do not propose to proceed by reference to her reasoning because much of it depends on points which are no longer live before us or on which I have respectfully differed from her in my analysis of the *Apozyt* exemption.

140. I will leave mode 1 till last since it is *sui generis*.

MODE 2: CB COMPOUNDED "IN-HOUSE"

LAWFULNESS

141. It follows from my analysis of the *Apozyt* exemption that the preparation of CB by a hospital pharmacy and its supply to a doctor within the same hospital to treat a patient with WAMD will not be in breach of the Medicines Directive or the EMA Regulation provided the no modification requirement and the individual prescriptions requirement are satisfied. I take those two requirements in turn.

142. As to the no modification requirement, it follows from my conclusion at paras. 94-101 above that Avastin is not to be treated as modified only because of any risk of contamination or other changes to its substance as a consequence of poor quality control. What matters is changes which are necessarily inherent in the compounding process. There is no evidence that the process involves any such changes. The no modification requirement is therefore satisfied.

143. As to the individual prescriptions requirement, there is clearly no legal reason why a hospital could not apply a system under which CB was prepared only against individual prescriptions, as happens in Italy.

REALITY

144. Ms Stratford submitted that the Policy does not contemplate a system under which each hospital prepared its own CB. It was her case that the Policy clearly contemplated implementation by modes 3 and/or 4. She said that that could be inferred from the pricings referred to in the Report and its Appendices, which were only consistent with the supply of CB in bulk from commercial suppliers and/or one or more NHS hospital pharmacies preparing CB on a large scale. She also referred to a letter from the CCGs to the Trusts dated 24 August 2017 which confirmed that "we have identified a manufacturer who is able to supply appropriate quality and quantities of [CB]".

145. In addition, Ms Stratford sought to rely on evidence which had not been before the Judge, in the form of a statement by Mr Brian Kelly, a partner in Covington & Burling ("Covington"), Novartis' solicitors, exhibiting correspondence between his firm and the five Trusts identified at para. 13 above. Covington made formal Freedom of Information Act requests to each Trust asking whether they "possess facilities that produce, or are capable of producing, CB in-house at the scale necessary to implement the Policy for the Trust's patients" and, if so, giving particulars of those facilities. Three answered that they did possess such facilities, although one of those said that it did not intend to make use of them but would purchase CB "externally". Two said that they did not. Mr Lock did not challenge that part of the evidence, and I would admit it as far as it goes.[24] It does not of course establish that the two Trusts which said that they had no such facilities might not decide to make the necessary

[24] I should record that the Appellants say that it is in fact clear from the particulars given by the three Trusts that their facilities could not lawfully be used to prepare CB, because they only had "specials' licences", which are licences required by hospital pharmacies which prepare drugs under the exemption in article 5. But that depends on whether they are right on the issues raised by the appeal.

investments to acquire them, but that would no doubt be an expensive course and might be thought unlikely if the CB could be lawfully obtained from another source.

146. In my view the correct conclusion from the evidence is that there is no practical reason why any of the Trusts could not, if they chose, prepare their own CB, though that is more likely in the case of the three who claim already to have the necessary facilities. Mode 2 is in that sense (and subject to para. 148 below) realistic.

147. As to what was actually intended, I do not accept that the terms of the Policy would not cover mode 2. Nothing express is said to the effect, and the rationale given would apply equally to the preparation of CB in-house as to its purchase from outside. No clear inference can be derived from the figures which it mentions. I do, however, accept, on the basis of the evidence relied on by Ms Stratford, which Mr Lock did not seek to contradict, that that was not in fact contemplated at the time that the Policy was promulgated: what the makers of the Policy had in mind was that CB would be obtained by modes 3 and/or 4.

148. There is a distinct question about whether it was realistic for a Trust preparing CB in-house to implement a system of individual prior prescriptions and in any event whether that was contemplated by the Policy. I return to that question below, in connection with mode 3.

MODE 3: CB COMPOUNDED BY ANOTHER NHS HOSPITAL PHARMACY

149. I should make one point by way of preliminary. Whipple J's definition of mode 3, which I have adopted, refers to CB compounded "in another NHS hospital". It is in principle possible – though I suspect it is rather unlikely – that a hospital in a particular Trust might obtain CB from the pharmacy of another hospital in the same Trust. However the argument before us proceeded on the basis that mode 3 was in practice concerned with supply by a different Trust. That reflects a sensible recognition that the principles governing mode 2 would apply equally to intra-Trust supply.

LAWFULNESS

150. As to lawfulness, my conclusions at paras. 141-143 above apply equally to mode 3. The rationale of the *Apozyt* exemption as analysed above is not limited to the case of the in-house preparation of CB: *Apozyt* itself was of course a case where the compounding was done externally, and it seems likely that the Italian system considered in *AIFA* also involved supply by one hospital to another.

151. However Mr de la Mare submitted that the supply and preparation of CB involved in mode 3 was unlawful irrespective of whether it satisfied the *Apozyt* exemption, for two distinct reasons, both deriving from domestic law:

    (1) Even if the *Apozyt* exemption means that as a matter of EU law a pharmacy may supply CB without a marketing or manufacturing authorisation (subject to the requirements specified), that is not the case as a matter of domestic law because section 10 of the 1968 Act does not fully give effect to the exemption.

(2) The compounding pharmacy would require a wholesaler dealer's licence under regulation 18 of the HMR, which implements article 77.1 of the Directive (see paras. 36 and 46 above).

Neither point was considered by Whipple J, and Mr de la Mare conceded that point (2) at least was taken for the first time before us; indeed it did not feature in either the Appellants' skeleton argument or their supplementary skeleton argument. Sensibly, however, Mr Lock did not object to the points being taken. I consider them in turn.

(1) Section 10 of the Medicines Act

152. The starting-point of Mr de la Mare's submission is the regulations in the HMR which implement articles 6 and 40 of the Medicines Directive. Regulation 46 (1) makes it unlawful to "sell or supply" a medicinal product without a marketing authorisation, and regulation 17 (1) makes it unlawful to "manufacture [or] assemble" such a product: see para. 43 above. A hospital pharmacy which prepared CB would be "assembling" a medicinal product – see the definition quoted at para. 44 above. And its supply to a different Trust would plainly be a "supply" (whether or not it were also a sale).

153. Those prohibitions are of course disapplied where section 10 of the 1968 Act – "Exemptions for Pharmacists" – so provides: see para. 49 above. In particular, sub-section (1) (a) applies to anything done in a hospital by or under the supervision of a pharmacist which consists of "preparing or dispensing a medicinal product in accordance with a prescription given by a practitioner". But Mr de la Mare submitted that section 10 did not assist the Respondents. I take in turn regulation 17 and regulation 46.

154. As regards regulation 17, on the face of it the compounding of CB in a pharmacy would fall within the meaning of "preparing" in section 10 (1) (a). But Mr de la Mare submitted that that term was not apt to cover the kind of preparation of CB "in bulk" which mode 3 would in practice entail. He referred us to a passage in the witness statement of Novartis' "Business Head – Ophthalmology", Mr James Porter, which quotes from the response given by the MHRA following consultation on the draft of the HMR (for which the MHRA had responsibility as an agency of the Department). We were not shown the draft itself, but Mr Porter says that it had been "intended to replace the term 'prepare' with 'manufacture'". In its response the MHRA explained that following responses from consultees it had decided to retain the language of "prepare". It said, as quoted by Mr Porter:

> "[T]here is a perceived difference between 'prepare', which is viewed as being done under section 10 exemptions, as opposed to 'manufacturing', which is undertaken under a 'specials' manufacturing licence. The changes risk confusion for professionals and the public.
>
> 'Prepared' and 'manufactured' are currently understood to be different scales of production. The change risks blurring understanding about volumes of production.

> The change risks blurring the boundary between the quality of products prepared under Good Manufacturing Practice standards and extemporaneous dispensing, or suggests that additional standards and requirements will be placed on extemporaneous dispensing as a result."

155. I do not accept that the language of section 10 (1) (a) does not cover the production of CB in bulk. As a matter of ordinary language, the word "prepare" is perfectly apt to the compounding process. The provision contains no express limitation by reference to volume, and it would be hard to imply one: how would the borderline between "small-scale" and "large-scale" be identified? I see no ambiguity of the kind that might make it legitimate to have regard to the MHRA's consultation response. But even if that were legitimate, the response is not particularly helpful. It appears to reflect an understanding that it is appropriate for "high-volume" production to be carried out under a "specials' licence" (see n. 24) whereas "low-volume" production need not be. But there is no reason to suppose that the consultees had in mind the particular case of compounding, i.e. simply aliquoting the contents of a larger vial between a number of syringes; and it is not clear whether its concerns about "volume" would apply to such a case. And even if there were room for doubt on the point, it is in my view right to prefer a construction which produces a result that conforms with the Directive as construed by the CJEU.

156. As regards regulation 46, I see no difficulty in construing the term "dispensing" in section 10 (1) (a) to cover the supply of CB which would occur under mode 3. The pharmacy will have prepared the CB in response to an individual prescription, and it is supplying it to the hospital at which the treating clinician will administer it in accordance with that prescription. Again, if there were room for doubt, we should adopt a construction which produces a result that conforms with the Directive as construed by the CJEU. Another route to the same result could in any event be achieved by the construction of the phrase "sell or supply" in regulation 46 itself: as to this, see para. 162 below.

(2) Wholesale Dealer's Licence

157. The Appellants' case on this point can be summarised as follows:

(1) Paragraph (1) (a) of regulation 18 of the HMR makes it unlawful for a person to "distribute a medicinal product by way of wholesale dealing" without a wholesale dealer's licence: see para. 46 above.

(2) That phrase is defined in paragraphs (4) and (5) as covering, so far as relevant, the sale or supply of the product to someone who receives it for the purpose of causing it to be administered in the course of a business: again, see para. 46.

(3) An NHS Trust is a business: see regulation 8 (1) (c) (para. 47 above).

(4) Under mode 3 Trust A would be supplying (and in fact no doubt selling) CB to Trust B to be administered to patients in the course of its business. *Ergo*, it would require a wholesale dealer's licence.

(5) Even if a Trust applied for and were granted a wholesale dealer's licence it could only supply products which had a marketing authorisation – see regulation (6) – which CB does not.

158. Mr Lock's answer to that case started with the position in EU law. He submitted that it is clear that the supply of CB in mode 3 would not require an authorisation under article 77.1 of the Directive, which regulation 18 is intended to implement. What the relevant parts of articles 76 and 77 are concerned with is "wholesale distribution": the definition of that phrase expressly excludes "supplying medicinal products to the public". The effect of the *Apozyt* exemption is that the supply of CB by a compounder to the treating hospital is not a "placing on the market" (within the meaning of article 6) and is a retail supply (within the meaning of article 40.2 *bis*). The reasoning underlying those conclusions necessarily means also that it is not a "supply to the public". Mr Lock referred us to para. 82 of the Opinion of the Advocate General in *AIFA* (see para. 89 above), which says in terms that the Italian system there in question does not involve wholesale supply. It is not clear whether hospitals supplying services under the Italian national health system each have separate legal personality but it would be extraordinary if the availability of the Apozyt exemption depended on the accident of how a particular member state organised its health service in that respect[25] and there is nothing in the reasoning of the Court to suggest that that is a material consideration.

159. That being so, Mr Lock submitted that it would be wrong to construe regulation 18 of the HMR, which were made under the powers conferred by section 2 (2) of the European Communities Act 1972 and in order to conform with the requirements of the Directive, as having any different effect. It was certainly not impossible to construe the language of regulation 18 (4) and (5) in such a way as to exclude arrangements falling within the *Apozyt* exemption.

160. Mr de la Mare did not accept that the supply of CB from one Trust to another under mode 3 would not constitute wholesale distribution within the meaning of the Directive. But he had no real answer to Mr Lock's submission that the rationale of the *Apozyt* exemption applied equally in this context, and that submission seems to me plainly correct.

161. Mr de la Mare's fallback argument was that even if a "mode 3 supply" did not constitute wholesale distribution within the meaning of the Directive it did not follow that regulation 18 of the HMR should be construed so as to have the same effect. The language was perfectly clear. If it extended the requirements for a wholesale dealer's licence to particular circumstances not covered by the Directive, so be it. As is well known, section 2 (2) (b) of the 1972 Act empowers the Secretary of State to make regulations "for the purpose of dealing with matters *arising out of or related to*" rights or obligations deriving from EU law, and there is plenty of case-law showing that that provision need not be construed narrowly: we were referred to *Oakley Inc v Animal Ltd* [2005] EWCA Civ 1191, [2006] Ch 337; *ITV Broadcasting Ltd v TV Catchup Ltd* [2011] EWHC 1874 (Pat), [2011] FSR 40; and *United States of America v Nolan* [2015] UKSC 63, [2016] AC 463.

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[25] It is worth recalling in this context that until about twenty years ago none of the various bodies responsible for NHS hospitals had legal personality: they were simply emanations of the Secretary of State.

162. I do not accept that submission. Regulation 18 was intended to implement article 77 of the Directive, and unless the contrary intention is clear it should not be construed as having any wider effect. I see no difficulty about reading the term "selling or supplying" in a manner that excludes supply pursuant to an individual prescription in accordance with the *Apozyt* exemption. We only enter "*Oakley* territory" where the implementing legislation expressly makes provision of a kind not required by the primary EU instrument, typically for the purpose of what May LJ in that case called "tidying things up" or enacting a detailed scheme to give effect to some more generally expressed requirement. This is not that kind of case.

Reality

163. It was not of course part of the Appellants' case that the Policy does not contemplate Trusts acquiring CB by mode 3. Nor was there any evidence that it would be impracticable for them to do so.[26] However, Ms Stratford submitted that it was clear that the makers of the Policy did not contemplate that it would be necessary to operate a system of individual prior prescriptions, and that if, as I would hold, such a system is required it would mean that the Policy could not realistically be implemented: it would involve a very large and unanticipated administrative, and therefore financial, burden.

164. I agree with the first part of that submission but not the second. The Policy itself says nothing about the mechanics of implementation, but Mr Lock tacitly acknowledged that the Respondents had not envisaged that compounders could only produce CB against individual prescriptions. But he said in his oral submissions that his instructions were that the Trusts could and would put such a system in place if the Court held that it was a necessary condition for the use of CB. That statement in itself cannot be decisive (not least because he was instructed by the CCGs rather than the Trusts), but the burden must be on the Appellants to establish that it would be impracticable to implement an individual prior prescriptions system, and there was no evidence before the Judge (or before us) that that was the case. In any event, that seems inherently unlikely. No doubt a system requiring pre-preparation individual prescriptions would be administratively more complex than one under which hospital pharmacies simply prepared stocks of CB which could then be drawn down as required, and thus also more expensive; but that would appear to be, as Mr Lock said, a price worth paying in view of the savings to be made.

MODE 4: CB SUPPLIED BY A COMMERCIAL ENTITY

165. The description of mode 4 as constituting supply "by a commercial entity" derives from Whipple J's judgment. It is perfectly acceptable as a working label but it is important to appreciate that the essential distinction is not that the CB is supplied

[26] Mr de la Mare, answering a question from the Court in the course of Ms Stratford's submissions, mentioned figures about the quantity of CB produced by the Royal Liverpool in 2010 which he said were far lower than the quantities which the Policy would require. But there are no findings about this by the Judge and the figures mentioned could not possibly be the basis for a finding by us that the Policy was incapable of being implemented by mode 3. We do not know that Royal Liverpool was the contemplated sole supplier, and the volumes produced in 2010 are no guide to its capacity.

"commercially" but that the compounding is not done in a pharmacy (which in this context for all practical purposes means a hospital pharmacy)[27].

166. The lawfulness of mode 4 is an aspect of the case where the Policy's silence about the intended modes of implementation is particularly problematic. Although it seems clear, and Whipple J indeed found, that there is in the UK an established market in commercially compounded CB, there is no evidence about who the suppliers are (save for the single commercial supplier identified in the Respondents' evidence: see n. 7) or the basis, if any, on which such suppliers seek to ensure that their operations conform to the requirements of EU law. It is thus impossible for this Court to reach any definitive conclusion about whether the Policy could lawfully be implemented by mode 4; and indeed it would not be desirable for us to do so in circumstances where no commercial compounder is before the Court. I would only make the following brief observations.

167. The *Apozyt* exemption does not as such distinguish between commercial suppliers and hospital pharmacies: after all, Apozyt itself was a commercial enterprise. A commercial compounder adopting an individual prescription system could thus supply CB without infringing article 6 provided they adopted an individual prescriptions system. However, there remains the question of article 40. It seems very unlikely, though we do not definitively know, that any commercial manufacturer has been granted a manufacturing licence in respect of CB. The exemption under article 40.2 *bis* only applies where the compounding is carried out either (i) in a "dispensing pharmacy" or (ii) by a person legally authorised to carry it out: see para. 92 (2) above. As regards (i), we heard no argument about whether a commercial compounder might in some circumstances properly be characterised as a dispensing pharmacy. As regards (ii), although this shows that the Directive recognises that national law may permit operations of the kind covered by article 40.2 *bis* to be carried out otherwise than in a pharmacy (as in *Apozyt* itself), it was common ground before us that there was no UK legislation that has this effect.

168. If the lawfulness of mode 4 were crucial to our determination of this appeal, those uncertainties would create a very unsatisfactory situation. Fortunately, as will appear, I do not believe that it is. I proceed on the basis that the lawfulness of mode 4 is unclear.

169. I should say that Whipple J floated the possibility, acknowledging that she had heard no submissions on the point, that even if the preparation and supply of CB by commercial entities was contrary to the Directive, it might not be unlawful for an NHS Trust to acquire it given that there was already an established market for it: see para. 232 of her judgment. Mr Lock did not adopt this submission and we too heard no argument about it. I am bound to say that I am provisionally unpersuaded.

MODE 1: SINGLE VIAL USE

170. I have already explained what mode 1 consists of: see para. 125 above. It does not involve compounding at all.

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[27] I would assume, though there is no evidence about this, that Trusts whose pharmacies supplied CB under mode 3 would expect a reward for their services, though the workings of the intra-NHS market are arcane.

171. As to lawfulness, the Appellants did not contend that mode 1 would involve any breach of the Directive (or the EMA Regulation) or the implementing legislation. Even on their construction, the extraction of a single dose from the original vial would not constitute a "placing on the market" within the meaning of article 6 and would not involve any of the processes described in article 40.2.

172. As to "reality", Mr Lock accepted that the makers of the Policy did not have mode 1 in mind at the time of its promulgation: he could hardly have done otherwise since the possibility was raised for the first time during the hearing below. But he contended that it was nevertheless a way in which it could realistically have been implemented. I do not accept that. It may indeed be that if modes 2-4 prove to be either unlawful or impracticable the Respondents may encourage Trusts to adopt mode 1 on the basis that, however wasteful, it is still cheaper than the alternatives. But it is perfectly clear that that is not what the Policy is concerned with: it is concerned, and concerned only, with the use of *compounded* bevacizumab.

THE GROUNDS OF APPEAL

173. Against the background of those conclusions on the four modes I can finally turn to the grounds of appeal. As noted above, I will take ground 1 last.

GROUNDS 2 AND 3

174. I take ground 2 with ground 3 because the ultimate question into which both of them feed is whether the Policy can be implemented without breaching the requirements of the Directive (or the EMA Regulation) or the domestic implementing legislation.

175. As to ground 2, I have already held that the Judge was wrong to find that the Policy could be implemented without the adoption of an individual prescription system for CB: see paras. 102-106 above. But that is not determinative of the question of unlawfulness if such a system can in fact be adopted.

176. As to ground 3, I have also already expressed my conclusions on issues 3A and 3B: see paras. 94-101 and 150-162 above. It remains to consider issues 3D and 3E.

Issue 3D: Unlawful Undermining of the Regulatory Scheme

177. This issue raises what was ground (2) before Whipple J: see para. 119 above. In essence, what the Appellants say is that, even if the Trusts' use of CB to treat WAMD in accordance with one or more of the four modes could be brought within the terms of the *Apozyt* exemption, "the invariable and systematic use" of that exemption would undermine the scheme of the Directive. As Ms Stratford put it in her oral submissions, it would "take what is supposed to be an exception, the small-scale supply of unlicensed products, and turn it into the rule". The unlawfulness of such conduct was characterised in the Appellants' skeleton argument in one or more of three ways – (a) that it must be taken to be implicitly prohibited by the Directive because it would thwart its fundamental aims; (b) that it would constitute an "unlawful circumvention" of the Directive analogous to the kind which the General Court had held to be unlawful in *CTRS*; or (c) that it would be a breach of the duty of sincere co-operation in article 4.3 of the TFEU.

178. Although the "unlawful undermining" point is developed in various ways in the Appellants' skeleton argument, the submission on which Ms Stratford placed most emphasis was that the systematic use of CB in accordance with the *Apozyt* exemption would erode the primacy which the Directive gives to the promotion of patient safety. She reminded us of recitals (35) and (40) (see para. 22 above) and emphasised the importance from the point of view of safety of control being maintained over the entire chain of distribution. The principal points which she made in that regard are essentially the same as those relied on by Mr de la Mare in connection with the modification issue: see para. 96 above. She referred in particular to the account given of the compounding process in the MHRA review, which notes the risk of contamination and other quality control failures and refers to some specific episodes where such risks eventuated. She also referred to the limited shelf-life of CB, the absence of an SMPC and the fact that the use of an unlicensed product would not fall within the pharmacovigilance obligations imposed by Title IX.

179. The Appellants did not accept that the question of the safety of CB was sufficiently answered by the Judge's finding on her "key issue (iii)", i.e. that the NICE Guideline had established that the use of CB to treat WAMD was safe. In his reply Mr de la Mare argued that NICE's conclusion did not involve any consideration of the specific question of the safety of the processes under which CB might be prepared in an NHS hospital pharmacy: NICE was concerned with "safety by design" rather than product quality – that is, it was concerned with safety issues arising from the use of product which had been produced to an optimum standard rather than with safety issues arising from how well the compounding was performed. He said that the particular trials on which it had relied had involved CB produced in hospital pharmacies which held specials' licences.

180. An important aspect of the Appellants' case in this regard was that it had not been shown that there was any system in place for the regulation and/or monitoring of quality control either in hospital pharmacies of the kind in which compounding would take place in the case of modes 2 and 3 or in the facilities of a commercial compounder (mode 4). I need to explain in a little detail how this point developed.

181. The Respondents' evidence below appears to have been that facilities for compounding Avastin were regulated and inspected by the Care Quality Commission ("the CQC"), but it also seems that there was some question about this, since the Judge found only that that "may" be the case (see para. 177 of her judgment). Following the judgment Covington on behalf of the Appellants sought to investigate this question further, and the relevant correspondence was exhibited to the witness statement of Mr Kelly (see para. 145 above). That appeared to confirm that the CQC had no such role; but a letter from NHS Improvement said that "where operating under Section 10 of the Medicines Act 1968 NHS England through the NHS Specialist Pharmacy Service ["the SPS"] audits aseptic services in line with EL (97) (52)[28]". There was no evidence before us (nor before the Judge) about the SPS. Mr

[28] I need not complicate matters by giving a detailed explanation of "EL (97) (52)". In effect, however, the reference is to a publication issued by the Royal Pharmaceutical Society and the NHS Pharmaceutical Quality Assurance Committee entitled *Quality Assurance of Aseptic Preparation Services: Standards*. We were referred to some of its requirements by Mr de la Mare, but only in the context of the prior prescriptions issue.

Lock, who pointed out that he did not represent the NHS, was not able to enlighten us further about the role of the SPS; but on the last day of the hearing Mr Peretz was able to give us a little more detail on instructions from the Secretary of State. He told us that the SPS reviews "quality matters, including the preparation activities that we are concerned with here". He said that it had no formal statutory powers, though he observed that that might be thought unnecessary since the entities which it was supervising were themselves within the NHS. If it identifies quality failings the SPS reports to the relevant NHS Trust, which has its own governance structures; he pointed out that the chief pharmacist at the Trust will be accountable not only to the Trust itself but to the General Pharmaceutical Council. As to the quality control regimes operated by commercial compounders, there was no evidence before us at all; that is unsurprising, since, as already noted, neither the Judge nor we had any information about such compounders or the basis on which they operate.

182. Ms Stratford submitted that this state of affairs revealed "a regulatory black hole". In his reply Mr de la Mare (picking up the baton from her) described Mr Peretz's account as revealing "a very weak toothless form of light-touch premises regulation", which was not remotely comparable to the regime that would apply if pharmacies were subject to the requirement for a manufacturing authorisation.

183. Ms Stratford candidly accepted in the course of her oral submissions that the case based on ground 3D was "ambitious", and in my view it is indeed misconceived. The asserted ill-consequences might in principle – I do not say that they do – call in question whether the CJEU was right to recognise (or, it might be said, to create) the *Apozyt* exemption in the first place. But that boat has sailed. The exemption exists, and its effect is that, in the specified circumstances, the compounding of Avastin and the supply of CB falls outside the requirements of the key operative provisions of the Directive (and the EMA Regulation). That being so, it makes no sense to complain that the preparation and supply of CB in accordance with the *Apozyt* exemption unlawfully "undermines" or "evades" the legislative scheme. The unspoken premise of such a complaint is that the requirements of the Directive were intended to apply to the compounding of Avastin; but the Court has held the opposite[29]. I can see no basis for the argument that the *Apozyt* exemption was only intended to apply to "small-scale" preparation and supply of CB: as I have already said, that was not the case in either *Apozyt* or *AIFA*. The limitation which the Court placed on the scope of the exemption was based not on scale but on the "downstream", or "retail", nature of the supply, as manifested by the requirement for prior individual prescriptions.

184. Since for that reason I would reject the criticism that the Policy undermines EU law I need not consider the various ways in which Ms Stratford submitted that such undermining might be unlawful (see para. 177 above).

185. It follows also that we need not reach any conclusion about whether the systems in place as a matter of domestic law and practice for ensuring the safety of the compounding process are in fact inadequate. It has never been part of the Appellants' pleaded case that the use of CB was unsafe, whether for that or any other reason: the issue has only been raised in the context of the original ground 2 (now "issue 3D")

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[29] In fact Ms Stratford's arguments have a strong echo of, and at one point directly evoked, the Opinion of the Advocate General in *Apozyt*. But the Court did not follow that Opinion: see para. 63 above.

and, in this Court, in connection with the "modification" issue discussed above. As we have seen, the Judge did in fact make an explicit finding, based on the NICE Guideline, that such use was safe, and that finding was not challenged in the grounds of appeal. Even if I were inclined to express any view on the points made about inadequate regulation (and about whether that qualified the NICE guideline), we are not in a position to do so. We simply do not have the evidence on which to reach any view about the adequacy of the SPS regime or the EL (97) (52) standards. I would only say that any NHS hospital pharmacy which decides to undertake the preparation of CB, particularly on a large scale, will need to give careful thought to how to ensure that its processes are safe and accord with any professional or other domestic regulatory rules that apply, bearing in mind among other things the contents of the MHRA review. There is no reason to doubt that they will do so or that the CB produced by them will be of proper quality.

Issue 3E: GMC Guidance

186. I should start by setting out the passage from para. 58 of Whipple J's judgment where she sets out the GMC guidance to which this issue relates.

> "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.'"

187. Whipple J also set out passages from a document entitled "Leadership and management for all doctors" published by the GMC in January 2012. These included a statement to the effect that "whatever their role, doctors must … use resources efficiently for the benefit of patients and the public". This statement was glossed, further on in the document, under the heading "allocating resources":

> "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."

188. In January 2018 the GMC issued further guidance in response to the publication of NICE guideline NG 82. It read:

> "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.'"

189. Before Whipple J Ms Stratford argued that the effect of paras. 68-70 of the Guidance was that it was impermissible for a clinician to prescribe an unlicensed drug on grounds of cost, when a licensed alternative was available. The Judge rejected that submission. At para. 151 of her judgment she said:

> "(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."

190. She continued, at para. 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."

191. In their skeleton argument the Appellants accept that, as the Judge said in her points (i) and (ii) under para. 151, the Guidance did not purport to be exhaustive; but they maintain their submission that "it is plain that [it] does not allow the prescription of unlicensed medicines to save costs when licensed alternatives exist". In her oral submissions Ms Stratford did not seek to develop that proposition, saying that it was a straightforward matter of how the Guidance was to be read.

192. In those circumstances I do not think it is necessary to say more than that I agree with the Judge, for the reasons she gave. The circumstances surrounding the use of Avastin to treat WAMD are indeed unusual, for the reasons she gives. That is clearly illustrated by the terms of the specific guidance issued in January 2018: while expressed in cautious terms, this clearly indicates that in the light of the NICE Guideline (which itself reflects the policy of the RCO) the GMC does not regard it as a breach of good medical practice for a clinician to prescribe Avastin off-label on the basis that it is cheaper than the licensed alternatives. (The Policy of course involves patients being told why Avastin is the preferred treatment and that they are entitled to choose Lucentis or Eylea: see para. 12 above – final bullet point.)

Conclusion on Grounds 2 and 3

193. I do not believe that, provided the requirements of the *Apozyt* exemption are satisfied, the implementation of the Policy will involve any of the forms of unlawfulness alleged by the Appellants.

GROUND 4

194. In my view the argument about the lawfulness of single-vial use of Avastin to treat WAMD is irrelevant to the issue of the lawfulness of the Policy since it is seems to me clear that the Policy is directed only to the use of CB, i.e. compounded Avastin: see para. 172 above.

195. However, if, as Mr Lock insists, there is a realistic prospect that single-vial use might be resorted to if it were not possible to obtain CB, it may be of value for me to say that it is plainly not unlawful. As already noted, the Appellants accept that "mode 1" would not directly contravene the provisions of the Medicines Directive (or the EMA Regulation) or the domestic implementing legislation. Their case that it is unlawful is only that it would undermine the EU legislative scheme, i.e. "issue 3D". I have already rejected that case as regards grounds 2 and 3. It is even harder to see how it could be advanced in relation to mode 1. Such use would of course be "off-label", but that does not make it unlawful.

GROUND 1

196. This ground is directed to the way in which the test of unlawfulness should be formulated and applied. As noted at para. 125 above, Whipple J directed herself at para. 198 of her judgment that the determinative question as regards the lawfulness of the Policy was:

> "[I]s the Policy realistically capable of implementation by the NHS Trusts in a way which does not lead to, permit or encourage unlawful acts?"

The phrase "lead to, permit or encourage unlawful acts" derives from the judgment of Green J in *R (Letts) v Lord Chancellor* [2015] EWHC 402 (Admin), [2015] 1 WLR 4497: see para. 118 (p. 4531H). She went on at para. 238 to hold that that test was satisfied as regards all four of the modes considered, on the basis that "each of [them] at least *might* be lawful": see para. 126.

197. The Appellants' essential submission is that to ask whether the Policy was "capable of" being implemented lawfully led to the Judge taking what Ms Stratford in her oral submissions called a "hypothetical" approach, "divorced from the reality of how the Policy was envisaged to be implemented": her words quoted from para. 238 confirm that that was her approach. The Judge should have applied the *Letts* formulation without any gloss: that is, she should have asked whether the Policy would (when construed objectively and purposively) lead to, permit or encourage unlawful acts.

198. The most obvious reason why this issue assumed the importance that it did both before the Judge and in the Appellants' submissions to us was that one of the bases on which the Respondents sought to defend the lawfulness of the Policy was that it could

be implemented by mode 1 – and indeed the Judge accepted that submission. Since it was clear that mode 1 was not originally intended as a means of implementing the Policy, and only became part of the Respondents' case in the course of the proceedings, it is not surprising that the Appellants criticise the Judge for adopting a "hypothetical" approach and insist on the importance of testing the lawfulness of the Policy on the basis of what was actually and realistically intended. In the context of my conclusions to date, which treat mode 1 simply as an irrelevance, the issue does not arise in such a stark way. I agree that the lawfulness of the Policy should be based on a realistic (and indeed purposive and objective) construction, but modes 2-4 are far less obviously susceptible to the criticism that they are "hypothetical" or "divorced from reality".

199. Nevertheless, I do not think that ground 1 can be treated as having disappeared. The result of my conclusions to date is that the Respondents are promoting a course of action – that is, the use of CB by the Trusts – which it would be realistically possible to implement by, broadly, two alternative routes. The first is to obtain CB from an NHS hospital pharmacy (i.e. modes 2 or 3). I believe that to be lawful, provided that an individual prescription policy is adopted. The second is to obtain it from a commercial compounder (i.e. mode 4). It is impossible to say whether mode 4 is lawful (see paras. 166-168 above), but I am content to assume for present purposes that it is not. As I understand it, the Appellants would contend that on that basis the Policy is still unlawful because it leaves open the possibility of Trusts seeking to implement it by the (assumedly) unlawful mode 4 rather than the (as I would hold) lawful modes 2 or 3.

200. I do not believe that it would be right to hold the Policy to be unlawful on this basis. This is not a case where a policy (or guidance or other such document) itself promotes a course which the Court holds to be unlawful. On the contrary, the Policy is entirely silent about how the Trusts should obtain CB. The Trusts are independent entities, with access to their own legal advice, and capable of making their own decision about that question. I can see no principled basis on which the Policy should be treated as unlawful simply because it does not itself prescribe the lawful alternative and proscribe the unlawful. It neither "leads to" nor "encourages" the choice of the unlawful route. I can see that it might be said, in one sense of the word, to "permit" it inasmuch as it does not forbid it; but, as Floyd LJ observed in the course of argument, "permit" must in this context mean something like "sanction", i.e. positively approve. It would of course be different if the Policy expressly recommended mode 4, whether as the only route or as an acceptable alternative; but it does not. It would also be different if there were no (realistic) lawful source of CB, because, as Mr Lock conceded, CCGs should not adopt a Policy which could not (realistically) be lawfully implemented; but that is not the case.

201. That was essentially the stance taken by the Judge and espoused also by Mr Lock. Ms Stratford protested that it was unrealistic. She took us to documentary evidence that showed that the CCGs liaised extensively with representatives of the Trusts in developing the Policy and indeed sought to persuade them, in the light of some expressions of unease, that it should be pursued. This was not, she submitted, in truth an arm's length relationship in which the Trusts were expected to make their own choices; and the Policy should be construed as positively permitting, albeit as one alternative, the use of mode 4.

202. As to that, I am willing to accept that there was indeed a high degree of liaison between the CCGs and the Trusts, and that both may *in fact* have regarded purchase from commercial suppliers as one way in which the Policy could be implemented. But I do not think that that makes any difference in principle. It is necessary to respect the legal (and deliberate) separation of CCGs and Trusts. The point could in truth only go anywhere if CCGs were under a duty to advise Trusts as to what routes were lawful, because their silence on the issue would then be a breach of that duty; but the case was not put that way, and no basis for the existence of any such duty was identified. It is necessary to construe the Policy, objectively, by reference to its terms. As I have said, it says nothing about where Trusts should obtain their supplies of CB from. Indeed the letter from the CCGs relied on by Ms Stratford (see para. 144 above) after saying that a manufacturer of CB had been identified went on at once to say that "of course the choice of supplier is an issue for individual trusts". If a Trust chose to obtain CB from a commercial supplier rather than an NHS hospital pharmacy that would (on the assumption I am making) be an unlawful act on its part, but that is another matter. This is the distinction made by Whipple J at the end of para. 196 of her judgment (see para. 215 above).

203. The question whether the lawful modes of implementation are "realistic" does not arise. I have concluded that both mode 2 and mode 3 were realistic, and mode 1 is out of the picture.

204. As to whether modes 2 and 3 were hypothetical, in the sense that they were not contemplated at the time that the Policy was promulgated, there is no issue as regards mode 3: the Appellants accept that the expectation was that CB would be obtained either by mode 3 or by mode 4 (or perhaps both). That being so, I do not think it can make a difference that mode 2 was probably not contemplated (see para. 147 above).

205. Nor do I think that it matters that it was not originally appreciated that mode 3 could not be lawfully implemented unless an individual prescription system were adopted. The starting-point is the analysis in paras. 200-202 above. There are two ways in which an NHS hospital pharmacy could prepare CB, one lawful (using a prior prescription system) and one unlawful (not using such a system). The Policy is entirely silent as to which should be adopted, nor can any preference be inferred. For the reasons given, I do not believe that that silence can be said to lead to, permit or encourage the choice of the unlawful route. I do not believe that it can make a difference to that analysis that the makers had not appreciated the full legal requirements of one of the modes by which they envisaged the Policy being implemented: it would be another matter if the result were that that mode was not realistically possible, but it has not been shown that that is the case. But the point can be put more broadly. Even if it were necessary that the Respondents should have positively identified a means by which the Policy could be lawfully implemented, as they did (namely modes 2 and 3), it would be absurd to hold that that the Policy was unlawful unless they had also identified and worked through every detail. It is important not to lose sight of the fact that, however much liaison there may be, CCGs are commissioners of services: it is for the Trusts to provide them and to work out how they may be provided.

206. In short, I do not believe that the fact that one of the ways in which Trusts might seek to implement the Policy may be unlawful means that the Policy itself is unlawful. It

is sufficient that there were lawful means of implementation which were both realistic and (at least in outline) envisaged at the time that it was promulgated.

207. Although we were referred to a number of authorities in connection with ground 1, I did not find them particularly relevant to the present case. The Appellants placed considerable weight on the *Letts* formulation (which derives from, but to some extent glosses, language used in *Gillick v West Norfolk and Wisbech Health Authority* [1986] AC 112), but Green J was doing no more than providing a useful encapsulation of the law applicable in that case. It was not a situation where the silence of the guidance there in question on a particular issue left open the possibility that the person to whom it was directed might choose an unlawful mode of implementation. The issue in *R (Refugee Legal Centre) v Secretary of State for the Home Department* [2004] EWCA Civ 1481, [2005] 1 WLR 2219, and *R (Tabbakh) v Staffordshire and West Midlands Probation Trust* [2014] EWCA Civ 827, [2014] 1 WLR 4620, to which we were also referred, was likewise different. In both cases the policy-maker had, or had undertaken, the responsibility of prescribing the procedure to be followed in the circumstances in question, and the issue was whether that procedure carried an inherent risk of unlawful outcomes, distinct from the possibility of individual aberrant decisions. In the present case, by contrast, the CCGs did not have the responsibility for sourcing CB and the Policy is silent on the issue.

208. I agree with the helpful further observations of Rose LJ at para. 214 below.

CONCLUSION

209. I would dismiss the appeal and uphold the Judge's decision that it is legally open to Trusts to use compounded Avastin off-label to treat WAMD patients in line with the Policy. In short, the preparation and supply of CB does not require a marketing or a manufacturing authorisation provided that the requirements of the "*Apozyt* exemption" are observed; nor is it contrary to GMC guidance for clinicians to recommend it to patients in preference to Lucentis or Eylea even though that the preference may be based on cost considerations.

210. However, the route by which I reach that result, particularly as regards the issue whether a marketing or a manufacturing authorisation is required, is at least as important as the result itself. Two points from my analysis are particularly important for the CCGs' and the Trusts' future course of action:

(1) I do not believe that the Court is able to rule either way on the lawfulness of Trusts obtaining CB from commercial suppliers as opposed to from a hospital pharmacy. That is regrettable but it is the result of the way in which the issues have come before the Court. I hope that my analysis of the legislation will at least assist Trusts in reaching a decision on this question if it is a course which they are interested in pursuing.

(2) If Trusts wish to obtain CB from a hospital pharmacy, whether within their own Trust or from elsewhere in the NHS, that will only be lawful if an individual (prior) prescription system is in place.

211. I should say, finally, that the Appellants in the course of their submissions sought from time to time to suggest that a decision that the Policy was lawful would open the

door to widespread evasion of the requirements of the licensing system, which are essential for patient safety, in the interests of saving costs. That submission was also advanced by Ms Carss-Frisk in her written and oral submissions on behalf of ABPI. I do not accept that. The *Apozyt* exemption operates in very specific circumstances and is subject to strict requirements. There is nothing inherently illegitimate in prescribing decisions being influenced by cost considerations where the evidence shows no differences in efficacy or safety.

Lord Justice Floyd:

212. I agree.

Lady Justice Rose:

213. I am grateful to the Vice-President for the clarity of his exposition of the complex EU and domestic legislation and his careful unpicking of the meaning and consequences of the CJEU's jurisprudence. I agree with his analysis of the scope of the *Apozyt* exemption and his conclusion at para. 103 that the language and the logic of the CJEU's judgment in that case mean that the requirement for individual prescriptions is an essential element in that Court's justification for the exemption.

214. The consequence of that, together with the uncertainties over the legality of the different proposed modes of supply, is that the implementation of the Policy was not at all as straightforward as the wording might suggest. The point made by the Vice-President in paras. 202 and 207 is key to understanding why in this case the omission from the Policy of any mention of these problems did not render the Policy unlawful. Most of the case law dealing with challenges to published policy concern policy or guidance issued by the Secretary of State to his or her staff explaining to them the legal framework in which they perform their functions. For example, in *Letts* the guidance challenged was issued by the Lord Chancellor to caseworkers considering the applications from next of kin for legal aid and was held to be unlawful because it was misleading and inaccurate in providing a materially misleading impression of what the law was. In such cases there can be no question of those who are expected to implement the policy taking independent legal advice and making up their own minds as to what the law is. Some of the cases to which we were referred are similar to the present case in that they involve guidance given by the Secretary of State for Health to independent NHS Trusts, for example *R (A) v Secretary of State for Health* [2009] EWCA Civ 225, [2010] 1 WLR 279, where the guidance issued by the Secretary of State concerning when the NHS Trust should provide medical treatment to overseas visitors who could not or would not pay was held to be unlawful. I do not regard the Vice-President's judgment as casting doubt on the correctness of those decisions. The important factors here are first that there are modes of implementation that are both lawful and realistic and secondly that the Policy does not purport to guide the Trusts on how to implement the Policy should they choose to adopt it, given that it is the task of the Trusts to work out how to provide the services which are commissioned by the CCGs.