[2019] IEHC 814

THE HIGH COURT
COMMERCIAL

[2018 No. 3485 P.]

BETWEEN

MERCK SHARP & DOHME CORP

PLAINTIFF

AND

CLONMEL HEALTHCARE LIMITED

DEFENDANT

JUDGMENT of Mr. Justice Denis McDonald delivered on 29 November, 2019

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The issues to be decided

1. These proceedings were commenced by the plaintiff against the defendant seeking relief in relation to the alleged infringement of the plaintiff's rights under Supplementary Protection Certificate ("*SPC*") no. 2005/2001 granted in 2005 in respect of a cholesterol-reducing medicinal product comprising a combination of two active ingredients namely ezetimibe and simvastatin. Ezetimibe is a member of a class of compounds known as azetidinones. As described in more detail below, simvastatin is a statin. In response to the plaintiff's claim, the defendant raised a counterclaim in which it challenged the validity of the SPC on three grounds. This judgment addresses the invalidity claim. The issues raised by the defendant are as follows:-

   (a) In the first place, the defendant contends that the SPC breaches Article 3 (a) of Regulation (EC) No. 469/2009 ("*the SPC Regulation*") on the ground that the combination of ezetimibe and simvastatin is not protected by the underlying patent "*and/or was not the core inventive advance to which the …Patent pertained"* (to quote from para. 6 (a) of the Particulars of Objection annexed to the counterclaim). The patent in question is described in more detail in para. 2 below and is referred to in this judgment as the *"599 patent";*

   (b) Secondly, it is claimed that, in breach of Article 3 (c) of the SPC Regulation, the only compound protected by the 599 Patent (which the defendant contends is solely ezetimibe) was already the subject matter of an earlier SPC granted in 2003. In addition, during the course of the hearing, this contention appears to have been expanded to also make the case that, if the 599 patent protects the combination of ezetimibe and simvastatin, that combination had previously been the subject of the earlier SPC granted in 2003 (described further below). In those circumstances, it is contended that the 2005 SPC is not valid; and

   (c) Thirdly, the defendant claims that the marketing authorisation for the combination was not the first marketing authorisation for such combination and that, in the circumstances, the SPC was granted contrary to the provisions of Article 3 (d) of the SPC Regulation.

Background

2. The plaintiff is the holder of Irish Patent 0 720 599 ("*the 599 patent*") which was granted by the European Patent Office ("*EPO*") on 19th May, 1999 with a priority date of 21st September, 1993. The patent relates to a treatment for atherosclerosis. There is no dispute between the parties that the 599 patent covers a number of azetidinone compounds including ezetimibe. There is equally no dispute between the parties that ezetimibe inhibits the resorption of cholesterol (known to be a cause of atherosclerosis) at the brush border of the intestinal villus in the small intestine. The mode of action of ezetimibe is different to that of other cholesterol lowering agents such as HMG-CoA reductase inhibitors commonly known as statins (including simvastatin) which act by increasing the breakdown of cholesterol in the liver. As described further below, there are also a number of other agents (each with their own mode of action) which are used to treat elevated levels of cholesterol.

3. In 2003, a marketing authorisation was granted in respect of a medicinal product under the trade name Ezetrol pursuant to national measures implementing Directive 2001/83/EC ("*the Medicinal Products Directive*") which permitted the marketing of 10mg tablets of ezetimibe for the following therapeutic indications namely:-

   (a) In the case of primary hypercholesterolemia, the tablets were to be administered with an "*HMG-CoA reductase inhibitor (statin) or alone*" as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolemia. It should be noted that heterozygous familial hypercholesterolemia occurs where the relevant gene is inherited from one parent alone.

   (b) For homozygous familial hypercholesterolemia, the tablets were to be administered with a statin and were indicated for use in patients with this condition. By way of explanation, homozygous hypercholesterolemia occurs where a child inherits the relevant gene from both parents.

   (c) For homozygous sitosterolemia, the tablet was indicated for use in patients with this condition. In other words, the tablet was to be administered alone for this condition. I should explain that homozygous sitosterolemia is an inherited disorder of sterol metabolism in which an excess of plant sterols is absorbed and not enough is excreted.

4. In circumstances where a marketing authorisation was granted for ezetimibe (on the terms set out above), the plaintiff was in a positon to apply for the grant of an SPC. In 2003, an SPC was issued in respect of ezetimibe. This is the SPC on which the defendant relies in support of its case under Article 3 (c) of the SPC Regulation.

5. Subsequently in 2005, a new marketing authorisation was issued to the plaintiff in respect of a medicinal product with the trade name Inegy. This was in respect of tablets containing a combination of ezetimibe and simvastatin. The authorisation extended to four specific compositions namely 10 mg ezetimibe and 10 mg simvastatin, 10 mg ezetimibe and 20 mg simvastatin, 10 mg ezetimibe and 40 mg simvastatin and 10 mg ezetimibe and 80 mg simvastatin. According to the clinical particulars set out in the marketing authorisation, the therapeutic indications for this combination were:-

   (a) In the case of primary hypercholesterolemia, Inegy was indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidaemia where use of a combination product is appropriate.

   (b) For homozygous familial hypercholesterolemia, Inegy was indicated as adjunctive therapy to diet for use in patients with this condition.

6. Thereafter, the SPC, the subject matter of these proceedings was issued in 2005. It was issued in respect of ezetimibe or a pharmaceutically acceptable salt of ezetimibe in combination with "*a cholesterol biosynthesis inhibitor such as simvastatin*".

7. It should also be noted that simvastatin was previously the subject of Irish Patent No. 51478 which was filed on 2nd February, 1981. Simvastatin also had the benefit of an SPC. However, that SPC expired on 5th May, 2003.

The SPC Regulation

8. In order to understand the issues which the defendant raises in relation to the validity of the SPC, it is necessary to refer, at this point in broad terms, to the provisions of the SPC Regulation. Under Article 3 (a) of the SPC Regulation, an SPC may only be granted where the product, the subject matter of the SPC is protected by "*a basic patent in force*". As noted above, the defendant maintains that the combination of ezetimibe and simvastatin is not protected by the 599 patent and/or that it was not the "*core inventive advance to which the 599 Patent pertained*". According to the evidence adduced on behalf of the defendant, the patent does not disclose anything about a combination product comprising ezetimibe and simvastatin. The defendant claims that the patent does not teach that there is any advantage to taking ezetimibe and simvastatin in the same tablet compared to taking a medicinal product containing ezetimibe alone and another medicinal product containing simvastatin alone. The defendant maintains that the innovation of the patent is the demonstration that the different structure of the compounds represented by formula 1 (which are represented in the patent and which include ezetimibe) can be made in a pure form. According to the defendant, the combination of ezetimibe and simvastatin does not represent a separate invention. The defendant also maintains that combination treatment with lipid lowering compounds belonged to the state of the art in the early 1990s (i.e. before the priority date of September 1993) such that the combination could not, of itself, be considered to be an invention. In order to resolve this issue, it will be necessary to consider the terms of the 599 Patent in some detail. It will also be necessary to consider the case law of the Court of Justice *("the CJEU*") in relation to what is meant by the words used in Article 3 (a) namely that: "*the product is protected by a basic patent in force".* The case in relation to Article 3 (a) is addressed in detail in paras. 43 to 95 below.

9. Under Article 3 (c) of the SPC Regulation, an SPC cannot be granted if the product (the proposed subject of the SPC) has already been the subject of a previous SPC. In this case, the defendant has pleaded in its particulars of objection, that the compound protected by the 599 Patent (which it contends was confined to ezetimibe) was already the subject of the 2003 SPC. In addition, during the course of the hearing, the defendant maintained that the combination product has also been the subject of the SPC granted in respect of Ezetrol. This is largely on the basis that (a) the marketing authorisation for Ezetrol required the 10 mg tablets containing ezetimibe to be administered with a statin for patients suffering from homozygous familial hypercholesterolemia and (b) that, thereafter, the Ezetrol SPC was granted on foot of that authorisation. In those circumstances, the defendant contends that Article 3 (c) prohibited the grant of the SPC

in issue in these proceedings (i.e. the SPC granted on foot of the Inegy marketing authorisation). The case in relation to Article 3 (c) is considered in detail in paras. 96 to 103 below and also 124 and 125 below.

10. Insofar as Article 3 (d) is concerned, it makes clear that, if an SPC is to be granted, the relevant marketing authorisation under the Medicinal Products Directive must be the first such authorisation to place the product on the market as a medicinal product. For this purpose, Article 1 (b) defines a "*product*" as:-

> *"The active ingredient or combination of active ingredients of a medicinal product".*

11. In turn, Article 1 (a) defines a "medicinal product" as:-

> *"any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals".*

12. Insofar as Article 3 (d) is concerned, the defendant argues that the marketing authorisation in respect of Inegy is not the first authorisation to place the combination product on the market as a medicinal product. The defendant argues that the first such authorisation was that issued in respect of Ezetrol. As noted in para. 3(b) above, this argument proceeds on the basis that, according to para. 4.1 of the clinical particulars relating to the Ezetrol authorisation, ezetimibe was required to be administered with a statin for use in patients with homozygous familial hypercholesterolemia. The defendant submits, accordingly, that the combination of ezetimibe and simvastatin was authorised by the 2003 authorisation. The defendant makes the case that, in those circumstances, the requirements of Article 3 (d) are not satisfied in the case of the Inegy marketing authorisation issued in 2005. The case in relation to Article 3 (d) is addressed in paras. 104 to 123 below.

Atherosclerosis

13. Before proceeding to consider the legal issues in more detail, it may be helpful, at this point, to briefly describe the role which cholesterol is generally believed to have in the development of atherosclerosis which is the relevant medical condition for present purposes. It would be impracticable to set out, in this judgment, all of the expert evidence that was given in the course of the hearing. The best that can be done is to set out a broad overview which, I hope, will be sufficient to identify the relevant features of the factual background against which the legal issues fall to be determined. Insofar as atherosclerosis is concerned, the disease arises as a consequence of the accumulation of atherosclerotic plaques in the inner layers of artery walls. This leads to the gradual narrowing of blood vessels. Atherosclerosis is typically asymptomatic especially in the early stages. Patients may only become aware of the condition after clinical complications occur such as a heart attack or a stroke.

14. One of the risk factors for the development of atherosclerosis is the presence of low-density lipoproteins ("*LDL*") in the blood. Human blood plasma contains a series of lipoprotein classes (including LDL, high density lipoprotein ("*HDL*") and very low-density lipoprotein ("*VLDL*")) which act as transport vehicles for fat molecules such as triglycerides, cholesterol and a number of other lipid species in the blood. Although cholesterol is essential for the human body (in that cholesterol is a building-block for cell membranes) an excessive supply of lipid molecules (exogenous) or an excess of biosynthesis of lipid molecules (endogenous) may exceed the body's demands. As a consequence, it is believed that this can lead to the accumulation of atherosclerotic plaques. There are a number of reasons why LDL may be elevated. These include an increased supply of saturated fatty acids. Another risk factor is a genetic disorder of the lipoprotein metabolism as observed in familial hypercholesterolemia.

The development of cholesterol treatments

15. In circumstances where high concentrations of LDL are generally associated with an enhanced risk of atherosclerotic disease, attempts have been made over the years to develop treatments designed to reduce LDL levels in a patient's blood. Again, it is important to identify, in broad terms, the relevant treatment background that existed as of the priority date of the patent. While there was disagreement between the experts as to when combination therapy was first used for the treatment of hypercholesterolemia, there was general agreement between the experts on both sides about the development of a number of monotherapies for the treatment of LDL cholesterol. According to Prof. Dr. Winfried Marz ("*Prof. Marz*") who gave evidence on behalf of the defendant, one of the first active ingredients observed to reduce both cholesterol and triglycerides in humans was nicotinic acid (e.g. niacin). The reduction effected by treatment with nicotinic acids were associated with a decrease in lipoprotein synthesis, resulting in a drop in LDL levels. However, Prof. Marz gave evidence that side effects were frequently observed with administration of these acids.

16. A further treatment used to reduce LDL levels comprised bile acid sequestrants (also referred to as ion-exchange resins). These agents act by binding bile acids within the intestinal lumen, interfering with their reabsorption and increasing their excretion. As a consequence, bile acid synthesis is stimulated in the body, requiring an increased amount of cholesterol in the liver. According to Prof. Marz, cholestyramine is an example of such an agent which was found to be highly effective in treatment. However, one of the downsides was that it was not well tolerated by many patients.

17. Another agent which was used in the early 1990s consisted of fibrates. According to Prof. Marz, clorfibrate and its derivatives were amongst the most commonly used agents for cholesterol reduction at that time.

18. Another treatment comprised the use of plant sterols. These target the intestinal absorption of exogenous (principally dietary) and endogenous (biliary) cholesterol and they thus act to lower serum levels of LDL.

19. Finally, statins (also known as HMG-CoA reductase inhibitors) had been developed as a therapy as early as the 1980s. Statins are, in general, more effective and better tolerated compared to many of the compounds mentioned above. Statins were first authorised for use by humans in the United States. According to the evidence, they were first authorised for use in Ireland in January 1990 which coincides with the date when they were first authorised in Germany. However, even in advance of the date of authorisation, the use of statins was recommended. This was acknowledged by Prof. Dr. Gerd Assmann ("*Prof. Assmann*") (who was called as an expert on behalf of the plaintiff) on Day 7 of the hearing. The professor explained that the LDL cholesterol lowering effects of statins was such that it was unjustifiable to delay their application since, to do so, would expose significant numbers of patients to myocardial infarction. Prof. Assmann also explained that it was not until the publication of the Scandinavian Simvastatin Survival Study (known as the "*4s study*") in November 1994 that it was demonstrated that long term treatment with simvastatin, in high risk individuals, not only lowered non-fatal myocardial infarction but also total mortality. Prof. Assmann described the 4s study as an "*absolute breakthrough study*". In turn, Prof. Marz accepted that the 4s study was a "*landmark study*" which showed for the first time that statins could not only reduce cardiovascular events but also total mortality. Nonetheless, it is clear that from all of the evidence that I heard in the course of the hearing and from the many papers that were produced in the course of the evidence, that statins were already in use as a cholesterol treatment well in advance of the priority date of the 599 patent and also well in advance of the 4s study. As of the priority date of the 599 patent, several statins were already commercially available on the market including lovastatin and simvastatin. Others (such as atorvastatin) were in development at that time.

20. As noted above, the 599 patent dealt with a different treatment for hypercholesterolemia namely a class of compounds known as azetidinones which includes ezetimibe. The background to the invention disclosed in that patent is set out in paras. 0001 to 0008 of the patent. In para. 0001, the invention is stated to relate to hydroxy-substituted azetidinomes which are useful as hyporcholesterolemic agents in the treatment and prevention of atherosclerosis. The same paragraph says that the invention also relates to the combination of such an azetidinone and a cholesterol biosynthesis inhibitor (which would include statins).

Combination therapy

21. It would be a mistake to think, however, that the concept of a combination of two cholesterol inhibitors was first disclosed in the 599 patent. The evidence very clearly establishes that, by the priority date of the patent, combination therapy was both known and in use. While there was a dispute on the evidence as to the extent to which combination therapy was in use at this time, there can be no doubt that the idea of combination therapy was not new at the priority date.

22. Paragraph 0008 of the patent itself refers to a pre-existing paper by Illingworth published in "*Cardiology*" in 1989 which suggested that combination therapy involving an HMG CoA reductase inhibitor (i.e. a statin) and a bile acid sequestrant has been demonstrated to be

more effective in human patients than either agent in monotherapy. In the summary at the beginning of the Illingworth paper, the author states:-

> *"Combined therapy with drugs which have different mechanisms of action can be effectively used in the treatment of patients with severe hypercholesterolaemia or combined hyperlipidaemia; for the former group, combinations which use bile acid sequestrants, HMG CoA reductase inhibitors and nicotinic acid are the most effective".*

23. Paragraph 0008 of the patent also refers to a paper by Witzum published in November 1989 which mentions combination therapy for individuals suffering from heterozygous familial hypercholesterolemia or severe hypercholesterolemia. The author states that in such cases:-

> *"A combination of two or occasionally even three medications will be required to achieve ideal LDL cholesterol values. Fortunately, effective combinations are available …".*

The author also states, at an earlier point in the paper, that "*dramatic*" results could be achieved by a combination of a bile acid sequestrant and a statin such as Lovastatin.

24. Similar statements had been made in publications as early as 1987. For example, in a paper presented in the European Heart Journal in 1987 authored by a prestigious study group from the European Atherosclerosis Society (co-chaired by Prof. Assmann) the following was stated:-

> *"Monotherapy is preferred, but resistant familial hypercholesterolaemia not infrequently requires treatment with two drugs possessing different modes of action".*

25. This paper in the European Heart Journal was an important document at the time. It represented the distilled knowledge of a wide range of experts in atherosclerosis including the late Prof. Risteard Mulcahy who was well known in this jurisdiction. According to Prof. Marz, the European Heart Journal is addressed to the entire medical community and is a "*really important*" journal. In addition, Prof. Assmann confirmed that the article represented the consensus view of approximately 30 of the most recognised experts in Europe on issues including the risk and benefit of cardiovascular drugs.

26. According to Prof. Assmann in the course of his evidence on Day 7 of the trial, the advantage of two drugs with different modes of action is that they may have an additive effect. The expert evidence on both sides also suggested that, where a combination of two inhibitors was used, the doses of the individual components of the combination could be lower thus reducing the risk of unwanted side effects.

27. I do not propose to here identify each of the papers which were discussed in the course of the evidence at the trial. They included a paper published in "*Cardiology*" in 1990 by Prof. Willem Erkelens in 1990, a further paper by Prof. Assmann published in May 1989 in

the American Journal of Cardiology, an article by Akira Endo published in the Journal of Lipid Research and a paper by Caroline J. Lintott and others published in the Medical Journal of Australia in October 1991. The paper authored by Caroline Lintott addressed simvastatin in particular and described a combination of simvastatin with bezafibrate as a "*potentially useful drug combination".* The paper by Erkelens also addressed statins. It contained a section providing practical advice (which Prof. Marz, on Day 4 of the hearing, suggested was addressed to medical practitioners) in the following terms:-

> *"The HMG CoA reductase inhibitor lovastatin is reportedly used by 1 million patients in the USA, and the use of simvastatin in Europe may reach this number in the coming years. The reported lack of serious adverse effects in widespread use and the paucity of adverse effects in clinical trials suggest that HMG CoA reductase inhibitors might be appropriate first-line drugs for the treatment of hypercholesterolemia, despite the fact that no data on long-term side effects are yet available. In my opinion, HMG CoA reductase inhibitors of which simvastatin is the most potent on a weight basis should be used as first-line therapy in heterozygous FHC. If this monotherapy fails to achieve an adequate reduction of the cholesterol level, cholestyramine or cholestipol should be added, initially in doses much lower than the recommended maximum doses of 8 and 10g …. respectively. …"* (Emphasis added)

By way of explanation, cholestyramine is a bile acid sequestrant. So is cholestipol.

28. In the 1989 article by Prof. Assmann, he also drew attention to the possible use of combination therapy in cases where both triglyceride and cholesterol levels remain elevated. In such cases, Prof. Assmann suggested that a combination of lipid-lowering agents may be appropriate. He continued:

> *"Suggested combinations include a bile acid sequestrant and a fibrate, or alternatively, an HMG CoA reductase inhibitor".*

29. In the 1992 article by Akira Endo, the author observed that statins (in particular lovastin, simvastatin and pravastatin) had been approved and marketed in many countries and were now well established as effective and safe cholesterol-lowering drugs used by many patients. In the course of the paper, the author refers to studies undertaken as early as 1983 and 1984 in Japan which showed that a combination of mevastatin and cholestyramine in patients with heterozygous familial hypercholesterolemia was reduced by as much as 50-60% by the combination without serious side effects. A similar rate of reduction was found in studies involving a combination of lovastatin and cholestipol. The author reported that this combination enhanced the control of LDL while permitting the use of smaller doses of both drugs.

30. However, Prof. Assmann, in his written statement submitted in these proceedings in July 2018, maintained that by the early 1990s, the *"theoretical combination*" of various cholesterol inhibitors was based on "*very limited clinical findings*" and, in light of "*fairly severe side effects and lack of appropriate safety and efficacy data*" such combinations

and "*other similar experimental combinations*" were seen as a "*a last resort for the small population of patients with severe hypercholesterolemia…*" and would "*certainly not have been considered state of the art for a GP at that time".*

31. The evidence of Prof. Assmann was flatly contradicted by the evidence of Prof. Marz. In his witness statement delivered in response to Prof. Assmann in October 2018 Prof. Marz said that, depending on the individual patient's needs for reduction of LDL cholesterol, it was established practice in the 1990s to administer more than one active ingredient to achieve target cholesterol levels. According to Prof. Marz, this was not only well documented in the literature but was also in agreement with his personal experience. In his evidence at the hearing, he explained that if monotherapy did not work, combination therapy would be applied and he said that the most frequent combination that was used was one involving a statin with a bile acid sequestrant. In this context, Prof. Marz referred not only to the scientific literature discussed above but also to a number of further articles co-authored by Prof. Assmann himself in a journal distributed to every general practitioner in Germany. The journal in question was *"Deutsches Arzteblatt*" (which I will refer to as the "*German Medical Journal*"). The first such article was published in 1987 and did not address combination therapy as such. However, it is clear from the text of the article that it was addressed to general practitioners. The article also stressed the importance of screening patients in respect of lipid levels at regular intervals by general practitioners.

32. Subsequently, in 1988, a further article was published in the German Medical Journal again co-authored by Prof. Assmann which provided more detailed recommendations for diagnosis and management of hyperlipidaemia patients. These were the recommendations made by the European Atherosclerosis Society (in which Prof. Assmann played a prominent role). As described in para 25 above, the recommendations of that society represented the synthesis of the views of 30 experts drawn from all around Europe. The introduction to the article stated that the recommendations were directed to all practising physicians and should be particularly helpful for those doctors working in primary care and in certain specialist units. Detailed recommendations were given in relation to the treatment of patients with elevated levels of cholesterol. These included dietary recommendations. If changes in diet did not succeed, drug therapies were recommended. In the case of Group D patients (namely patients with elevated levels of cholesterol and triglycrides) the paper recommended a number of treatments including some combinations.

33. The article in 1988 was followed up by an even more detailed article published in the German Medical Journal in April 1990 (again co-authored by Professor Assmann) which contained similar recommendations. The paper also contained a number of useful questions and answers including, at para. 29, a question as to which combinations of lipid lowering agents were recommended and which were not recommended. The answer given to this question was in the following terms:-

"Ion exchange resins are often used with nicotinic acid derivatives or fibrates. This results in further reduction of serum cholesterol, triglycerides and LDL cholesterol, while HDL cholesterol increases.

The combination of HMG-CoA reductase inhibitors with fibrates or nicotinic acid derivatives should be avoided due to the myopathy-rhabdomyolysis risk.

The combination of ion exchangers with cholesterol synthesis inhibitors (HMG-CoA reductase inhibitors) results in a dramatic reduction of LDL cholesterol by up to 50 percent".

34. The reference in that answer to "ion exchangers" is another name for bile acid sequestrants. It will be recalled that, in the paper by Akira Endo, the author referred to studies involving such a combination going back to the 1980s. In my view, the articles clearly demonstrate that significant efforts were made in the period between 1988 and 1990 to educate general practitioners in Germany as to the recommended treatments for hypercholesterolemia and to inform general practitioners of the treatments available including combination therapy. General practitioners were not told that combination therapy should only take place in specialist clinics. In my view, the sheer extent of the guidance given to general practitioners in Germany strongly supports the evidence given by Prof. Marz that combination therapy was in use in Germany among general practitioners in 1992. In this context, I do not believe that the evidence goes so far as to suggest that it was undertaken by a majority of general practitioners at that time. However, the evidence satisfies me that it was undertaken by some general practitioners and that it was also available in specialist clinics. I appreciate that the plaintiff has sought to undermine the evidence of Prof. Marz in this regard by reference to evidence that he gave in the course of proceedings in Norway. It was suggested to Prof. Marz during the course of cross examination that, in proceedings which took place in Oslo, Prof. Marz had said it was not common for a general practitioner to use combination therapy for the treatment of hyperlipidaemia. However, in response, Prof. Marz explained that his evidence in Norway related to a period after the priority date of the patent when stronger statins became available such as Atorvastatin which led to a shift back to monotherapy. He also explained that his impression (formed during interaction with general practitioners) was that a percentage of them were involved in combination therapy during the late 1980's and in the period before the priority date. While the evidence of Prof. Marz on this issue lacked detail, it seems to me that, in light of the way in which general practitioners were educated by the German Medical Journal, at least some of them must have been involved in combination therapy. The very fact that the 1990 article published in the German Medical Journal had a series of questions and answers supports this position. It appears to me to be obvious that the very reason why the Journal included these questions and answers was to assist general practitioners in their decision making in relation to appropriate treatment for their hyperlipidaemic patients.

35. Notwithstanding that these articles in the German Medical Journal are clearly directed to general practitioners and notwithstanding the very clear advice given in these articles,

Prof. Assmann, in his replying witness statement and in his oral evidence, sought to maintain the positon that combination therapy was not undertaken in general practice and was reserved for severe cases of hypercholesterolemia treated in specialist clinics. Remarkably, he offered no satisfactory explanation as to why he did not bring to the attention of the court, in his first witness statement, the approach taken by the European Atherosclerosis Society or the three papers co-authored by him and published in the German Medical Journal. I was unimpressed by the explanation given by Prof. Assmann for not drawing these journals to the attention of the court. They were clearly relevant to the pre-priority date practice of the medical community in Germany about which he had purported to give evidence in his first witness statement. When he was cross examined on Day 8 as to why he had not made reference to these papers, his answer, rather glibly, was:-

> *"okay, that's easy to explain. Because I was not asked to comment [on] my own papers or the European Heart Journal papers. All of that came up after the discussion with Prof. Marz. So he brought up these arguments and tried to outbalance my statement …".*

36. In my view, Prof. Assmann, as an expert, clearly should have brought these papers to the attention of the court in his own witness statement. It is unsatisfactory that an expert would not bring such manifestly relevant materials to the attention of the court and should only address them after they have been raised by an expert on the other side. Given that these journals were clearly addressed to general practitioners, and given that the journals did not themselves suggest that combination therapy was limited to specialised clinics, the journals are plainly of relevance to the issue which falls for consideration in these proceedings in relation to Article 3 (a) of the SPC Regulation. It is particularly difficult to understand how Prof. Assmann, as a co-author of the articles, did not address them of his own volition. At this point, it should be noted that the defendant has strongly questioned the independence of Prof. Assmann's testimony. The defendant does so not merely on the basis that these relevant materials were not brought to the attention of the court in the professor's first witness statement but also on the basis of the somewhat combative and, at times, unhelpful conduct of Prof. Assmann while giving evidence. In addition, the defendant draws attention to the professor's involvement with the proprietor of the 599 patent (Schering Plough) in relation to ezetimibe. In this context, it emerged during the course of Prof. Assmann's cross-examination that he had been on the advisory board of Schering Plough at the time when the 599 patent was filed and that he had had "*lots of discussions*" with the inventor, Dr. Harry Roger Davis (albeit that these related to the Niemann-Pick protein described in para. 28 below rather than to the subject matter of the patent). In the course of his evidence on Day 8, Prof. Assmann said that he did not reveal this relationship previously because he thought it was "*irrelevant*". Of course, prior involvement of that kind does not necessarily out rule the giving of expert evidence by someone in Prof. Assmann's position. However, the professor's failure to disclose it or to even consider it to be a relevant matter to be disclosed raises serious questions about his understanding of the role of an expert witness.

37. For completeness, it should also be noted that, in response to the evidence given by Prof. Marz in relation to the advice to German general practitioners in the German Medical Journal, Prof. Assmann also relied upon concerns from some clinicians, at the time, that lowering cholesterol does not reduce overall mortality. He referred, *inter alia*, to an advertisement which appeared in the same edition (i.e. the 1990 edition) of the German Medical Journal as the last of the articles described above which raised this issue and suggested:-

> *"The results of the long-term cholesterol studies do not come to a conclusion whether lowering the cholesterol is harmful or if the side effects of the treatment resulted in the increased number of deaths. In any case the cholesterol reduction was not beneficial.*

I have to say that I find it somewhat surprising that an expert would rely on an advertisement of this kind. The advertisement extolled the continued use of milk, butter, cheese, eggs and meat as an integral part of a healthy diet. It should be noted that the advertisement was published by the central marketing organisation of the German agribusiness industry. Prof. Assmann also referred to the views expressed by Prof. Michael Oliver of London who published material to similar effect in the Lancet in 1991. However, it emerged in the course of the cross-examination of Professor Assmann that Prof. Oliver had participated in the meetings with the other experts in the European Atherosclerosis Society which produced the consensus papers which ultimately fed into the articles published in the German Medical Journal. There was no addendum or qualification added to the papers published by the Society which reflected any objection or dispute on the part of Prof. Oliver. Moreover, it is clear from Prof. Assmann's evidence that, in any event, he himself regarded Prof. Oliver as an outlier on the issue and as a "*non-believer*" who did not share in the more generally held view.

The development of the combination in issue

38. While the relevance of his evidence is questioned by the defendant (for the reason that it relates to events post the priority date of the patent) it should be noted that Dr. Harry Roger Davis Jnr. gave evidence about the development of ezetimibe and of the subsequent experiments done which ultimately identified the utility, efficacy and relative safety of the combination of ezetimibe and simvastatin. Dr. Davis was a member of a group of researchers at Schering Plough that developed ezetimibe and later discovered its molecular target in the human body namely the intestinal sterol transporter Niemann-Pick C1-Like 1 protein ("*NPC*"). As I understand it, NPC acts as a cholesterol-sensing receptor and is responsible for cellular cholesterol absorption. It is found in the intestine and in the liver.

39. Several years after the patent was granted, Dr. Davis was involved in the carrying out of experiments relating to combinations of one of the azetidinone compounds covered by the 599 patent with statins. Dr. Davis explained that, at the outset, he did not know what the azetidinone compounds would do in combination with statins. The first experiment carried out involved a compound covered by the 599 patent which was given an internal name "*Schering 48461*". Early experiments with animals suggested that a combination of

Schering 48461 and statins synergistically lowered cholesterol. However, in the course of the experiments carried out, there was a drug-drug interaction with lovastatin which precluded it from further development. The experiments in question were carried out on dogs. When the experiments with the Schering 48461 compound proved problematic, the investigators turned to a number of backup compounds covered by the patent including ezetimibe. Ultimately, it was ezetimibe that, in the words of Dr. Davis, "*eventually made it to market".*

40. Dr. Davis explained that, in the course of his investigations, he combined ezetimibe with five or six different statins that were on the market or that were coming on the market and he ensured that ezetimibe did not interfere with the drug metabolism of those statins or have a drug-drug interaction.

41. Dr. Davis, in his evidence, also explained that it took twelve years of research to figure out how the mechanism of action of ezetimibe works. He explained that this point was not actually reached until 2003. Dr. Davis confirmed, under cross-examination, that ezetimibe itself was not first synthesised until 1994 and the first clinical studies in relation to ezetimibe in humans was in 1996.

42. As noted above, early experiments with animals suggested that a combination of an azetidinone compound and a statin worked synergistically. Ultimately, however, this did not transpire to be so in humans. Dr. Davis confirmed that the effect of the combination in humans was found to be additive rather than synergistic. Dr. Davis also confirmed that, at the time of these tests, Schering Plough did not have within its stable any of the statins that were being tested. In fact, Dr. Davis explained that, for the purposes of the studies in dogs, he "*actually bought the drugs from the pharmacy … and ground them up and fed them to the dogs…*". Dr. Davis was not entirely sure when the dog studies took place involving ezetimibe and simvastatin but he thought that they commenced somewhere between 1994 and 1996 and was completed by 1997.

The case made by the defendant in relation to Article 3 (a)

43. As noted in para. 8 above, the defendant maintains that the combination of ezetimibe and simvastatin is not protected by the 599 patent and/or that it was not the "*core inventive advance to which the 599 Patent pertained*". The principal argument made by the defendant in support of this contention is encapsulated in para. 6.22 of the defendant's closing written submissions in which the case is made that a skilled person reading the 599 Patent with the benefit of common general knowledge (in particular, common general knowledge in relation to combination therapy as at the priority date of the patent) would not deduce from the references in the patent to combining a compound of Formula 1 with a statin that such a combination is an independent innovation (as distinct from the compounds of Formula 1 *simpliciter* which include ezetimibe). The defendant submitted that, in effect, the 599 Patent says nothing other than: "*here is a new drug to be used in the treatment and prevention of high cholesterol that will join the pool of other such drugs already being used for this purpose, including statins, with which it can be combined".*

44. In order to understand the legal basis for this argument, it will be necessary to address some of the case law of the Court of Justice ("*CJEU*") including the decision of the Grand Chamber in Case C-121/17 *Teva v. Gilead*. Both sides have sought to rely on that decision in support of their respective positons in relation to the Article 3 (a) issue. The plaintiff strenuously argues, by reference to the decision of the CJEU in that case and by reference to some of its previous decisions, that a product will be protected by a basic patent in force (within the meaning of Article 3 (a)) where the product is expressly mentioned in the claims of the patent. The plaintiff contends that, here, the 599 Patent expressly contains a claim in respect of the combination in issue and that, as a consequence, the combination of ezetimibe and simvastatin is protected by the patent for the purposes of Article 3 (a). If the plaintiff is correct in that contention, that would be sufficient, of itself, to resolve the Article 3 (a) issue and it would not be necessary to consider any of the other arguments that arise in relation to Article 3 (a). It therefore makes sense to address this issue first. If I find against the plaintiff in relation to that issue, it will then be necessary to consider some of the other arguments that arise. However, before doing so, it is necessary, at this point, to consider the terms of the 599 Patent itself. It is also important to bear in mind, in considering the patent, the argument made by the defendant that it is not sufficient that the patent should make a claim in relation to a combination. The defendant urges that, on the basis of the decision in *Teva v. Gilead*, the relevant combination must fall within the ambit of an invention the subject of the patent.

Relevant terms of the 599 Patent

45. As noted briefly above, para. 0001 of the patent records that the invention relates to hydroxy-substituted azetidinones used as hypocholesterolemic agents in the treatment and prevention of atherosclerosis and also to "*the combination of a hydroxy-substituted azetidinone of this invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of Atherosclerosis."*

46. The same paragraph says that the invention also relates to a process for preparing hydroxy-substituted azetidinone. Thereafter, again as briefly described previously, reference is made in para. 0008 to the articles by Witzum and Illingworth which both address combination therapy. Paragraphs 0001 to 0008 are all under the heading *"BACKGROUND OF THE INVENTION".* The defendant places some emphasis on the fact that, as noted above, the articles by Witzum and Illingworth both refer to combination therapy and that the patent itself acknowledges that this forms part of the relevant background.

47. Paragraphs 0009 to 0019 contain a summary of the invention. Paragraph 0009 refers to the novel compounds of the present invention represented by Formula 1 or pharmaceutically acceptable salts of such compounds. In para. 0014, it is stated that the invention also relates to a method of lowering the serum cholesterol level in a mammal by administering an effective amount of a compound of Formula 1. The same paragraph again uses the phrase "*a compound of the present invention".*

48. Thereafter, para. 0016 provides as follows:-

"The present invention also relates to a method of reducing plasma cholesterol levels and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of Formula 1 and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a hydroxy-substituted azetidinone cholesterol absorption inhibitor of Formula 1 for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a hydroxy-substituted azetidinone cholesterol absorption inhibitor of Formula 1) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels".

49. Paragraph 0017 is in similar terms but, rather than referring to a combination, it deals with a kit comprising, in one container, an effective amount of the relevant Formula 1 compound and, in a separate container, an effective amount of a biosynthesis inhibitor in a pharmaceutically acceptable carrier.

50. A detailed description of the invention is given at paras. 0020 to 0133. For present purposes, it is sufficient to refer to a small number of those paragraphs. The first such paragraph which is relevant to combinations is para. 0028 which expressly mentions the possibility of a combination with, among other inhibitors, simvastatin. Paragraph 0028 provides as follows:-

Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin and CI-981".

51. Paragraph 0028 refers to a number of other potential combination partners but concludes by stating that the preferred HMG CoA reductase inhibitors are lovastatin, pravastatin, fluvastatin, and simvastatin.

52. Paragraph 0029 provides that the compounds of Formula 1 can be prepared by known methods but a number of such methods are then set out in considerable detail. No equivalent information is provided in relation to the preparation of any combination of any of the Formula 1 compounds with a statin.

53. Subsequently, at para. 0061, the patent states that compounds of the invention lower serum lipid levels (in particular serum cholesterol levels) by inhibiting the intestinal absorption of cholesterol and reducing the formation of liver cholesteryl esters in animal models.

54. In the following number of paragraphs, a method of treating the in vivo activity of the compounds of Formula 1 can be determined by following a procedure derived from trials in hamsters.

55. Paragraph 0065 and following paragraphs deal with dosage. Paragraph 0065 deals with dosage of Formula 1. Paragraph 0066 deals with dosages of combinations and sets out

typical daily doses depending on body weight. Paragraph 0066 also makes clear that precise dosages are a matter for the treating clinician. Clearly, the patent envisages that the clinician will use his or her general knowledge and expertise for that purpose. In this context, para. 0066 provides:-

> *"The exact dose of any component of the combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patent".*

56. Paragraph 0068 identifies that, where plasma cholesterol levels are to be treated with a combination of active ingredients, these ingredients may be administered separately. Paragraph 0068 states that, in such circumstances, the invention also relates to combining separate pharmaceutical compositions in "*kit form*". The same paragraph explains that a kit is contemplated where two separate units are combined, a cholesterol biosynthesis inhibitor and a hydroxyl substituted azetidinone cholesterol absorption inhibitor. Paragraph 0069 to 0130 all deal with examples of preparing compounds of Formula 1. These paragraphs take up the next eleven pages of the patent. Having described the method of manufacture of the compounds of Formula 1, para. 0132 of the patent then deals with cholesterol biosynthesis inhibitors. Counsel for the defendant placed some emphasis on the language of this paragraph and suggested that the paragraph shows clearly that simvastatin could not be considered to be part of the invention. He argued that the skilled addressee is informed at para. 0132 that representative formulations comprising cholesterol biosynthesis inhibitors (which are not confined to statins) are well known in the art and that the dosage is a matter that can be adjusted by reference to the knowledge of the skilled addressee. This is an argument which is not directly relevant to the issue as to whether it is sufficient to simply claim a combination in the claims of a patent. Nonetheless, it is important to note it at this point since it is relevant to the case made by the defendant as to the extent of protection provided by the 599 Patent. For completeness, para. 0132 is in the following terms:-

> *"Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using the knowledge of one skilled in the art".*

57. The claims of the patent include a claim in relation to ezetimibe (which is covered by Claim 8). Claim 9 refers to combinations in the following way:-

> *"A pharmaceutical composition for the treatment or prevention of Atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound as claimed in any one of claims 1 to 8 alone or in combination with a cholesterol biosynthesis inhibitor, in a pharmaceutically acceptable carrier".*

58. Claim 12 claims a process for preparing a pharmaceutical composition comprising the admixing of a cholesterol biosynthesis inhibitor and a compound within any one of Claims

1 to 8 with a pharmaceutically acceptable carrier. However, it should be noted that there is no description given in the patent itself of any process of admixture. Claims 12 – 13 both make claims in respect of combination use. Claim 15, consistent with para. 0068 deals with the kit comprising separate containers in a single package for use in combination comprising, in one container, the cholesterol biosynthesis inhibitor and, in a second container, a pharmaceutical composition comprising an effective amount of the Formula 1 compound.

59. It is clear from Claim 16, that, when the patent speaks of cholesterol biosynthesis inhibitors, it is not confining itself to statins. Claim 16 is in the following terms:-

> *"A pharmaceutical composition of any of claims 9,12 or 15 wherein the cholesterol biosynthesis inhibitor is selected from the group comprising of HMG CoA reductase inhibitors, squalene synthesis inhibitor and squalene epoxidase inhibitors".*

60. This is confirmed by the terms of Claim 17 which contains a list of named biosynthesis inhibitors including simvastatin (among other statins) together with a number of other inhibitors. Claim 17 is in the following terms:-

> *"A pharmaceutical composition of Claim 16 wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of lovastatin, pravastin, fluvastatin, simvastatin, CI-981, DMP-565, L-659, 699, squalestatin 1 and NB-598".*

As I understand it, NB-598 is not a statin but a squalene epoxidase inhibitor.

The argument of the plaintiff based on the claims of the patent

61. While it is essential to keep in mind that the onus of proof of invalidity rests on the defendant, it is convenient at this point to address the argument made by the plaintiff that, once the combination has been the subject of a specific claim in the patent, that is a complete answer to the defendant's case.

62. The case made by the plaintiff derives some support from a number of decisions of the CJEU which predate the decision in *Teva v. Gilead* including the decision in Case C-322/10 *Medeva v. Comptroller General of Patents, Designs and Trade Marks* [2011] ECR I-12095. The "*key role*" of the claims was also emphasised by the CJEU in Case C-493/12 *Eli Lilly v. Human Genome Sciences Inc*. Similar views were also expressed in a number of other decisions but it is unnecessary to list them all. The critical decision for present purposes is *Teva v. Gilead*. The facts giving rise to that decision have previously been described by me in paras. 95-100 of my judgment in *Gilead Sciences Inc v. Teva BV* [2019] IEHC 683 and I therefore do not propose to repeat that material here. It is sufficient to record that the patent in issue related to a treatment for the HIV retrovirus. A number of compounds were claimed in the patent including a nucleotide reverse transcriptase inhibitor called tenofovir disoproxil ("*TD*"). The patentee (Gilead) subsequently obtained an SPC in respect of a combination sold under the brand name Truvada which contained two anti-retroviral agents namely TD and emtricitabine ("*FTC*"). The issue was whether that combination could be said to be protected by the patent in question. Claim 27 of that

patent did not claim FTC by name but it was suggested that the reference to "*other therapeutic ingredients*" in Claim 27 of the patent would be construed by the skilled person as referring to FTC. Claim 27 was in the following terms:-

> *"A pharmaceutical composition comprising a compound according to any one of claims 1-25 together with a pharmaceutically acceptable carrier and optionally other therapeutic ingredients".*

63. There is an obvious factual distinction between that patent and the 599 patent. The latter specifically contemplates, in claims 16 and 17, that one or more of the Formula 1 compounds will be combined with a named statin, a squalene synthesise inhibitor or a squalene epoxidase inhibitor. More particularly, simvastatin is specifically identified as one of the statins with which the Formula 1 compound can be combined. Thus, if the plaintiff is correct in its submission that a product will be protected by a basic patent where it is expressly mentioned in the claims of that patent, there would be a good basis to dismiss the defendant's counterclaim founded on Article 3 (a). The defendant, however, argues that the submission made by the plaintiff is not consistent with the approach taken by the CJEU in *Teva v. Gilead.*

64. In *Teva v. Gilead*, the CJEU devised a comprehensive two stage test to assist in determining whether a product is protected by a basic patent for the purposes of Article 3 (a). As outlined above, the plaintiff argues that this test was not intended to apply where an identified combination is specifically claimed in the patent. The plaintiff argues that the test is confined to cases where one of the components of the combination is not specifically identified in the claims of a patent. The plaintiff placed particular emphasis in this context on what was said by the CJEU in para. 37 of the judgment which is in the following terms:-

> *"37. Therefore, a product cannot be considered to be protected by a basic patent in force within the meaning of Article 3 (a) … unless the product which is the subject of the SPC is either expressly mentioned in the claims of that patent or those claims relate to that product necessarily and specifically".* (Emphasis added).

65. The plaintiff argues that, in that paragraph, the CJEU, very clearly, made a distinction between those cases (such as the present) where a product is expressly mentioned in the claims of a patent and cases such as *Teva v. Gilead* itself, where a product (or a component of the product) is not expressly mentioned in the claims. The plaintiff draws attention to the use of the word "*or*" in para. 37 of the judgment (as highlighted in para. 64 above). The plaintiff submits that the balance of the judgment (in which the two stage test is set out) is solely concerned with the latter case and is of no relevance to the 599 Patent.

66. In support of its position, the plaintiff also relies on a number of other observations in the judgment of the CJEU. In particular, the plaintiff draws attention to para. 32 which refers to Article 69 of the European Patent Convention ("*EPC*") and the Protocol (which, in broad brush summary, emphasise the importance of the claims of a patent). The plaintiff

derived further support for this argument from what was said by the CJEU in para. 35 of its judgment where, again referring to Article 69 of the EPC, the CJEU noted that the extent of the protection conferred by a European patent is determined by the claims.

67. In addition, the plaintiff placed some emphasis on what was said by the CJEU at para. 34 of its judgment where, referring to the *Eli Lilly* case, the CJEU said:-

> *"…the Court has repeatedly emphasised the key role played by the claims for the purpose of determining whether a product is protected by a basic patent…".*

68. While I can see how the plaintiff has come to make that argument, I do not believe that it is correct. I have reached that conclusion for a number of reasons:-

(a) In the first place, the question posed by the referring court to the CJEU in *Teva v. Gilead* was framed by Arnold J. in very broad terms. It simply asked the CJEU to identify the criteria for deciding whether a product is protected by a basic patent in force for the purposes of Article 3 (a). Because of the concerns expressed by Arnold J. as to a lack of clarity in the law arising from previous decisions of the CJEU, a Grand Chamber was assembled in order to provide definitive guidance. The judgment of the Grand Chamber addresses the broad question posed and seeks to clarify the law in relation to the meaning and effect of Article 3 (a).

(b) Secondly, I cannot see any basis in the judgment to suggest that the CJEU intended that all of its judgment from para. 38 onwards is confined to cases where the relevant combination is not expressly mentioned in the claims of a patent. On the contrary, para. 38 of the judgment commences with the words "*For that purpose…".* Those words seem to me to refer back to the entire of what was said in the preceding paragraph (i.e. para. 37). I can see nothing in the language used in para. 38 of the judgment to support the suggestion that the CJEU only intended to refer back to the second part of para. 37 (i.e. the part dealing with cases where the relevant combination is not expressly mentioned in the claims of a patent);

(c) Thirdly, it is clear from the text of para. 38 that the CJEU was mindful of the requirements of Article 69 of the EPC that the description and drawings of the basic patent must be taken into account. One does not look solely at the claims. In that paragraph, the CJEU stated:-

> "…the description and drawings of the basic patent must be taken into account, as stipulated in Article 69 of the EPC read in the light of the Protocol…, where that material shows whether the claims of the basic patent relate to the product which is the subject of the SPC and whether that product in fact falls under the invention covered by that patent". (Emphasis added).

(d) Fourthly, and most importantly, the CJEU, in paras. 39-41 of its judgment, emphasised the underlying objective of the SPC Regulation which is to compensate for the delay in the commercial exploitation of an invention. The CJEU highlighted,

in stark terms, that it would be contrary to the objective of that Regulation to grant an SPC for a product which does not fall under the invention covered by the patent. The CJEU stressed that the purpose of the additional period of exclusivity is to encourage research and to ensure that the investment in research is appropriately compensated. If an SPC were to be granted for a product which does not fall within the ambit of the invention covered by the patent, then the SPC would not relate to the results of the research claimed under that patent. In addition, the CJEU invoked Recital 10 to the preamble to the SPC Regulation which refers to the need to take into account all the interests at stake including those of public health. The court stated that, to accept that an SPC could grant to the holder of the patent protection which goes beyond the scope of the invention it covers would be contrary to the requirement to balance the interests of the pharmaceutical industry and those of public health. All of these considerations led the CJEU to say, in para. 43 of the judgment:-

> "43. Accordingly, having regard to the objectives pursued by [the SPC Regulation], the claims cannot allow the holder of the basic patent to enjoy, by obtaining an SPC, protection which goes beyond that granted for the invention covered by that patent. Thus for the purposes of the application of Article 3(a) of that regulation, the claims of the basic patent must be construed in the light of the limits of that invention, as it appears from the description and the drawings of that patent." (Emphasis added).

(e) In my view, it is critically important, to have regard to the rationale expressed by the CJEU in paras. 38-43 of its judgment. Those paragraphs illustrate the concern of the CJEU to ensure that an SPC should not be granted for a product which does not fall within the invention covered by the patent. The paragraphs also stress that the claims of the basic patent must be construed in the light of the limits of that invention. That rationale and concern are equally applicable whether or not a product is expressly mentioned in the claims of the patent. If the plaintiff's interpretation of the judgment is correct, it would have the bizarre consequence that the concerns expressed by the CJEU in those paragraphs could be readily sidestepped by those patentees who had taken the course of assiduously listing expressly in the claims of the relevant patent a large range of products or combinations of products even where those claims went beyond the limits of the underlying invention. In my view, the approach suggested by the plaintiff would subvert the rationale expressed by the CJEU in its judgment in *Teva v. Gilead*. I therefore cannot accept the approach which the plaintiff suggests. Accordingly, I have come to the conclusion that the test set down in *Teva v. Gilead* must be applied in this case in order to determine whether the combination of ezetimibe and simvastatin is protected by the 599 patent.

The Teva v Gilead test

69. As noted above, there are two parts to the test laid down by the CJEU in *Teva v. Gilead.* These are:-

(a) As set out in para. 47 of the judgment, the first element considers whether the product which is the subject of the SPC necessarily falls under the invention covered by the patent. The approach to be taken in considering that question is set out in para. 48 of the judgment where the CJEU made clear that it is necessary to consider the matter from the perspective of the person skilled in the art and to ask whether such a person can understand, without any doubt, on the basis of their general knowledge, and in the light of the description and drawings of the invention, that the product to which the claims of the basic patent relate is "*a specification required for the solution of the technical problem disclosed by that patent*". The language quoted is not, subsequently, replicated by the CJEU in its specific answer to the question posed by Arnold J. The answer given by the CJEU to that question is set out in para. 57 of the judgment and the language used there refers to whether the active ingredient: "*must necessarily, in the light of the description and drawings of that patent*, fall under the invention covered by that patent". Similar language emphasising the importance of the invention is used elsewhere in the judgment. In my view, as I previously noted in my judgment in *Gilead v. Teva*, the approach taken by the CJEU is invention focussed rather than claims focussed. While the claims are important, a product will not be considered to be protected by a basic patent for the purposes of Article 3 (a) unless it falls within the ambit of an invention the subject of that patent.

(b) The second limb of the test is set out in para. 49 of the judgment where the CJEU explained that, for the purposes of assessing whether a product falls under the invention covered by a basic patent, account must be taken exclusively of the prior art at the filing date or priority date of the patent *"such that the product must be specifically identifiable by a person skilled in the art in the light of all the information disclosed by that patent".*

70. In my judgment in *Gilead v. Teva* I have sought to analyse, in more detail, the judgment of the CJEU. It is therefore unnecessary to repeat that analysis here. For the reasons explained in that judgment, I take the view that the reference to "*prior art*" must be read in context. As set out in para. 128 of my judgment in *Gilead v. Teva*, it seems to me to be clear that the CJEU envisaged that, in assessing the state of general knowledge as of the priority date in a patent, one cannot have regard to any materials which only came into existence after the priority date. In my view, the CJEU has made it clear that, in a case of this kind, in assessing common general knowledge as of the filing date or priority date of a patent, it is impermissible to have regard to material which came into existence after those dates. In my judgment in *Gilead v. Teva*, I also addressed the question of whether the CJEU had intended to lay down a "*core inventive advance*" test. I took the view (which I continue to hold) that it would be unsafe to consider that the CJEU had laid down such a test. Since my judgment was given in that case, a similar view has been expressed by Advocate General Hogan in Joined Cases C-650/17 and C-114/18 *Royalty Pharma* at paras. 50-54. As the Advocate General noted in para. 53 of his opinion, at no point in *Teva v. Gilead* did the CJEU refer to the concept of "*core inventive advance*". In light of the approach taken by the CJEU, I took the view in *Gilead v Teva* that I should

decide the case by reference to the language used more consistently in the CJEU judgment, i.e. by reference to whether the product in question falls within the ambit of the "*invention covered by [the] patent*". That is the approach which I believe should also be taken in this case.

The role of the "skilled person"

71. It is important to keep in mind that the CJEU test involves a consideration of the issue by reference to the standpoint of the skilled person. That is consistent with the general approach taken to the construction of patents as explained by Clarke J. (as he then was) in *Rambaxy Laboratories Ltd v. Warner-Lambert Co*. [2007] IEHC 256 at paras. 3.9-3.10 as follows:-

> *"3.9 The other key concept involved in the construction of the patent is that it must be approached from the standpoint of what has been described in the authorities as the 'skilled addressee'. The skilled addressee is taken to be a person … with practical knowledge and experience of the kind of work in which the invention was intended to be used …It is common case that I should attempt to read the patent and construe it in the way in which the so called skilled addressee would have done so.*
>
> *3.10 The knowledge which will be attributed to the notional skilled addressee is the knowledge that any worker in the area concerned would be expected to have as part of their general knowledge. … The knowledge is that which a skilled addressee would have had as of the 'priority date' …. It is, therefore, agreed between the parties that I should approach the construction of this patent on the basis of the common general knowledge that would have been available to a person working in the field … as of that date. …".*

72. At a later point in his judgment in that case, Clarke J. drew an analogy between the approach to be taken in construing a patent and the approach taken by the courts in construing a contract. In both cases, the relevant context (or factual matrix) is relevant. At para. 3.25 of his judgment, Clarke J. observed that there was no "*magical difference"* between the proper approach to the construction of a patent, on the one hand, or any other document intended to effect legal obligations and entitlements (such as a contract), on the other hand. At para. 3.23-3.24 he explained his reason for taking this approach. While he stressed the fundamental importance of the nature of the document itself, he drew attention to the need for a court, in a contractual context, to know the relevant factual background. He then suggested that a similar approach should be taken in the context of a patent. In particular, he said at paras 3.23-3.24:-

> *"3.23 a court may need to know the overall context of the circumstances leading to the negotiation of the contract in the first place. This is because the contract should be construed in the way in which a reasonable and informed person entering into a contract of that type would be likely to interpret it. That person will not come to the interpretation of the contract with a blank mind. The contractual negotiations will*

commence against a particular factual backdrop and the parties will be seeking to advance their commercial interests against that factual back drop.

3.24 The position of the skilled addressee in relation to a patent is, in reality, in my view, no more than a special case of that generality. The equivalent, in a commercial context, of the skilled addressee may be the person who understands the overall context within which the contract is entered into and who is, thus, in a position to interpret properly any terminology used. The skilled addressee also has his counterpart in the bystander by reference to whom implied terms may be found to exist."

Who is the skilled person for the purposes of the 599 Patent?

73. In the course of making its case, the defendant argued that the skilled addressee, for the purposes of the 599 Patent, was the general practitioner. In making this case, the defendant referred to the articles in the German Medical Journal (summarised above) and to the evidence of Prof. Marz to the effect that general practitioners were involved in combination therapy. While I accept that there was evidence that general practitioners were, at least to some extent, involved in combination therapy, I do not believe that it could be suggested that combination therapy was part of the day to day general practice of all or most general practitioners as of the priority date of the patent. I do not believe that the evidence goes that far. Prof. Marz was not able to give any detail as to the extent to which it was in use at that level. On the basis of the evidence which I have heard, I believe that it is reasonable to conclude that there were some general practitioners who were involved in combination therapy. However, the evidence suggests that combination therapy was more likely to be encountered among specialist clinicians involved in the treatment of atherosclerosis. Ultimately, I do not believe that very much turns on the extent to which combination therapy was used by general practitioners. What is clear is that combination therapy was in use as at the priority date, the most common form being a combination of a statin and a bile acid sequestrant. It is also clear that, as of the priority date, general practitioners were educated as to the existence of combination therapy for more difficult cases of hypercholesterolemia. The articles published in the German Medical Journal demonstrate this. I reject the evidence of Prof. Assmann that, as of the priority date, combination therapy was still "theoretical" or that it was used only for a small number of patients. In my view, that evidence flies in the face of the contemporaneous materials placed before the court, including the German Medical Journal. I should add that I do not believe that any useful purpose would be served by attempting to resolve all of the other matters in dispute between Prof. Marz and Prof. Assmann. They do not appear to me to be crucial to the issues that I have to decide.

74. It would be unreal, however, to believe that the skilled person would be represented solely by clinicians of that kind. Professor Klaveness, a medicinal chemist, who gave evidence on behalf of the plaintiff suggested that the skilled addressee would comprise a group of scientists interested in or involved in the development of cholesterol lowering drugs which would include scientists involved in medicinal chemistry, biology and clinical science. The plaintiff makes the point that, under cross examination, Professor Klaveness

was not significantly challenged in relation to this evidence. That may well be so. However, I must form my own view in relation to the identity of the skilled addressee through whose eyes I must construe the patent. I am not bound by the evidence of any particular expert. The question of construction of the patent is ultimately a matter for the court.

75. In my view, as with most patents dealing with a pharmaceutical compound, the skilled addressee will comprise a team. That team will include a clinician familiar with the treatment of atherosclerosis (including the use of combination therapy for that purpose) and also an appropriately qualified medicinal chemist. There are elements of the patent that could only properly be understood by an appropriately qualified chemist. There are other elements of the patent which would require a clinician's skills. Thus, for example, para. 0066 of the patent that is dealing with dosages in the context of combination therapy envisages that the exact dose of any component of such a combination will be determined by the attending clinician.

The application of the first limb of the Teva v. Gilead test

76. Bearing in mind that the nature of the skilled addressee (as described above) I must now consider whether the combination of ezetimibe and simvastatin, on the basis of the general knowledge of such a skilled addressee, and in the light of the description and drawings of the invention in the 599 Patent, necessarily falls under the invention covered by the patent.

77. In considering that issue, I must bear in mind that the patent is to be construed against the relevant factual backdrop. As noted earlier, the patent itself treats the existence of combination therapy as part of the relevant factual context. Paragraph 0008 (contained in the first section of the patent dealing with the "*background of the invention")* specifically mentions combination therapy involving a statin and a bile acid sequestrant. It explains that such combination therapy has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy. The papers by Witzum and Illingworth are specifically referenced in this context. In addition, I bear in mind, as part of the relevant factual backdrop, the extensive literature which existed in relation to combination therapy involving combinations of various kinds of cholesterol inhibitors. In particular, it is clear from the publications of the European Atherosclerosis Society and the publications by Prof. Assmann in the German Medical Journal that, by the priority date of the patent, combination therapy (in particular combination therapy involving statins) was already well recognised and established for certain types of cholesterol treatments. This is also supported by the evidence of Prof. Marz who said that, at the priority date, he was using combination therapy to treat patients. He was also receiving referrals from general practitioners who were doing likewise. I do not believe, however, that his evidence establishes that, in 1992, it was common for general practitioners to use combination therapy themselves. As noted in para. 73 above, Prof. Marz was unable to provide any detail to support that suggestion.

78. As correctly stated in para. 6.21 of the defendant's closing witness submissions, this was the backdrop against which the 599 patent disclosed the compounds of Formula 1. The

defendants made the case that those compounds were being introduced into a world where:-

(a) Lipid lowering drugs were used in combination with other lipid lowering drugs. This contention is consistent with the evidence.

(b) The choice of which lipid lowering drugs should be combined with other lipid lowering drugs was informed by whether the respective partner drugs would have different modes of action. This is also largely consistent with the evidence although there was some controversy as to whether a combination with a new "*first in class*" drug such as ezetimibe would be undertaken. This is an issue which I address in more detail in paras. 88 -91 below.

(c) Statins were a well-established therapy in the treatment of hypercholesterolemia and were already recommended in the context of a number of combinations. This contention is well supported by the evidence which was adduced in the course of the hearing.

79. Against that background, the defendant argues that a skilled person reading the 599 Patent with the benefit of this common general knowledge would not deduce from the references to combinations involving a compound of Formula 1 (such as ezetimibe) with a statin (such as simvastatin) that the combination (as distinct from the compounds of Formula 1) could be said to be an independent innovation.

80. In my view, there is considerable force in this submission on the part of the defendant. This is especially so when one comes to consider the terms of the patent itself. The patent provides very significant detail in relation to the compounds in Formula 1. However, it is devoid of detail in relation to any of the potential combinations between compounds in Formula 1 and any of the combination partners identified in the patent. In this context, I do not wish to suggest that it is a necessary requirement for the validity of a patent that the patent should demonstrate by experiment that a claimed invention will work or that it is necessary to explain why it will work. As Barrett J. observed in *Boehringer Ingelheim* [2017] IEHC 495 at para. 165 no particular information or test data is required of a patent so long as the disclosure is plausible. However, on a reading of the 599 Patent, the absence of data in relation to the combination is striking. In contrast, there is very significant detail in relation to the compounds in Formula 1. When read against the factual backdrop (summarised above), the lack of detail in relation to the combination provides significant support for the case made by the defendant that, the skilled addressee, would not deduce from the references to combinations that such combinations were an independent innovation (i.e. independent of the innovative compounds comprised in Formula 1).

81. The defendant's case also derives significant support from the evidence given by Professor Hegarty. Professor Hegarty is a former professor of organic chemistry at University College Dublin. He is not a medicinal chemist. Nor is he a patent expert. He did not profess to be either of those things. He was entirely frank and objective in his

evidence. Of the four expert witnesses who gave evidence in relation to the patent, he was by far the most impressive. His evidence both under direct examination and cross-examination was clear, straight forward, authoritative and frank. He did not prevaricate or dissemble. He clearly had the necessary scientific background to understand the patent and, in particular, the chemistry described in the patent. This understanding was demonstrated by him very clearly in the course of his evidence.

82. Under cross-examination, Prof. Hegarty confirmed that he did have occasion to consider patents. He readily admitted that he did not know whether a patent in respect of a drug was required to contain test data. That is, in any event, a legal issue.

83. Although Prof. Hegarty is not a medicinal chemist, he was clearly in a position to read and understand the patent. His extensive expertise as an organic chemist allowed him to understand all of the chemistry. He explained that he was asked to review the patent by the solicitors for the defendant. At that point, he was told nothing about the facts of the case. After he carried out his review, he reported to the defendant's solicitors to the effect that the focus of the patent was on the family of compounds represented by Formula 1. He made no reference to the claimed combination. On receipt of his views, the defendant solicitors asked him to explain what the patent said about the combination of a hydroxy-substituted azetidinone and a cholesterol biosynthesis inhibitor. He reviewed the patent again and expressed the view that he did not think the reference to this combination was a particularly important element of the patent. He explained that this was because all of the testing of the biological activities was limited to the compounds within Formula 1. His view was that the patent contains only very superficial information about combinations and does not contain any experimental data or any information beyond what he described as "*cursory references*". He also observed that there was no data in the patent to show the usefulness of the claimed combination. His views (as summarised in the preceding two sentences) are entirely correct as a reading of the 599 patent will confirm.

84. Insofar as the drawings are concerned, Prof. Hegarty drew attention to the fact that, although there are a large number of drawings in the patent, the structure of a cholesterol biosynthesis inhibitor is not shown anywhere in the patent and, even more importantly, the structure of a combination of a hydroxy-substituted azetidinone and a cholesterol biosynthesis inhibitor is likewise not shown anywhere in the patent.

85. He communicated these views to the solicitors for the defendant who, only at that stage, gave him basic details of the proceedings and asked him to review the patent again and to provide his opinion on what it said about the combination of ezetimibe and simvastatin. In response, he observed that there was no experimental data in the patent in relation to any combination product, no information as to whether any testing of the combination of ezetimibe and any statin was carried out, whether in vivo or otherwise (and that this was in contra-distinction to the information provided in relation to the compounds within formula 1). Likewise, there was no data (experimental or otherwise) or information in the patent which shows, discloses or teaches that administering ezetimibe and simvastatin

together to a patient has any effect. In addition, there was no data or information to suggest that one of the components of the combination would assist the efficacy of the other. The patent provides no information or data as to whether the combination of ezetimibe and any statin is better, worse or the same as using ezetimibe alone.

86. In these circumstances, Prof. Hegarty expressed the view that the combination of ezetimibe and simvastatin could not be considered to be the innovation of the patent. In his view, the innovation is the demonstration that the different structure of the compounds represented by formula 1 (which are represented in the patent and which include ezetimibe) can be made in a pure form together with the results of the in vivo testing of those compounds. He expressed the view that the combination of ezetimibe and simvastatin does not represent a separate invention and there is no evidence whatever in the patent that the combination is efficacious at all.

87. Prof. Klaveness (the medicinal chemist who gave evidence on behalf of the plaintiff) disagreed with Professor Hegarty. In his witness statement and in his evidence, Professor Klaveness drew attention to a number of patents relating to potential new drug substances "*that contain some phrases relating to the option to combine drug substances with additional drugs*". He suggested that this was in general use in patent documents. With regard to Prof. Hegarty's view that the combination of ezetimibe and simvastatin could not be considered to be the innovation in the patent, Prof. Klaveness disagreed. His response was that the combination "*is a topic raised several times throughout the whole document and I read the 599 Patent to include this invention. The combination was at priority date new and inventive and has been shown to be useful. Based on the extensive description of the combination invention in the whole patent and my understanding of patentability criteria, my view is that this is an invention in the 599 patent*." Prof. Klaveness also suggested that it was unsurprising that the patent should only provide detailed information in relation to the new compounds disclosed in it. His evidence was that it was "*natural*" that the focus of the inventors should be on the synthesis of various new compounds and on the evaluation of biological efficacy in a relevant model (which, in the case of the 599 Patent was an in vivo model using hamsters).

88. However, Prof. Klaveness did not justify his view that the extensive references to a combination in the patent meant that the combination was itself an innovation. When he came to give evidence, he advanced a proposition (which had not been put in these terms to any of the witnesses who gave evidence on behalf of the defendant) that a combination of a new drug with an existing drug (whatever that might be) is an invention. This is a point that was also taken up, very strongly, in the plaintiff's submissions. It was argued on behalf of the plaintiff that the 599 patent told the skilled addressee that there was an entirely new, first in class molecule which could be used in reducing LDL cholesterol and therefore to treat atherosclerosis and that it could be combined with a statin also for the purposes of treating atherosclerosis. The plaintiff maintains that the skilled addressee did not know – other than from the 599 Patent – that this new first in class molecule could be combined with a statin to treat atherosclerosis. The plaintiff maintains that the skilled addressee would also know that putting an entirely new drug into the human body with

an existing drug may not result in the hoped-for efficacy and may even result in toxic effects.

89. I do not believe that the approach suggested by the plaintiff is correct. In the first place, as counsel for the defendant urged during the course of his closing submissions, the addition of an existing compound to a novel compound cannot, without more, make the combination an invention in itself. If that was all that was required, it would mean that an SPC would automatically be available for any combination product containing a combination of a novel product disclosed in a patent and a pre-existing product available off the shelf. Having regard to the approach taken by the CJEU in *Teva v. Gilead*, a product will only be protected by a basic patent for the purposes of the SPC Regulation where the product falls within the limits of the invention, the subject of the patent in issue.

90. I appreciate that Prof. Klaveness sought to suggest in his evidence (and in particular in para. 194 of his witness statement) that the combination at the priority date was new and inventive and that it "*has been shown to be useful".* However, as was clear from the evidence of Dr. Davis, the combination of ezetimibe and simvastatin was only demonstrated to be efficacious several years after the priority date. It is clear from the decision of the CJEU in *Teva v. Gilead* (at para. 50) that it is impermissible to have regard to developments which have taken place since the priority date or filing date of a patent. In this case, the 599 Patent must therefore be construed by reference to the state of knowledge that existed as of the priority date. Neither side is entitled to draw attention to post-priority date material. There is nothing in the patent itself to suggest that the combination, to use the words of Professor Klaveness, "*has been shown to be useful*". On the contrary, as previously noted, all of the relevant chemical data and testing data in the patent relates to the compounds within formula 1.

91. Moreover, there is a very obvious tension between the positon taken by Professor Klaveness that it is understandable that the patent should only include data in relation to a first in class compound and the case made by the plaintiff that the combination of two different compounds (namely ezetimibe and simvastatin) with different modes of action must itself be novel. If that combination is itself novel, then, having regard to the approach advocated by Professor Klaveness, it is surprising that the "*inventor*" of the combination would not provide some level of data akin, at least to some extent, to the data supplied in relation to the first in class compound.

92. It is also striking that when Prof. Klaveness was asked, in the course of cross-examination, to explain why the combination disclosed in the patent should be regarded as an innovation, his principal response was to point to the "*very many different places in the document"* where combinations are mentioned. That falls far short of identifying an invention. The mere fact that combinations are mentioned in the patent does not mean that the combination must, *ipso facto*, be treated as an invention. It is clear from the approach taken by the CJEU in *Teva v. Gilead* that is necessary to identify what is an invention. The fact that a patent makes a claim in relation to a product or that it makes

mention of a product is not enough in itself. I should have thought that, if Prof. Klaveness genuinely believed that the combination was an invention, he would readily have been able to explain why this was so. I regret to say that, in my view, Prof. Klaveness provided no satisfactory explanation as to why he considered the combination to be an innovation in itself.

93. It is true that he suggested, in the course of cross-examination, that:

> *"The combination aspect is not just added in a line or a few sentences … but it is through all the documents. That's why I look at it and I understand that this concept, and I can go to the lab or it is possible to perform such combination study if you would like to do it".*

94. At the conclusion of his evidence, I asked him to explain what he meant when he said that it is possible to perform some combination studies by reference to the patent. I asked him why he would need to refer to the patent to carry out such studies. I assumed that, in his response, Prof. Klaveness would explain why it was essential to refer to the patent. However, his answer was telling. His answer was, simply, that ezetimibe is protected by the patent. He accepted that the statin was already available but he explained that ezetimibe was subject to the 599 patent. Thus, Prof. Klaveness did not identify anything in the patent itself which, from a scientific perspective, required consideration. His concern was that, from a legal perspective, ezetimibe was protected by the patent. Again, that seems to me to undermine any suggestion that the combination per se was an innovation of the patent.

My conclusion in respect of Article 3 (a)

95. In light of the matters discussed in paras. 76 to 94 above, I have come to the conclusion that the combination of ezetimibe and simvastatin is not an invention covered by the patent. On the contrary, it seems to me that, by reference to the detailed information contained in the patent and the drawings contained in the patent and in light of the factual context described in paras. 21 to 37 above, the invention relates to the Formula 1 compounds. There is nothing in the evidence or in the materials before the court to explain how the combination can be said to be an invention in itself. Having regard to the approach taken by the CJEU in *Teva v. Gilead*, the fact that the patent makes claims in relation to the combination is not sufficient of itself. For the patent to protect the combination, the combination must itself be an invention covered by the patent. On the basis of my reading of the patent (informed by the evidence which I have heard in the course of the hearing and the materials put in evidence) I believe that the case made by the defendant that the combination was not an independent innovation itself is correct. In the circumstances, there is no need to apply the second limb of the *Teva v. Gilead test*. Accordingly, I must hold that the combination is not protected by the 599 patent within the meaning of Article 3 (a) of the SPC Regulation. The defendant is therefore entitled, on that ground, to a declaration that the SPC is invalid and must be revoked.

The case made under Article 3 (c)

96. In light of the findings which I have made in relation to the defendant's case under Article 3 (a), it is not strictly speaking necessary for me to consider the case made under Article 3 (c) or Article 3 (d). Nonetheless, lest I am wrong in my conclusion in relation to Article 3 (a) I will, for completeness, address both the case made under Article 3 (c) and also the case made under Article 3 (d).

97. The first point to be made about Article 3 (c) is that if I am correct in my conclusion that the only products which are protected under the 599 Patent are the azetidinones (including ezetimibe) then the defendant must also succeed in its counterclaim made on the basis of Article 3 (c). As noted in para. 4 above, an SPC was issued in respect of ezetimibe in 2003. As a consequence, the provisions of Article 3 (c) (under which an SPC cannot be granted if the product has already been the subject of a previous SPC) would prohibit the grant of the SPC in issue in these proceedings. However, if I am wrong in my conclusion that ezetimibe is the only relevant product protected by the 599 Patent, then it is necessary to consider the alternative case made by the defendant during the course of the hearing that the combination product has already been the subject of the SPC granted in respect of Ezetrol. That case does not appear to me to be pleaded. However, if I have correctly understood the submissions made by counsel on behalf of the defendant, that is nonetheless a case which the defendant seeks to make. In his closing submissions, counsel for the defendant spoke of the case under Article 3 (c) "*segueing*" into the case under Article 3 (d). I will, for completeness, address this alternative case. As I understand it, the defendant makes this case on the basis that:

    (a) The marketing authorisation for Ezetrol required the 10mg tablets containing ezetimibe to be administered with a statin for patients suffering from homozygous familial hypercholesterolemia; and
    (b) that, thereafter the Ezetrol SPC was granted.

98. On that basis, the defendant argues that the combination of ezetimibe and a statin such as simvastatin had previously been the subject of the Ezetrol SPC and that accordingly Article 3 (c) prohibited the grant of the SPC in issue in these proceedings. In making this case, the defendant relies on the terms of the marketing authorisation granted in 2003 in respect of Ezetrol. As described in para. 3 above, the marketing authorisation for Ezetrol required that the ezetimibe tablets should be administered with a statin in the case of patients suffering from homozygous famial hypercholesterolemia. Since the 2003 SPC was granted on the basis of this marketing authorisation, the argument appears to be that, even if the product here is to be regarded as the combination of ezetimibe and simvastatin, that product was already the subject of the 2003 SPC. The factual basis for this element of the defendant's counterclaim is therefore substantially the same as the factual basis for the case made by it under Article 3 (d). It therefore seems to me to be more appropriate to turn first to the Article 3 (d) element of the counterclaim before reaching any final conclusion in relation to the case made by reference to Article 3 (c).

99. Before turning to the case made under Article 3 (d), it is necessary, however, to address some of the legal issues that were debated in the context of Article 3 (c). In particular, it is necessary to address the contention of the plaintiff that it may be necessary to make a

reference to the CJEU for guidance in relation to Article 3 (c). This submission appears to proceed on the basis that, in the event that I were to uphold the defendant's case as to what product is protected for the purposes of Article 3 (a), that opens up a gap or dichotomy between the nature of the "*product*" protected under Article 3 (a), on the one hand, and Article 3 (c), on the other. The plaintiff points to a decision of the High Regional Court of Dusseldorf which suggests that a reference to the CJEU might well be necessary on this point. In my view, there is no need for a reference in this case. In the first place, it seems to me that there can be no difference between the "*product*" for the purposes of Article 3 (a) on the one hand and Article 3 (c) on the other. It is quite clear from Article 1 (b) that "*product*" has a consistent meaning throughout the SPC Regulation. As noted in para. 10 above, Article 1 (b) defines a "*product*" as: "*The active ingredient or combination of active ingredients of a medicinal product*". That is the relevant definition for the purposes of both Article 3 (a) and Article 3 (c).

100. Secondly, I can see no dichotomy in the case made by the defendant. The defendant makes the simple case that, for the purposes of both Article 3 (a) and 3 (c), the "*product*" protected by the 599 Patent is ezetimibe alone (along with the other azetidinones covered by the patent). The same case is made under Article 3 (c). However, an alternative case is made that, if the "*product*" protected by the 599 patent for the purposes of Article 3 (a) is the combination, then the defendant makes the case summarised in para. 97 above. In other words, the defendant would, for the purposes of making that argument, treat the "*product*" as the combination of ezetimibe and simvastatin.

101. Secondly, while the plaintiff seeks to suggest that there may be a difference in approach taken by the CJEU under Article 3 (a) and Article 3 (c), I cannot accept that there is such a difference in approach. It seems to me that, following the decision of the CJEU in *Teva v. Gilead,* the task of the court is clear. While the CJEU may, in previous case law, have referred to the "*core inventive advance*" of a patent in the context of Article 3 (c), I do not believe that there is any scope to take the view, subsequent to the decision of the CJEU in *Teva v. Gilead*, that this continues to the relevant test. While *Teva v. Gilead* addressed the meaning of "*product*" in the context of Article 3 (a), the court referred back to some of the decisions in which Article 3 (c) had been considered. I cannot identify any basis in the judgment in *Teva v. Gilead* to suggest that the CJEU had in mind that a different approach should be taken in relation to the meaning of the word "*product*" in the context of Article 3 (a) to its meaning in Article 3 (c).

102. Thirdly, in light of the conclusion which I have reached in relation to Article 3 (a), it cannot be said that it is necessary to make a reference to the CJEU. To make a reference, in these circumstances, would amount, in substance, to a request to the CJEU to make a determination on a moot issue. While I propose to address the case made under Article 3 (c) for completeness, there would be no basis for me to make a reference to the CJEU on an issue which, strictly speaking, does not require to be addressed in order to reach a conclusion on the counterclaim.

103. As noted in para. 98 above, I propose, before going further in relation to Article 3 (c) to address the case made by the defendant by reference to Article 3 (d).

The case made under Article 3 (d)

104. For the defendant to succeed in relation to Article 3 (d), it would be necessary to demonstrate that the marketing authorisation in respect of Inergy is not the first authorisation to place the combination product on the market as a medicinal product. As noted in para. 12 above, the defendant argues that the first such authorisation was that issued in respect of Ezetrol. This argument proceeds on the basis that, according to the Ezetrol authorisation, ezetimibe was required to be administered with a statin for use in patients with homozygous familial hypercholesterolemia. In this context, para. 4.1 of the relevant Summary of Product Characteristics ("*SmPC*") for Ezetrol states, with regard to homozygous familial hypercholesterolemia:-

> *"Ezetrol co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments …"* (Emphasis added).

105. The defendant also draws attention to the dosage instructions in para. 4.1 of the Ezetrol SmPC which states that the recommended dose of ezetimibe is 10mg tablets *"used alone or with a statin*". The same section of the SmPC states that if the 10mg are used in combination with a statin therapy, the dosage instructions for that particular statin should be consulted.

106. The defendant also highlights the text of the Ezetrol SmPC dealing with clinical trials involving co-administration of ezetimibe with a statin. The relevant table in the SmPC identifies that the quantities of statin tested with ezetimibe were 10mg, 20mg, 40mg and 80mg.

107. In turn, the SmPC for Inergy relates to precisely similar dosages. Paragraph 1 of the SmPC identifies that the dosages are 10mg of ezetimibe with, respectively, 10mg, 20mg, 40mg or 80mg of simvastatin.

108. In addition, the clinical trials described in the SmPC for Inergy involved co-administered ezetimibe and simvastatin "*equivalent to INEGY".* The trials did not feature the combination product as such.

109. Expert evidence was called by both sides in relation to the Article 3 (d) issue. I am not all convinced that expert evidence is either necessary or admissible in relation to a legal issue of this kind. Nonetheless, the evidence was of some utility in teasing out some of the issues that arise in the context of Article 3 (d). In support of this part of its case, the defendant called an expert witness namely Dr. Birka Lehmann who, in the course of her career, worked at the German Federal Institute for Drugs and Medical Devices and also worked, on secondment, as a regulatory expert with the European Commission. In her written statement and in her evidence, Dr. Lehmann noted that para. 4.1 of the Ezetrol SmPC made the co-administration of ezetimibe with a statin "*mandatory*". She also gave

evidence to the effect that the marketing authorisation for the Ezetrol product covered the co-administration of ezetimibe with a statin such as simvastatin. She suggested that, from a regulatory point of view, the authorisation for Ezetrol constituted an authorisation for the (non-fixed) combination of ezetimibe and simvastatin for the treatment of hypercholesterolemia. Dr Lehmann also noted that the majority of the clinical studies described in the Ezetrol SmPC related to the co-administration of ezetimibe with a statin (including simvastatin).

110. Dr Lehmann noted that the clinical studies described in the SmPC for Inegy were based on the co-administration of ezetimibe and simvastatin rather than on any combination tablet. At para. 38 of her witness statement Dr. Lehmann stated:-

> *"…all essential clinical studies regarding the efficacy of the combination product INEGY as well as the studies that are the basis for the EZETROL authorization were conducted with a combination of active ingredients being administered wherein simvastatin and ezetimibe were administered in parallel in the form of the mono products i.e. ezetimibe was administered in its own separate tablet and simvastatin was administered in its own separate tablet. The authorization for INEGY therefore contains no additional scientific findings compared to the data in the authorization for EZETROL. Therefore, the INEGY product (the fixed dose single combination tablet) does not show any surprising added value in any way exceeding the mere parallel administration of the active ingredients as separate individual tablets being co-administered."*

111. Prof. Dr. Vincenzo Salvatore ("*Prof. Salvatore*") gave evidence on behalf of the defendant. In the course of his evidence Professor Salvatore stated that there is a very clear difference, in regulatory terms, between a treatment comprising a combination of two different products administered together, each containing a specific active ingredient and a treatment comprising a product which contains both active ingredients in one. He accepted that a physician may well prescribe a combination of two medicinal products (both of which have been granted a separate marketing authorisation) but he maintained that "*the scenario is different*" when a single medicinal product is subsequently launched containing a combination of the two active ingredients in question. The latter requires a separate marketing authorisation. The individual marketing authorisations for both of the "*mono*" products do not allow for a sale of a combination product containing the two active ingredients. Prof. Salvatore expressed the view that Inegy is a combination product consisting of two separate and independent active ingredients (namely ezetimibe and simvastatin) and that accordingly it was required to have a separate and independent marketing authorisation from those granted in respect of ezetimibe (i.e. the Ezetrol marketing authorisation) and the independent marketing authorisation issued in respect of simvastatin. Against that backdrop, Prof. Salavatore expressed the opinion that the marketing authorisation for Ezetrol is incapable of constituting the first authorisation to place a combination product containing ezetimibe and simvastatin on the market.

112. Under cross-examination, Prof. Salvatore acknowledged that, in the context of homozygous familial hypercholesterolemia, a patient treated with a 10mg tablet of ezetimibe under the Ezetrol marketing authorisation would also be treated by a statin co-administered with the ezetimibe tablet. He also accepted that prior to the grant of the marketing authorisation in respect of Inegy, the dose ranges for simvastatin were 10mg, 20mg, 40mg and 80mg. Professor Salvatore accepted that, under the Inegy marking authorisation, the amount of ezetimibe does not change. It remains at 10mg. He also accepted that the amount of the simvastatin does not change. It is still at the same strength of 10, 20, 40 and 80 mg respectively. From the perspective of a patient, Prof. Salvatore accepted that if the patient was already being treated with ezetimibe under the Ezetrol marketing authorisation together with simvastatin, the patient would receive the very same active ingredients under the Inegy marketing authorisation. Professor Salvatore also accepted that, under the Ezetrol marketing authorisation, there was no doubt that, in the case of homozygous familial hypercholesterolemia, the authorisation was to use ezetimibe with a statin.

113. On behalf of the plaintiff, it has been submitted that a therapeutic indication which provides that Ezetrol can or should be administered with a statin (without indication of the exact statin) cannot transform the marketing authorisation for Ezetrol into a marketing authorisation for ezetimibe and simvastatin. The plaintiff placed significant reliance on Article 1 (2) (a) of the Marketing Authorisation Directive which defines a medicinal product as: "*any substance or combination of substances presented as having properties of treating or preventing disease in human beings…".*

114. The plaintiff submitted that, in circumstances where a marketing authorisation is in respect of "*any substance or combination of substances* …", it cannot be suggested that the Ezetrol marketing authorization was granted in the context of a co-administration. The plaintiff also placed emphasis on the fact that a co-administration contemplated by the Ezetrol marketing authorization was not limited to simvastatin or even the four statins identified in the clinical data. The relevant text (quoted above) simply said that it was to be used in combination with a statin. The Ezetrol authorization does not direct what statin a physician might use. The plaintiff makes the case that the co-administration cannot be equated to a medicinal product authorized by the Medicinal Products Directive and that, as a consequence, the Ezetrol authorisation could not constitute the first authorisation to place the combination of ezetimibe and simvastatin on the market for the purposes of Article 3 (d). The plaintiff drew attention, inter alia, to the decisions of the Court of First Instance in Paris and a court in Oslo in support of this proposition. The plaintiff also relied on the decision of Lewison J. (as he then was) in *Yeda v. Comptroller General of Patents Designs and Trademarks* [2010] EWHC 1733 (Pat). In that case (which I examine in more detail below) Lewison J. held that the concept of "*product*" for the purposes of the SPC Regulation does not include the therapeutic use of an active ingredient. In that case, the relevant marketing authorisation was in respect of a named product. The authorisation made clear that, in certain circumstances, the named product was to be used in combination with another agent. Lewison J. came to the conclusion that the only "*product*" that was authorised for the purposes of the SPC Regulation was

the named product. The authorisation could not be interpreted as an authorisation for the combination notwithstanding that the authorisation contemplated that the named product would be used, in certain circumstances, in combination with the additional agent.

My findings in relation to Article 3 (d)

115. *In my view, the starting point for the analysis of this issue is Article 3 (b). Under Article 3 (b), an SPC cannot be granted unless: "a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with [the Medicinal Products Directive] …". It is significant that Article 3 (b) focusses on an authorisation for a product. Article 3 (b) must be read in conjunction with the definitions of "product" in Article 1 (b) (set out in para. 10 above) and the definition of "medicinal product" in Article 1 (a) (set out in para. 11 above).*

116. In contrast to the definition of "*medicinal product",* the definition of "*product*" is confined to the active ingredient of a medicinal product or to a combination of such active ingredients. This was highlighted by the CJEU in Case-431/04 *Massachusetts Institute of Technology*. In that case, the CJEU also drew attention to the fact that there is no definition in the SPC Regulation of "*active ingredient*". The CJEU explained in para. 17 of the judgment that, in the absence of such a definition, the meaning and scope of "*active ingredient*" must be determined by considering the general context in which those words are used and their usual meaning in everyday language. At para. 18 of the judgment, the CJEU explained that it is generally accepted in pharmacology that an active ingredient will not include substances forming part of a medicinal product which do not have an effect of their own on the human or animal body.

117. Thus, for the purposes of Article 3 (b) (and in turn for the purposes of Article 3 (d)) the "*product*" to be considered is solely the active ingredient (or where appropriate the combination of active ingredients) which are the subject of a marketing authorisation. Crucially, for the purposes of Article 3 (d), the authorisation must be the first authorisation to "*place the <u>product</u> on the market as a medicinal product*" (emphasis added). The question in this case is whether the Ezetrol authorisation was an authorisation to place the combination product comprising two active ingredients namely ezetimibe and simvastatin on the market as a medicinal product. That word "*product*" is to be given a strict definition. That was made clear by the CJEU in the *Massachusetts Institute of Technology case*. It is also clear from the decision of the CJEU in Case C-31/03 *Pharmacia Italia SpA* (and re-affirmed in Case C-202/05 *Yissum Research and Development v. Comptroller-General of Patents)* that the decisive factor is not the intended use of a medicinal product but the product itself. In making that finding in the *Pharmacia Italia* case the CJEU placed particular reliance on (a) the definition of "*product*" in Article 1 (b) quoted in para. 10 above; (b) the fact that Article 3 (b) also refers to a valid authorisation "*to place <u>a product</u> on the market…"* (emphasis added); and (c) the provisions of Article 4 which make it clear that the protection conferred by an SPC is to extend only to the product covered by the marketing authorisation for the corresponding medicinal product. Article 4 expressly states the SPC: "*shall extend only to the product*

covered by the authorisation to place the corresponding medicinal product on the market…".

118. The approach taken by the CJEU was subsequently applied by Lewison J. in the *Yeda Research* case mentioned in para. 114 above. There, the relevant patent related to a combination treatment for cancer. The treatment involved the use of two active ingredients, one of which was cytotoxic (i.e. it killed the cancer cells) while the other was cytostatic (i.e. it stopped the replication of the cancer cells but did not itself kill the cells). The cytostatic agent in the combination was known as cetuximab (also known by the trade name Erbitux). The cytotoxic agent was irinotecan. The relevant authorisation in that case was granted in respect of the medicinal product "*Erbitux-cetuximab*". In the clinical particulars of the authorisation, it was expressly stated that Erbitux was indicated in combination with irinotecan for the treatment of patients with a particular type of cancer where treatment with irinotecan as a monotherapy had failed. The authorisation described the dosage of Erbitux and also stated that, for the dosage of the *"concomitant irinotecan*" reference should be made to the product information for the latter and the dosages for that product must be followed. The patentee applied (*inter alia*) for an SPC in respect of a product which was described in the application as "*cetuximab in combination with irinotecan*". This was refused by the Patents Office on the basis that, contrary to Article 3 (b), the application was based on an authorisation for cetuximab alone. The hearing officer drew attention to the fact that the medicinal product is clearly identified as Erbitux (the active ingredient of which was cetuximab). The hearing officer took the view that this was distinguishable from how the product is used. He also drew attention to the lack of any detail in relation to irinotecan in the marketing authorisation.

119. On appeal to the English High Court, counsel for the applicant submitted that the data about Irinotecan were incorporated by reference into the marketing authorisation with the consequence that, on its true interpretation, it authorised the combination of cetuximab and Irinotecan. That submission chimes quite closely to the case made by the defendant in these proceedings. This argument was rejected by Lewison J. who said, at para. 26:-

> *"…article 1 of the decision [of the hearing officer] plainly identifies the medicinal product, 'Erbitux – cetuximab' as the subject-matter of the authorisation. No other medicinal product is identified. The direction to enter that product in the Community Register of Medicinal Products is to the same effect. Article 3 specifies the form of the labelling and package leaflet. The outer packaging makes no mention of irinotecan at all. The package leaflet contains two brief mentions of irinotecan in explaining how cetuximab is used. The summary of the product characteristics likewise contains brief mentions of irinotecan in explaining how cetuximab is used. But as the case law shows, how a medicinal product is used does not form part of the identification of the product itself. In my judgment the brief references to irinotecan in explaining how cetuximab is used are wholly insufficient to amount to a marketing authorisation of a product consisting of both cetuximab and irinotecan. …"*

120. As counsel for the defendant emphasised, there is significantly more information about statins in the Ezetrol marketing authorisation than appears to have been contained in the authorisation considered by Lewison J. in relation to irinotecan. The Ezetrol marketing authorisation contains extensive information in relation to clinical trials relating to the co-administration of ezetimibe with a statin. The trials related to four different statins namely atorvastatin, simvastatin, pravastatin and lovastatin. However, as in the *Yeda Research case*, the Ezetrol marketing authorisation informs the reader to refer to the SmPC for the "*particular statin*" when ezetimibe is to be administered with a statin. Furthermore, all of the data dealing with the pharmacokinetic properties of the product relate to ezetimibe.

121. Moreover, it seems to me that the fundamental reason why Lewison J. came to the conclusion quoted above was that the manner in which a medicinal product is used does not form part of the identification of the product itself. That conclusion is consistent with the case law of the CJEU discussed in paras. 116 to 117 above. The case law of the CJEU is binding on me. The decision in *Yeda Research* is a useful illustration of the application of the principles laid down in the case law of the CJEU. There is a very clear parallel between the facts in *Yeda Research* and the facts in issue in these proceedings. In *Yeda Research*, the use of Erbitux in combination with irinotecan was expressly indicated for the treatment of patients with a particular form of cancer after failure of irinotecan as a monotherapy. Similarly, in the case of the Ezetrol marketing authorisation, the co-administration was indicated for use in patients with homozygous familial hypercholesterolemia. I cannot see any distinction, in substance, between the therapeutic indication in *Yeda Research* and the therapeutic indication for homozygous familial hypercholesterolemia under the Ezetrol marketing authorisation. What the latter does is to require that a statin should be co-administered with the ezetimibe product. That clearly relates to the manner in which ezetimibe is to be used in such cases. It is to be used in conjunction with a statin. It therefore seems to me to fall squarely within the principle laid down in *Pharmacia Italia* and in *Yissum Research*. Just as in *Yeda Research,* the product is identified in the SmPC as Ezetrol. That product comprises ezetimibe exclusively. The statin is not part of the product authorised. Any such statin required its own authorisation with its own SmPC. The qualitative and quantitative composition of the product authorised by the authorisation refers only to ezetimibe and the various excipients. The pharmaceutical form relates only to the Ezetrol tablet. The fact that, in the case of homozygous familial hypercholesterolemia, the Ezetrol product was to be used in conjunction with a statin does not make that combination the subject of the authorisation for the purposes of the SPC Regulation. While Prof. Salvatore accepted that there was "*no doubt*" that the authorisation was to use Ezetrol with a statin in such cases, use is not sufficient in itself to bring the relevant statin within the ambit of the product authorised by the marketing authorisation. The case law of the CJEU makes that clear.

122. I can find nothing in the submissions made by the defendant in this case which adequately addresses the effect of the case law of the CJEU. In the circumstances, I am compelled to conclude that the case under Article 3 (d) has not been made out insofar as

the defendant contends that the combination of ezetimibe and simvastatin should be regarded as authorised by the Ezetrol marketing authorisation.

123. Nor has the defendant sufficiently explained how it can plausibly be suggested that the Ezetrol authorisation extends in particular to a combination of ezetimibe and simvastatin. As noted above, the terms of the authorisation refer solely to a statin without identifying any particular statin. While it is, of course, the case that simvastatin is one of the statins which were the subject of clinical trials discussed in the SmPC, the relevant text of the therapeutic indications for homozygous familial hypercholesterolemia does not confine itself in any way to simvastatin. Thus, the effect of the defendant's argument would be that any combination of ezetimibe and any statin should be regarded as the subject of the Ezetrol marketing authorisation. I do not believe that the authorisation for Ezetrol can be construed in that way. On the contrary, the marketing authorisation is specific to the product Ezetrol. The sole active ingredient of which is ezetimibe.

The impact of the Article 3 (d) finding on the case made under Article 3 (c)

124. As noted in para. 9 above, an SPC cannot be granted if the product (the proposed subject of the SPC) has already been the subject of a previous SPC. If ezetimibe is the only relevant product protected by the 599 patent, then it is clear that an SPC was previously granted in respect of ezetimibe. That SPC was granted in 2003 following the granting of the Ezetrol marketing authorisation. To that extent, the defendant's counterclaim on the basis of Article 3 (c) must succeed.

125. However, if I have correctly understood the position, the defendant also maintains that, if it be the case that the combination product is protected by the 599 patent, the SPC granted on foot of the Ezetrol marketing authorisation means that the SPC, the subject matter of these proceedings, is not the first SPC granted in respect of the combination.

126. As noted previously, I do not believe that this element of the defendant's case has been pleaded. A serious question therefore arises as to whether the defendant was entitled to make any such argument. In any event, in light of my finding in the context of Article 3 (d) that the Ezetrol marketing authorisation is not in respect of the combination product, it seems to me that this alternative case of the defendant must fail.

Conclusion

127. In light of the findings which I have made above, it seems to me that the defendant's counterclaim under Article 3 (a) of the SPC Regulation must succeed. The SPC must accordingly be revoked. It seems to me to be unnecessary in the circumstances to make any order in respect of the defendant's pleaded counterclaim insofar as Article 3 (c) is concerned.

128. On the other hand, in light of the findings which I have made in paras. 120 – 123 above, it seems to me that the counterclaim of the defendant, insofar as it relies on Article 3 (d) in respect of the combination of ezetimibe and simvastatin must be dismissed. Similarly, insofar as the defendant makes an alternative case under Article 3 (c) in relation to the combination of ezetimibe and simvastatin, it seems to me that this case (although not pleaded) must also be dismissed.

129. I will, of course, hear counsel as to the form of the order to be made. I will also hear counsel in relation to costs or in relation to any other issues that may arise.

130. Finally, it should be noted that neither side made any application to defer this judgment pending publication of the decision of the CJEU in *Royalty Pharma.*