Mylan Health Pty Ltd v Sun Pharma ANZ Pty Ltd **[2020] FCAFC 116**

FEDERAL COURT OF AUSTRALIA

MIDDLETON, JAGOT, YATES, BEACH AND MOSHINSKY JJ

THE COURT:

INTRODUCTION

1 The appellants, Mylan Health Pty Ltd (**Mylan Health**) and BGP Products Operations GmbH (**BGP**), unsuccessfully sued the first respondent, Sun Pharma ANZ Pty Ltd (**Sun Pharma**), for threatened patent infringement: *Mylan Health Pty Ltd (formerly BGP Products Pty Ltd) v Sun Pharma ANZ Pty Ltd (formerly Ranbaxy Australia Pty Ltd)* [2019] FCA 28; 138 IPR 402. Mylan Health and BGP are related entities. We will refer to them as a single entity (**Mylan**), unless it is necessary to distinguish between them.

2 Three patents were in suit. The first was Patent No. 2006313711 (the **711 patent**), the complete specification of which is entitled "Use of fenofibrate or a derivative thereof for preventing diabetic retinopathy". The second was Patent No. 2003301807 (the **807 patent**), the complete specification of which is entitled "Nanoparticulate fibrate formulations". The third was Patent No. 731964 (the **964 patent**), the complete specification of which is entitled "Pharmaceutical composition of fenofibrate with high biological availability and method for preparing same".

3 BGP is the patentee, and Mylan Health is the exclusive licensee, of the 711 patent and the 964 patent. BGP is also the co-patentee of the 807 patent. The other co-patentee is the second respondent in this appeal, Alkermes Pharma Ireland Ltd. Mylan Health is a licensee of the 807 patent.

4 Fenofibrate is a fibric acid derivative (or fibrate) that is used to regulate lipoproteins and triglycerides in the blood. It is also used to treat diabetic retinopathy. The knowledge that fenofibrate is useful to treat diabetic retinopathy is more recent than the knowledge that fenofibrate is useful to regulate lipoproteins and triglycerides in the blood. The 711 patent is concerned with the second, and later-discovered, medical use of fenofibrate as a known active pharmaceutical ingredient.

5 At the time of the primary proceeding, Lipidil was the only fenofibrate product on the Australian market. It had been on the market since August 2006. Since February 2015, Mylan Health has marketed and sold Lipidil into that market.

6 Mylan sued Sun Pharma because, on 29 February 2016, Sun Pharma obtained entry on the Australian Register of Therapeutic Goods (**ARTG**) of certain fenofibrate film-coated tablets, which it proposed to market and supply in Australia. The primary judge described these products as the **Ranbaxy Products**. We will do likewise.

7 The primary judge dismissed Mylan's case on threatened infringement. With regard to the 711 patent, his Honour found that the claims in suit (some of which are Swiss type claims and some of which are method of treatment claims) were invalid on the ground that the invention, as claimed, was not novel in light of the publication of The ACCORD Eye Study Protocol: Version January 2004 (the **ACCORD Protocol**). His Honour also found that the invention, as claimed in the relevant claims, lacked an inventive step.

8 For completeness, we note that the primary judge found that some of the claims in suit were not novel in light of the publication of European Patent Application EP D 482 498A, when read with the Physicians' Desk Reference, 59th Edition 2005 at pages 523 – 525 and 1325 – 1328. No appeal is pursued in respect of that finding.

9 We also note that the primary judge rejected Sun Pharma's case that the claims in suit were not novel having regard to the conduct of the study to which the ACCORD Protocol was directed (the **ACCORD Study**) and another study called the **FIELD Study**.

10 Aside from his findings on validity, the primary judge found that Mylan had not established that there was a threatened infringement of the Swiss type claims in any event. In essence, his Honour found that claims in this form imported a purposive element which, in order to establish infringement or threatened infringement, require proof of the manufacturer's intention when making the medicament. In this case, the intention to be proved was use of the Ranbaxy Products for the prevention or treatment of diabetic retinopathy. The primary judge was not satisfied that Mylan had proved that intention.

11 Finally, with respect to the method of treatment claims in respect of which threatened infringement would have been established had the claims been valid, the primary judge said that he would not have granted quia timet injunctive relief, as sought.

12 With regard to the 807 patent, his Honour found that the claims in suit were invalid on the ground that the invention, as claimed, lacked an inventive step. The primary judge was not in a position to make any finding as to whether these claims would have been infringed had they been valid. This was because it had been recognised prior to the hearing that extensive experimental evidence would need to be adduced on that question. Therefore, as a matter of case management, the question of infringement was deferred until after the determination of other issues in the proceeding, including the validity of those claims.

13 With regard to the 964 patent, his Honour found that some of the claims in suit were invalid. As to the other claims in suit, he was not satisfied that Mylan had established its case on threatened infringement.

14 After judgment had been given dismissing Mylan's case on threatened infringement, Mylan moved the Court for interim injunctive relief to restrain Sun Pharma from marketing and supplying the Ranbaxy Products in Australia pending the determination of this appeal. A hearing was conducted on 4 April 2019. The application for interim relief was dismissed on 11 April 2019: *Mylan Health Pty Ltd v Sun Pharma ANZ Pty Ltd (No 2)* [2019] FCA 505; 141 IPR 26.

15 For the reasons which follow, the appeal should be dismissed, with costs.

SOME MEDICAL CONDITIONS

16 The 711 patent is concerned with the second medical use of fenofibrate as an active pharmaceutical ingredient. In his reasons for judgment, the primary judge discussed various medical conditions and their treatment. Knowledge of these matters was necessary to understand the 711 patent and the evidence given in respect of it. For the purposes of this appeal, it is not necessary for us to summarise all his Honour's findings in this regard. It will suffice for us to note some of the key findings, none of which are controversial.

17 **Dyslipidaemia** is a condition in which a patient presents with abnormal levels of lipids (fats) in the body, specifically cholesterol and triglycerides.

18 **Cholesterol** is insoluble in blood and exists as one of the following complexes: (a) very low density lipoprotein cholesterol (**VLDL-C**); (b) low-density lipoprotein cholesterol (**LDL-C**); and (c) high density lipoprotein cholesterol (**HDL-C**).

19 VLDL-C is the form in which cholesterol is secreted from the liver, where most cholesterol is made. As it enters the bloodstream, it is converted into LDL-C, which transports the cholesterol around the body. HDL-C (so-called "good cholesterol") transports cholesterol present in the body back to the liver, to remove it from circulation. A patient's total cholesterol is the sum of these complexes.

20 **Triglycerides** are principally used for energy. A large proportion of dietary fat is transported around the body in the form of triglycerides.

21 A patient will have dyslipidaemia (abnormal lipid levels) or **hyperlipidaemia** (elevated lipid levels) if he or she has: (a) elevated LDL-C levels; (b) elevated triglyceride levels; and/or (c) low HDL-C levels. Elevated triglycerides coupled with reduced levels of HDL-C are a hallmark of a condition sometimes called **diabetic dyslipidaemia**.

22 **Statins** have been the primary drug treatment for patients with elevated total cholesterol and LDL-C levels. For patients with elevated triglyceride levels and/or low HDL-C levels, **fibrates** are a primary drug treatment.

23 Fenofibrate is a fibrate which became available in Australia in late 2004. As we have noted, at the time of the primary proceeding, Lipidil was the only fenofibrate product on the Australian market.

24 As at 10 November 2005, fenofibrate was also an effective cholesterol-lowering agent that was approved for use in Australia for the treatment of hypercholesterolaemia. It was believed to be more effective at lowering cholesterol than other fibrates available at the time. However, fibrates, including fenofibrate, were not prescribed for the treatment of hypercholesterolaemia if target lipid levels could be achieved by the use of a statin, unless there was some other reason (such as side-effects) why a patient's elevated lipid levels could not be treated by statins.

25 Diabetes mellitus (**diabetes**) is an endocrine (or hormonal) disorder characterised by an absolute or relative deficiency of insulin. Insulin is a hormone produced in the pancreas. It is responsible for regulating glucose metabolism in the body. Patients with diabetes are at risk of developing a wide variety of acute and long-term complications including macrovascular complications, such as coronary artery disease (leading to heart attack), cerebrovascular disease (leading to strokes), peripheral vascular disease (leading to infection or gangrene), microvascular complications (including diabetic retinopathy), diabetic nephropathy (kidney disease) and diabetic neuropathy (nerve damage).

26 There are two forms of diabetes. **Type 1** diabetes is most often diagnosed in children and young adults, although it can present at any stage of life. It is an autoimmune condition. In affected patients, there is a progressive destruction of the cells in the pancreas that are responsible for insulin synthesis and release. Patients affected by type 1 diabetes may present with a range of symptoms and signs, including fatigue, increased thirst, increased urine production, weight loss, increased appetite and dehydration. In some cases, patients affected

by type 1 diabetes may develop life-threatening acute complications, such as the metabolic disturbance known as diabetic ketoacidosis.

27 **Type 2 diabetes** is the more common form of diabetes in Western countries. Affected patients suffer from insulin resistance, whereby insulin is less efficient in transporting glucose from the blood stream into cells. To exert its normal biological action, insulin must attach to specific receptors on the surface membranes of cells. With insulin resistance, there is typically a reduction in the number of these receptors, as well as a reduction in the affinity (or attraction) between insulin and the receptors. In the initial stages of type 2 diabetes, the body responds to insulin resistance by increasing the production of insulin in the pancreas, leading to an increase in the levels of insulin circulating in the blood (**hyperinsulinaemia**). Blood glucose levels typically remain within the normal range, but as the disease progresses, blood glucose levels rise. Over the longer term, insulin production typically declines to such an extent that insulin deficiency develops and insulin therapy is required to normalise blood glucose levels.

28 **Diabetic retinopathy** is a disease of the retina related to increasing changes to the blood vessels in the retina. It is a long-term complication associated with diabetes. The first stage of the development of retinopathy is non-proliferative retinopathy, which is characterised by lesions in the form of microaneurysms (macular swelling across the course of a retinal capillary), and then haemorrhages (which may indicate blood vessel leakage), in the retina. Both of these lesions occur in the capillary bed of the retina. The early signs of retinopathy generally do not affect vision, unless the macula is affected.

29 **Macular oedema** is the most frequent cause of vision loss in people with diabetic retinopathy. It is caused when capillaries (small blood vessels) in the retina close to the macula become occluded (closed or non-perfused), resulting in reduced flow through them. In response, adjacent capillaries start to leak fluid (oedema) into the retina. The macula is structured so that all of the supporting cells are aligned to give a maximum light signal to the cones at the base of the macula, which means that it can accumulate fluid easily, leading to swelling and damage to the macula. Because of its importance in providing sharp vision, the macula is critical to vision function. It should be noted that oedema can also occur at other parts of the retina, away from the macula. This generally does not need to be treated unless it threatens the macula.

30 In addition to the damage caused by swelling as a result of oedema, the leakage of fluid from the bloodstream into the retina can result in the formation of small deposits of lipid and other materials in the retina. These small deposits are called **hard exudates**. Hard exudates can

form at any stage of diabetic retinopathy, as a result of fluid leakage from the retinal capillary bed. Hard exudates tend to occur in the outer part of the retina and, in most patients, close to, or involving, the macula. Hard exudate deposition is damaging when it occurs at the macula because it can cause irreversible structural changes to the macula within a period of months and, if present for a long time, will result in permanent vision loss.

31 Persistently elevated (poorly controlled) blood glucose levels (**hyperglycaemia**) is the primary risk factor for diabetic retinopathy. The longer a patient has had diabetes, the more likely it is that diabetic retinopathy will develop.

THE 711 PATENT: BACKGROUND

The complete specification

32 The complete specification of the 711 patent describes the invention as relating to "the use of fenofibrate or a derivative thereof for the manufacture of the medicament for the prevention and/or treatment of retinopathy". At p 1 lines 29 to 36 and p 2 lines 1 to 5 of the specification, it describes diabetic retinopathy as a specific microvascular complication of both type 1 and type 2 diabetes, and one of its most debilitating complications:

> Diabetic retinopathy is a progressive diabetic complication. It advances from a stage referred to as "simple" or initial (background retinopathy) to a final stage referred to as "proliferative retinopathy" in which there is formation of fragile retinal neovessels, leading to severe haemorrhages, sometimes with detachment of the retina, and to loss of vision. The microvascular lesions in simple retinopathy are characterised by microaneurysms, small petechial haemorrhages, exudates and venous dilations. This simple retinopathy form can remain clinically silent for a long period of time. At this simple retinopathy stage cellular and structural deterioration of the retinal capillary can be observed in the post-mortem examinations of retinas from diabetic patients, compared to the retinas from normal subjects of comparable age. If proliferative retinopathy is left untreated, about half of those who have it will become blind within five years, compared to just 5% of those who receive treatment.

33 After briefly referring to the treatment of diabetic retinopathy with laser photocoagulation, the complete specification continues at p 2 lines 25 to 36:

> Preventing the development or progression of diabetic retinopathy has the potential to save vision at a relatively low cost compared to the costs associated with a loss of vision. Thus, it is an object of the present invention to provide further means which contribute to the prevention of the development or progression of diabetic retinopathy.
>
> The present invention is based on the discovery that patients taking fenofibrate or a derivative thereof need fewer treatment[s] by retinal laser therapy than placebo-allocated patients. The results obtained from a large clinical trial demonstrate the favourable effect of fenofibrate in the prevention of retinopathy.
>
> According to a first aspect, the present invention is directed to the use of fenofibrate

> or a derivative thereof for the manufacture of a medicament for the prevention and/or treatment of retinopathy, in particular diabetic retinopathy.

34 The complete specification uses "prevention" to mean preventing the development or progression of diabetic retinopathy: p 3 lines 1 to 2. It refers to "diabetic retinopathy" as severe non-proliferative grades of diabetic retinopathy, proliferative grades of diabetic retinopathy, macular oedema, and hard exudates: p 3 lines 3 to 5.

35 The complete specification provides certain pharmacological data, including from the FIELD Study at p 8 lines 21 to 35 and p 9 lines 1 to 2:

> As fibrates are known to correct the typical dyslipidaemia of diabetes, their role in cardiovascular risk reduction in diabetes may be especially important. A study called Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) has been carried out which study is a multicentre, double-blind, placebo-controlled [trial] evaluating the effects on coronary morbidity and mortality of long-term treatment with fenofibrate to elevate high-density lipoprotein (HDL) cholesterol levels and lower triglyceride (TG) levels in patients with type 2 diabetes and total blood cholesterol between 3 and 6.5 mmol/L (115 and 250 mg/dL) at study entry. In type 2 diabetes, rates of coronary heart disease (CDH) are 3 to 4 times higher than those of persons without diabetes at any given level of blood cholesterol, and at any given age. Evidence also suggests that in women with diabetes, the natural protection against CDH afforded by sex may be lost. Further, people with type 2 diabetes have both higher in-hospital mortality after myocardial infarction (MI) and a poorer outcome in the subsequent years, losing on average between 5 and 10 years of life expectancy. It follows the type 2 diabetes contributes significantly to the overall burden of premature CHD morbidity and mortality, far in excess of its prevalence in the community.

36 The complete specification describes the FIELD Study as having principal, secondary and tertiary outcomes. The principal study outcome was the combined incidence of first non-fatal myocardial infarction or coronary heart disease death among all randomised patients during the schedule treatment period. Secondary outcomes included the effects of fenofibrate on major cardiovascular events. Tertiary outcomes included the effects of treatment by fenofibrate on the development of vascular and neuropathic amputations, non-fatal cancers, the progression of renal disease, hospitalisation for angina pectoris and, importantly to the present case, laser treatment for diabetic retinopathy. In relation to the results concerning the effects of fenofibrate on laser treatment for diabetic retinopathy, the complete specification discloses at p 14 lines 23 to 27:

> These results provide the first evidence of the favourable effect of fenofibrate on the need for retinal laser therapy. As the patients taking fenofibrate had fewer treatment for retinal laser therapy than the placebo-allocated patients, the prevention and treatment of retinopathy by fenofibrate has been clearly demonstrated.

Relevant claims

37 Claim 1 of the 711 patent is:

> 1. Use of fenofibrate or a derivative thereof for the manufacture of a medicament for the prevention and/or treatment of retinopathy, in particular diabetic retinopathy.

38 Claim 5 is:

> 5. Use according to any of claims 1 to 4, wherein said medicament contains 200 mg, 160 mg, 145 mg or 130 mg of fenofibrate or a derivative thereof.

39 Claim 7 is:

> 7. A method for the prevention and/or treatment of retinopathy, the method comprising administration of fenofibrate or a derivative thereof to a patient in need thereof.

40 Claims 10 and 11 are:

> 10. The method according to any one of claims 7 to 9 wherein said method further comprises administration of a statin.
>
> 11. The method according to any one of claims 7 to 10 wherein 200 mg, 160 mg, 145 mg or 130 mg of fenofibrate or a derivative thereof is administered.

41 The priority date of the claims is 10 November 2005.

42 Claims 1 and 5 are Swiss type claims. At trial, Mylan also sued on these claims and another Swiss type claim—claim 6. Only claim 5 is relevant to this appeal.

43 Claims 7 and 10 - 11 are method of treatment claims. At trial, Mylan sued on these claims and another method of treatment claim—claim 12. Mylan's case on the threatened infringement of these claims relied on the application of s 117(1) read with s 117(2)(b) of the *Patents Act 1990* (Cth) (the **Act**). Only claims 10 and 11 are relevant to this appeal.

THE 711 PATENT: PRIOR ART

The ACCORD Eye Study Protocol

44 ACCORD is the acronym for The Action to Control Cardiovascular Risk in Diabetes. The ACCORD Trial was a randomised clinical trial on cardiovascular disease in patients with type 2 diabetes. It had three components—namely, determining the effects of (1) lowering blood glucose; (2) lowering blood pressure; and (3) lowering serum triglycerides plus raising serum HDL-C levels, in those patients. The ACCORD Study was conducted within the ACCORD Trial. It was designed to evaluate the effects of treatment on diabetic retinopathy.

45 In a section dealing with diabetic retinopathy, the ACCORD Protocol referred to various data, including data obtained from a study which the Protocol called "ETDRS" (Early Treatment Diabetic Retinopathy Study Report No 18) (**ETDRS 18**). In that regard, the ACCORD Protocol stated:

> The ETDRS study has shown a relationship between progression to high risk proliferative DR over 5 years and baseline serum triglycerides in the age group 50 – 69. Progression was 23% higher in those with serum triglycerides > 190mg/dl versus those whose serum triglycerides were normal, after adjustment for 11 significant covariates.

46 The ACCORD Protocol then stated:

> It is therefore reasonable to hypothesize that fibrate therapy which decreases serum triglycerides will reduce the risk of DR.

47 The ACCORD Protocol identified four aims for the ACCORD Study, the second of which was:

> 2. In type 2 diabetic patients whose low density lipoprotein cholesterol levels have been reduced appropriately by statin therapy, will the additional fibrate therapy, to reduce triglyceride levels and raise high density lipoprotein cholesterol levels, decrease the risk of DR?

48 The ACCORD Protocol referred to three primary hypotheses for the ACCORD Study in relation to middle-aged or older people with type 2 diabetes at high risk for having a cardiovascular event. One of those hypotheses was:

> 2. In the context of good glycaemic control, a therapeutic strategy that uses a fibrate to lower triglyceride levels and raise HDL cholesterol levels in patients already receiving a statin drug for treatment of LDL cholesterol levels, will reduce the rate of development or progression of DR compared to a strategy that only uses a statin drug for treatment of LDL cholesterol levels.

49 Thus, the ACCORD Protocol envisaged that, for patients having good glycaemic control, and having already received a statin to reduce LDL-C, a fibrate would be administered to lower triglyceride levels and raise HDL-C levels. The hypothesis was that the administration of the fibrate *will* reduce the rate of development or progression of diabetic retinopathy compared to a strategy that only used a statin for the treatment of LDL-C levels.

50 The ACCORD Protocol is relevant to Grounds 5 – 7 of the appeal concerning the primary judge's finding that the claims in suit of the 711 patent were invalid on the ground that the invention, as claimed, was not novel.

ETDRS 22

51 The Early Treatment Diabetic Retinopathy Study Report 22 (**ETDRS 22**) was an observational study undertaken as part of a larger clinical trial. The larger clinical trial was designed to evaluate the effect of photocoagulation and aspirin therapy in patients with mild to severe non-proliferative or early proliferative diabetic retinopathy. The data provided in the larger clinical trial provided an opportunity to assess the relationship between baseline serum lipid levels and the presence of retinal hard exudates at baseline, as well as the development of retinal hard exudates during follow-up in patients who had no evidence of hard exudates at baseline. This was the subject of ETDRS 22, the stated objective of which was:

> To evaluate the relationship between serum lipid levels, retinal hard exudate, and visual acuity in patients with diabetic retinopathy.

52 In an introductory paragraph, the authors of ETDRS 22 stated:

> Retinal hard exudate is thought to be the result of lipoproteins "leaking" from retinal capillaries into the extracellular space of the retina. The relationship of serum cholesterol level to the severity of retinal hard exudate has previously been assessed in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, a population-based study. These investigators found that elevated levels of serum cholesterol were associated with increased severity of retinal hard exudate in this cross-sectional evaluation of persons with diabetes mellitus.

53 The authors went on to describe the Early Treatment Diabetic Retinopathy Study. They recorded the fact that fasting serum lipid levels were measured at baseline (at the commencement of the study) with total serum cholesterol, LDL-C, HDL-C, and triglycerides separately evaluated for association with the presence of hard exudates. The authors found that only total cholesterol and LDL-C levels were statistically significantly associated with the presence of hard exudates at baseline. Based on stereoscopic photographs of the fundus taken at baseline, four months, and then annually for a seven-year follow-up period, the authors found that increased total cholesterol and triglyceride levels were associated with a more rapid onset of obvious retinal hard exudate:

> Patients with total serum cholesterol levels of 6.21 mmol/L (240 mg/dL) or more, or triglyceride levels greater than 4.50 mmol/L (399 mg/dL), developed hard exudate approximately 50% faster than patients in the ETDRS with serum cholesterol levels less than 5.17 mmol/L (200 mg/dL) or triglyceride levels less than 2.30mmol/L (204 mg/dL) … Increased levels of LDLC also resulted in a similarly shortened time to the development of retinal hard exudate …

54 The authors of ETDRS 22 concluded that the data demonstrated that elevated serum lipid levels were associated with an increased risk of retinal hard exudates in persons with diabetic

retinopathy and that lipid lowering may decrease the risk of hard exudate formation and associated vision loss in patients with diabetic retinopathy. Specifically, the authors stated:

> … Because lipid lowering is currently the standard of care for persons with elevated serum lipid levels, either with or without diabetes mellitus, a clinical trial designed to evaluate the effects of lipid lowering on retinal hard exudates or visual acuity is unlikely. However, long-term observational data from the ETDRS can provide important information on the association of lipids with both retinal hard exudate and change in visual acuity.
>
> In the ETDRS, the patients who had elevated serum total cholesterol or LDLC levels were more likely to have retinal hard exudate at baseline. In addition, patients with elevated serum total cholesterol, LDLC, or triglyceride levels, who did not have obvious retinal hard exudate at baseline, were at increased risk of developing retinal hard exudate during follow-up. These associations, along with the finding that the severity of hard exudate is associated with the risk of visual loss even after adjusting for the extent of macular oedema, may have important clinical implications.
>
> Lipid-lowering treatment is currently recommended by the National Heart, Lung, and Blood Institute, National Institutes of Health, for patients who are at high risk of cardiovascular disease. Although our data are observational, they suggest that a reduction of elevated serum lipid levels may help prevent vision loss associated with retinal hard exudate. Preservation of vision may be an additional motivating factor for lowering serum lipid levels in persons with diabetes in whom they are elevated.

55 As expressed in the abstract to ETDRS 22:

> These data demonstrate that elevated serum lipid levels are associated with an increased risk of retinal hard exudate in persons with diabetic retinopathy. Although retinal hard exudate usually accompanies diabetic macular edema, increasing amount of exudate appear to be independently associated with an increased risk of visual impairment. Lowering elevated serum lipid levels has been shown to decrease the risk of cardiovascular morbidity. The observational data from the Early Treatment Diabetic Retinopathy Study suggest that lipid lowering may also decrease the risk of hard exudate formation and associated vision loss in patients with diabetic retinopathy. Preservation of vision may be an additional motivating factor for lowering serum lipid levels in persons with diabetic retinopathy and elevated serum lipid levels.

56 It should be noted that ETDRS 22 did not itself demonstrate the effect of using lipid-lowering agents on retinal hard exudates or demonstrate a causative link between serum lipid levels and the development or progression of hard exudates. It did, however, make the association, and proffered the suggestion, quoted above, that lipid-lowering may decrease the risk of hard exudate formation and associated vision loss in patients with diabetic retinopathy.

57 ETDRS 22 is relevant to Grounds 10 – 15 of the appeal. It was central to the primary judge's finding that the invention as claimed lacks an inventive step. His Honour was satisfied that ETDRS 22 was common general knowledge in that it would have formed part of a consulting ophthalmologist's background knowledge as at 10 November 2005, the priority date of the claims in suit.

58 We mention ETDRS 22 in this part of our reasons because his Honour also found that, if he was wrong in his conclusion that ETDRS 22 was common general knowledge, he was nonetheless satisfied that it was prior art information which, for the purposes of s 7(3) of the Act, the person skilled in the art, as at 10 November 2005, would have ascertained, understood and regarded as relevant.

THE 711 PATENT: GROUNDS 5 – 7

The primary judge's reasons

59 The primary judge found that the claims in suit of the 711 patent were invalid on the ground that the invention, as claimed, was not novel in light of the publication of the ACCORD Protocol. He rejected Sun Pharma's case that the claims were not novel having regard to the conduct of the ACCORD Study and the FIELD Study. Grounds 5 – 7 concern Mylan's appeal in relation to the primary judge's findings on lack of novelty in light of the prior publication of the ACCORD Protocol. As pressed, only claims 5, 10 and 11 are relevant to these grounds.

60 The primary judge commenced his consideration of the question of lack of novelty by referring to a number of the leading cases on that question. His consideration included *AstraZeneca AB v Apotex Pty Ltd* [2014] FCAFC 99; 226 FCR 324 (***AstraZeneca v Apotex***) which included reference to *Bristol-Myers Squibb Company v FH Faulding & Company Limited* [2000] FCA 316; 97 FCR 524 (***BMS v Faulding***), and *Merck & Co Inc v Arrow Pharmaceuticals Ltd* [2006] FCAFC 91; 154 FCR 31 (***Merck v Arrow***). We mention *BMS v Faulding* and *Merck v Arrow* in particular because both cases featured prominently in Mylan's submissions on appeal.

61 The primary judge analysed the ACCORD Protocol which, he found, had been made publicly available before the priority date of the claims in suit. There is no appeal from that finding. The primary judge noted the aim and the hypothesis, which we have quoted at [47] and [48] respectively, and recorded Mylan's submission that the ACCORD Protocol did no more than articulate an hypothesis which may or may not be correct.

62 In that latter connection, the primary judge said:

> 160 In support of their submission the applicants referred to the evidence of Professor O'Brien and Professor Mitchell who said that on a reading of the Protocol as a whole, they would not have been directed to use fenofibrate in the prevention or treatment of retinopathy. This is because, as I understood their evidence, neither regarded the hypothesis articulated in the Protocol as likely to produce to a positive result. Professor O'Brien said that he would not have been confident that lipid lowering therapy could reduce the risk of microvascular complications such as diabetic retinopathy. He said that he

would not have prescribed fenofibrate for that purpose even if he was aware of the Protocol prior to November 2005 and would have awaited the outcome of the Eye Study before considering the use of fenofibrate therapy in patients with diabetic retinopathy. Professor Mitchell's evidence was to a similar effect.

161 I think this evidence is answered by the Full Court's observation in *Bristol-Myers* at [72]:

> Prudent practitioners might well take the view that they would prefer to await the final outcome of the trials, both as to efficacy and as to safety, before rushing to embrace the proposed method. But, in our view, there can be no serious doubt that the abstract teaches the [invention].

63 The primary judge then made the following findings:

> 162 In my view the Protocol suggested to the skilled addressee who read it prior to November 2005 that fenofibrate could be used in daily doses of 160 mg for the prevention and treatment of diabetic retinopathy. The fact that Professor O'Brien and Professor Mitchell would not have acted on this suggestion, preferring instead to await the outcome of clinical trials, is no answer to the proposition that the Protocol discloses the precise method of treatment that was later claimed. Nor is it an answer to say that the disclosure was made in the context of a proposed clinical trial aimed at testing a hypothesis.
>
> …
>
> 164 I am satisfied that the Protocol clearly discloses a method of administering fenofibrate in a daily dose of 160 mg to patients suffering from type 2 diabetes who were already taking a statin in the expectation that this would reduce the risk of development or progression of diabetic retinopathy in those patients beyond what it would be were they to have continued to take a statin alone. Use of fibrate in accordance with this method would clearly infringe each of the method of treatment claims which are therefore invalid for lack of novelty. Further, since the novelty of the Swiss-style claims depends upon the use described being new, those claims are also invalid for lack of novelty in light of the use it is proposed in the Protocol for fenofibrate in 160 mg dosages.

64 In light of Sun Pharma's notice of contention, it is convenient to record, at this juncture, the primary judge's findings and conclusions with respect to the conduct of the ACCORD Study and the FIELD Study. In relation to those studies, which were advanced as public acts, the primary judge held:

> 181 The acts of investigators administering fenofibrate during the course of the Eye Study were also relied upon by the respondent as novelty defeating. This aspect of the novelty case, which received little attention in closing submissions, appears to have assumed that the Eye Study was an open label study which enabled the investigators to know whether or not they were administering fenofibrate. However, this would not be possible in a double blind study in which neither the investigator nor the participant would know whether fenofibrate or placebo was being administered. The Protocol states at page 3 that the participants would be randomly assigned in "a double masked fashion to either placebo or fenofibrate" which clearly indicates that the Eye Study was double blinded.

> 182 The FIELD Study was also a double blind study. What I have just said in relation to the Eye Study applies to the FIELD Study as well.

65 The primary judge therefore concluded that Sun Pharma's lack of novelty case, based on prior public use, failed.

The appeal

66 As developed in oral submissions, Grounds 5 – 7 of the appeal repeat, in substance, Mylan's submission at trial that the ACCORD Protocol could not anticipate the invention as claimed because it advanced no more than a reasoned hypothesis for treatment, not a method of treatment as such. Mylan developed its submission by the following argument.

67 For a documentary disclosure to be anticipatory, it must contain a clear description of, or clear instructions to do or make, something that would infringe the patentee's claim: *General Tire & Rubber Co Ltd v Firestone Tyre & Rubber Co Ltd* [1972] RPC 457 (***General Tire***) at 485 – 486. Correspondingly, a method of treatment claim (involving the administration of a pharmaceutical compound for the treatment of the specified medical condition) can only be infringed if there is a deliberate administration of the compound for that purpose: *Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd* [2013] HCA 50; 253 CLR 284 (***Apotex v Sanofi***) at [172], [289] and [294]. Therefore, a prior art disclosure which merely teaches the administration of a compound for the purpose of evaluating its safety and efficacy for a claimed therapeutic purpose will neither infringe nor, correspondingly, anticipate, such a method of treatment claim because that would not be a disclosure of the deliberate administration of the compound for the purpose, aim or object of the claimed therapy. As Mylan put the argument in its written submissions with respect to the ACCORD Protocol:

> The Protocol might have anticipated the method of treatment claims of the 711 Patent if it had given a clear description of the deliberate administration of fenofibrate for the purpose, aim or object of preventing and/or treating retinopathy, or if it had given clear instructions to do so. The Protocol might also have anticipated the Swiss-style claims of the 711 Patent if it had disclosed that the fenofibrate was efficacious for the prevention and/or treatment of retinopathy. But the Protocol did neither of these things. Rather, it disclosed the administration of fenofibrate for the purpose of evaluating its efficacy for the claimed therapeutic purpose.

68 Adopting the language of the cases, Mylan submitted that the disclosure of a reasoned hypothesis that is yet to be evaluated does not constitute "clear and unmistakable directions" to perform the method (*Flour Oxidizing Company Ltd v Carr & Company Ltd* (1908) 25 RPC 428 (***Flour Oxidizing***) at 457); it does not "teach" the invention (*BMS v Faulding* at [67] and [72]); and is akin to a "proposition not true to its full extent" which will "not prejudice a

subsequent statement which is limited and accurate, and gives a specific rule of practical application": *Hill v Evans* (1862) 31 LJ Ch 456; 4 De GF & J 288; 45 ER 1195 at 1200 (***Hill v Evans***).

69 Mylan called in aid the analysis in *InterPharma Pty Ltd v Hospira, Inc* (No 5) [2019] FCA 960; 149 IPR 182 (***InterPharma***) of an allegedly anticipatory disclosure of a method claim directed to sedating a patient in an intensive care unit (**ICU**) with dexmedetomidine, and a corresponding Swiss type claim, by the publication of a patient consent form (the **249 Form**). In that case, the trial judge extensively analysed the 249 Form against the backdrop of a Phase II clinical trial and found that it was not an anticipatory disclosure because it disclosed only the possibility of the use of dexmedetomidine as an ICU sedative and that a study was to be conducted to evaluate that possibility—in other words, an hypothesis to be tested in order to establish if it was well-founded. Further, in the context of considering a submission based on the doctrine of anticipatory disclosure by "inevitable result" (*General Tire* at 485 – 486), the trial judge found that the 249 Form did not contain clear instructions to do or make something that would infringe the patent.

70 In this appeal, Mylan noted that, in finding that the ACCORD Protocol anticipated the invention as claimed, the primary judge relied, in part, on a statement by the Full Court in *Merck v Arrow* (at [110]) that the characterisation of an alleged anticipation as a "suggestion" in relation to the invention, is "not necessarily fatal to a novelty argument". We will return to consider *Merck v Arrow*. For present purposes, it is sufficient to note that Mylan submitted that, properly understood, this observation by the Full Court did not countenance "mere speculation" or "the presentation of no more than a reasoned hypothesis" as an anticipatory disclosure. Here, Mylan said, the ACCORD Protocol advanced no more than a reasoned hypothesis for treatment.

71 Mylan further submitted that if *Merck v Arrow* did countenance such a disclosure as anticipatory, then it was wrongly decided and should not be followed because it was contrary to the statement of principle established by the Full Court in *BMS v Faulding* that, in order to be anticipatory, the earlier documentary disclosure must "teach" that which the patent claims. According to Mylan, presenting a reasoned hypothesis does not amount to "teaching" in the requisite sense.

72 For the avoidance of doubt, we record that Mylan does not contend that the ACCORD Protocol did not disclose the administration of one of the dosages of fenofibrate referred to in claims 5 and 11 of the 711 patent.

Discussion

73 Relevantly to this appeal, s 7(1)(a) of the Act provides that an invention will be taken to be novel unless it is not novel in light of prior art information made publically available in a single document. In *BMS v Faulding*, the question was whether seven, separate prior documentary disclosures anticipated the invention, which was a method of administering a pharmaceutical compound (taxol) to a patient suffering from cancer, comprising infusing from 135 to 175 mg/m^2 of taxol over a duration not exceeding six hours. Five documents were reports of (or articles on) Phase I clinical trials of taxol, which the evidence showed were trials to establish a safe dosage limit of the compound. The sixth document was an editorial in December 1991 by Rowinsky and Donehower in the *Journal of the National Cancer Institute* entitled "Taxol: Twenty Years Later, the Story Unfolds" (**Rowinsky and Donehower**). The seventh document was an abstract by Dr W W ten Bokkel Huinink of the Netherlands Cancer Institute entitled "Taxol the First Available of Taxanes, a New Class of Anti Cancer Drugs" (the **Huinink abstract**).

74 The trial judge (*Bristol-Myers Squibb Co v FH Faulding & Co Ltd* (1998) 41 IPR 467) had held that each document anticipated the invention as claimed because each satisfied the test expressed in *Hill v Evans* (45 ER at 1200):

> … the information as to the alleged invention given by the prior publication must, for the purposes of practical utility, be equal to that given by the subsequent patent. The invention must be shewn to have been before made known. Whatever, therefore, is essential to the invention must be read out of the prior publication.

75 In expressing his conclusion, the trial judge made a number of preliminary observations, including (at 482):

> … it is not to the point that the information in the prior publication does not recommend to the skilled reader the utility of the method disclosed. The test is not whether such a reader would be persuaded by what is disclosed in the prior publication to work the invention. As already noted, there was much evidence from Bristol-Myers' witnesses to the effect that there was not enough data publicly available at the priority date to confirm that a three hour infusion period of taxol was safe. But disclosure of an invention is not a matter of scientific proof, nor warranty of effectiveness.

76 It is apparent that, in this passage, the trial judge was using the word "recommend" in its primary sense of favourably considering the information or presenting it as worthy of

acceptance. His Honour's observation was that there could be anticipatory disclosure without recommendation in this sense. However, his Honour was not saying that a recommendation, in this sense, could not be part of a disclosure that is anticipatory.

77 The trial judge also remarked (at 483) that:

> … publication of a method of medical treatment is none the less a disclosure because it takes the form of a report of clinical trials. Such trials are not solely experiments. It is to be assumed that the medical practitioners involved are also treating their patients with a rational and ethical objective of alleviating their condition and would only continue treatment if there was a reasonable prospect of success. (The side effects of taxol are at the very least unpleasant.)

78 On appeal, the Full Court (Black CJ and Lehane J, with whom Finkelstein J expressed general agreement) found that only the seventh document—the Huinink abstract—was an anticipation. While all the Phase I reports literally disclosed the administration of taxol at dosages falling within some or all the claims in suit, they were trials directed to, and reporting on, dosage safety, with the limited exception that two reports noted some clinical responses. As to these, one reported on responses to dosages that were not in the claimed range; the other (*Cancer Treatment Reports*, Donehower et al., December 1987) recorded only partial clinical responses in two cases, stating:

> The frequency and severity of acute reactions to taxol were similarly decreased, making further clinical development of this drug more realistic and worthwhile based on the antitumour activity seen. It does, however, seem prudent that initial Phase II studies of taxol with this or other schedules be conducted in institutions familiar with its use, and facilities should be readily available for the management of severe type I hypersensitivity reactions.

79 In reasoning to their conclusion that the five Phase I reports were not anticipatory disclosures, Black CJ and Lehane J posed this question:

> 60 … The substantial question, however, is whether the mere disclosure, in the context which we have described at some length, that in the course of the trials doses had been administered literally according to the claims of the petty patents, deprived the claimed invention of novelty. …

80 This passage is important because it presages their Honours' concern as to whether the prior documentary disclosure of mere dosages of taxol, within the range claimed in the invention, in reports on dosage safety, was enough to amount to an anticipatory disclosure of the invention that was claimed, which was a method of administering taxol to treat cancer.

81 This caused their Honours to turn to a number of the accepted case authorities in this area of discourse. Thus, like the trial judge, their Honours referred to the "reverse infringement" test

articulated by Aickin J in *Meyers Taylor Pty Ltd v Vicarr Industries Ltd* (1977) 137 CLR 228 (***Meyers Taylor***) at 235 and to the test stated by Lord Westbury in *Hill v Evans*, quoted above. As to the latter, their Honours also quoted the following further passages (45 ER at 1200):

> Apparent generality, or a proposition not true to its full extent, will not prejudice a subsequent statement which is limited and accurate, and gives a specific rule of practical application.
>
> The reason is manifest, because much further information, and therefore much further discovery, are required before the real truth can be extricated and embodied in a form to serve the use of mankind. It is the difference between the ore and the refined and pure metal which is extracted from it.
>
> Again, it is not, in my opinion, true in these cases to say, that knowledge, and the means of obtaining knowledge, are the same. There is a great difference between them. To carry me to the place at which I wish to arrive is very different from merely putting me on the road that leads to it. There may be a latent truth in the words of a former writer, not known even to the writer himself; and it would be unreasonable to say that there is no merit in discovering and unfolding it to the world.
>
> Upon principle, therefore, I conclude that the prior knowledge of an invention to avoid a patent must be knowledge equal to that required to be given by a specification, namely, such knowledge as will enable the public to perceive the very discovery, and to carry the invention into practical use.

82 The combined passages from *Hill v Evans* speak of the need for a prior documentary disclosure to provide information that is *equal* to the invention that is claimed, if the prior documentary disclosure is to be anticipatory and thereby deprive the invention of novelty. As *Hill v Evans* makes clear, equality in this context refers to both the *specificity* of the information and its *completeness*. Unless these twin qualities are present, the prior disclosure will not be sufficient to deprive the invention of novelty.

83 Thus, a prior documentary disclosure will not be anticipatory if it merely provides information at a level of generality which, while encompassing that which is claimed as the invention, nevertheless fails to identify the invention with sufficient specificity. The notion was explained by Parker J in *Flour Oxidizing* (at 457):

> But where the question is solely a question of prior publication, it is not, in my opinion, enough to prove that an apparatus described in an earlier Specification could have been used to produce this or that result. It must also be shown that the Specification contains clear and unmistakable directions so to use it.

84 In *General Tire* the Court of Appeal, in a similar vein, said (at 485-486):

> When the prior inventor's publication and the patentee's claim have respectively been construed by the court in the light of all properly admissible evidence as to technical matters, the meaning of words and expressions used in the art and so forth, the question whether the patentee's claim is new … falls to be decided as a question of fact. If the

> prior inventor's publication contains a clear description of, or clear instructions to do or make, something that would infringe the patentee's claim is carried out after the grant of the patentee's patent, the patentee's claim will have been shown to lack the necessary novelty, that is to say, it will have been anticipated. The prior inventor, however, and the patentee may have approached the same device from different starting points and may for this reason, or it may be for other reasons, have so described their devices that it cannot be immediately discerned from a reading of the language which they have respectively used that they have discovered in truth the same device; but if carrying out the directions contained in the prior inventor's publication will inevitably result in something being made or done which, if the patentee's patent were valid, would constitute an infringement of the patentee's claim, this circumstance demonstrates that the patentee's claim has in fact been anticipated.
>
> If, on the other hand, the prior publication contains a direction which is capable of being carried out in a manner which would infringe the patentee's claim, but would be at least as likely to be carried out in a way which would not do so, the patentee's claim will not have been anticipated, although it may fail on the ground of obviousness. To anticipate the patentee's claim the prior publication must contain clear and unmistakable directions to do what the patentee claims to have invented: *Flour Oxidizing Co. Ltd. v. Carr & Co. Ltd. (1908)* 25 R.P.C. 428 at 457, line 34, approved in *B.T.H. Co. Ltd. v. Metropolitan Vickers Electrical Co. Ltd. (1928)* 45 R.P.C. 1 at 24, line 1). A signpost, however clear, upon the road to the patentee's invention will not suffice. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee.

85 As the Full Court explained in *AstraZeneca v Apotex* at [294], the Court of Appeal's metaphor of planting the flag has been taken up in this Court. In *ICI Chemicals & Polymers Ltd v Lubrizol Corporation Inc* [2000] FCA 1349; 106 FCR 214, the Full Court at [51], after noting the metaphor, remarked that, in that case, the appellant's argument involved the skilled addressee rummaging through a "flag locker" to find a flag which the prior art possessed and could have planted. In *Apotex Pty Ltd v Sanofi-Aventis* [2008] FCA 1194; 78 IPR 485, Gyles J at [91] adopted a different metaphor when remarking that:

> … anticipation is deadly but requires the accuracy of a sniper, not the firing of a 12 gauge shotgun.

86 As the Full Court in *AstraZeneca v Apotex* remarked, each metaphor underlines the importance of the specificity required in order for a prior art document to anticipate an invention as claimed.

87 But even if the information given in a prior documentary disclosure is, in terms, sufficiently specific—at least as to part of what is claimed as the invention—it might not go far enough to disclose all the essential features of the invention. If the information fails to go far enough, the prior documentary disclosure will not be anticipatory so as to deprive the invention of novelty. Thus, in *Nicaro Holdings Pty Ltd v Martin Engineering Co* (1990) 91 ALR 513 at 528, Gummow J said:

> There was some discussion before us as to the significance of the reverse infringement test as a criterion for judging anticipation. In the *Meyers Taylor* case, *supra,* Aickin J was dealing with alleged anticipation of a combination patent; none of the alleged anticipations incorporated all the integers of any one of the claims. Therefore, as his Honour said (137 CLR at 235) none of them "could therefore possibly constitute an infringement". In such a situation, the adequacy of the reverse infringement test will be readily apparent, given the fatal effect upon an infringement suit of omission from the alleged infringement of an essential integer. But Aickin J described this test only as "generally" applicable. Where the alleged anticipation is a paper publication, particularly a prior patent specification, there may be ground for debate in a comparison with the specification in suit as to the presence of inessential integers and mechanical equivalents. King J pointed this out in his judgment at first instance in *Werner's* case, *supra* (IPR at 536; ALR at 702). There may also be dispute whether what has been disclosed sufficiently reveals an essential integer, in the light of the principles in *Hill v Evans* (1862) 4 De GF & J 288: see *Werner's* case (ALR at 683) per Lockhart J.

88 In *BMS v Faulding*, after discussing several authorities on anticipatory disclosure (including, as we have noted, *Meyers Taylor* and *Hill v Evans*, and also *Flour Oxidizing* and *General Tire*) Black CJ and Lehane J remarked:

> 67 What all those authorities contemplate, in our view, is that a prior publication, if it is to destroy novelty, must give a direction or make a recommendation or suggestion which will result, if the skilled reader follows it, in the claimed invention. A direction, recommendation or suggestion may often, of course, be implicit in what is described and commonly the only question may be whether the publication describes with sufficient clarity the claimed invention or, in the case of a combination, each integer of it. But in this case medical practitioners hardly needed to be told that it was possible to infuse a particular dose of taxol over three hours, or how to do it. Nor, equally obviously, is that the point of the claims. The claims of the earlier of the petty patents are for a method for administration of taxol to a patient suffering from cancer; the claims of the later one are for a method of treating cancer. In each case the method involves a particular regimen for the infusion of taxol. The context was that great difficulties had been encountered in using taxol, despite its known anti-carcinogenic properties, in the treatment of cancer, because of the drug's side effects. Each of the trials reported in the articles referred to was an investigation directed towards finding a solution of the difficulties: directed, particularly, to ascertaining safe dosage levels. But, though methods falling within the claims of the patents were used in each trial, none of the reports can be said to teach (a word which in this context encompasses direct, recommend and suggest) that which the petty patents claim.

89 Two things should be noted about this passage. First, when using the language of "teach", "direct", "recommend" and "suggest", Black CJ and Lehane J were not using—indeed, were not purporting to use—the statutory language of s 7(1)(a) of the Act which, relevantly to the present question, speaks of prior art information that is made publicly available in a single document. Thus, their Honours were not stating a statutory test. Rather, they were seeking to capture and explain the notion, conveyed by the cases, of the sufficiency of the disclosure that a prior art document must make before it can deprive an invention of novelty. This notion is

not elucidated by exploring the linguistic limits of "teach", "direct", "recommend" and "suggest" as ordinary English words. Indeed, it would be a distraction to do so. Nor would it assist to add to the catalogue of English words other words that might equally be used aptly to explain the sufficiency of the disclosure that must be made before a prior document can deprive an invention of novelty.

90 Secondly, the reason why, in their Honour's judgment, the reports of the Phase I trials were not anticipatory disclosures was because they were disclosures about finding a solution to the difficulties of ascertaining safe dosage levels of taxol. In short, in their Honours' view, the disclosures did not go far enough to disclose all the essential integers of the invention as claimed, which was directed to use of taxol, by means of a particular form of administration, to treat cancer. The challenge to novelty did not fail simply because the reports were about Phase I trials as such.

91 Having found that none of the reports of the Phase I trials were anticipatory disclosures, Black CJ and Lehane J turned to consider the two remaining publications—Rowinsky and Donehower, and the Huinink abstract. Their Honours summarised Rowinsky and Donehower as recording:

> 70 … a decision by the National Cancer Institute that future trials should utilise 24-hour infusions, together with pre-medication, and mentioned that the trials, leading to the claimed invention, were in progress: it mentioned them as trials the results of which might indicate whether a 24-hour infusion was indeed necessary and throw some light on the optimum therapeutic dose of taxol, particularly in patients who had previously received other therapy …

92 As to that disclosure, their Honours said:

> 70 … Applying the principles which we have discussed, that article is no more an anticipation than are the reports of the Phase I trials: it teaches the method no more than they do.

93 Their Honours then turned to consider the Huinink abstract from which their Honours quoted the following:

> 71 Toxicity of taxol so far consists of dose limiting neutropenia, general malaise, muscle cramps, alopecia and hypersensitivity reactions, maybe related to the carrier in so far used formulations: Cremophor. Due to these side effects and based on preclinical screening antitumor continues [sic] infusions of 24 hours have been used so far. Phase I and II studies revealed activity against cisplatin refractory ovarian cancer, breast cancer and lung cancer. Further studies to evaluate the feasibility of shorter infusion time, 3 hours versus 24 hours and a lower 135mg/m^2 versus a maximum tolerated dose of 175mg/m^2 are now in progress in relapsing ovarian cancer patients both in Canada and in Europe. Already more than 200 patients have been entered into this four-arm

> randomized, NCIC guided international study. Indeed, the 3 hours infusion time administration schedule proved to be feasible, if given concomitantly to profylactic [sic] measures as high dose dexamethasone, cimetidine and difenhydramine. This makes even outpatient treatment with this first available representative of this new class of antitumor agents possible. Major steps forward in medical oncology are rare. After doxorubicine in the seventies, and cisplatin and carboplatin in the eighties, taxol and its European pendant Taxotere ranks high to become the outstanding drugs of the nineties.

94 Their Honours found:

> 72 It was submitted that it was necessary to decide the question of anticipation by reference to what the skilled reader would have drawn from the abstract; and we were taken to evidence that skilled readers would have treated the words "feasibility" and "feasible" in the abstract as referring to safety, not efficacy. Even if that is right, however, other aspects of the abstract must be taken into account. We are told that earlier studies had revealed taxol's "activity against" certain forms of cancer; that the point of the studies then underway was to evaluate the "feasibility of shorter infusion time" and a lower dose "versus a maximum tolerated dose of 175mg/m^2". We are told (apparently) that what the tests have already revealed "makes even outpatient treatment with this first available representative of this new class of antitumour agents possible". In other words, it is already known that taxol is effective against certain cancers; it is known that 175mg/m^2 is a maximum tolerated dose; the purpose of the trial is to test the feasibility of a three hour infusion of that dose and a smaller dose; and the three hour infusion has already proved feasible, so that outpatient treatment has been demonstrated to be possible. Prudent practitioners might well take the view that they would prefer to await the final outcome of the trials, both as to efficacy and as to safety, before rushing to embrace the proposed method. But, in our view, there can be no serious doubt that the abstract teaches the shorter infusion period, with premedication, as a "treatment" of cancer. The necessary consequence, as it was conceded that the abstract was published in Australia before the priority date, is that the claimed invention lacked the novelty required by s 18(1)(b)(i). We note that that conclusion is consistent with the decision of the English Patents Court (to which we were not referred) concerning a similar European Patent (though on rather different evidence and under legislation which differs in significant respects from ours*): Bristol-Myers Squibb Co v Baker Norton Pharmaceuticals Inc* [1999] RPC 253.

95 We do not read *BMS v Faulding* as laying down any new or modified principle of anticipatory disclosure by the publication of prior art documents. Rather, the reasons for judgment must be taken as explaining, by reference to existing authority, why their Honours' factual conclusions differed from those reached by the trial judge in respect of the disclosures of six of the seven documents in question. Indeed, their Honours proceeded on the basis that they were undertaking an orthodox application of long-accepted legal principles. Importantly, we also note their Honours' acceptance (at [60]) that publication of a method of medical treatment may be an anticipatory disclosure even when it takes the form of a report of clinical trials.

96 In *Merck v Arrow*, the trial judge had found that certain articles published in *Lunar News* anticipated one or more claims of a patent directed to a method of treating or preventing osteoporosis in a human by administering specified doses of alendronate according to specified dosage schedules. One such article was published in the April 1996 issue of *Lunar News*, which included the following:

> One of the difficulties with alendronate is its low oral bioavailability. When taken with water in a fasting state, only about 0.8% of the oral dose is bio available. Even coffee reduces this by 60 % and a meal reduces it by > 85%. Alendronate must be taken, after an overnight fast, 30-60 minutes before breakfast. Subjects should remain seated or standing; a very small group of patients have reported some upper gastrointestinal distress if this is not done. This regime may be difficult for the elderly to maintain chronically. An intermittent treatment program (for example, one per week, or one week every three months), with higher oral dosing, *needs to be tested*. A sustained response has been demonstrated to intravenous administration of high dose alendronate.
>
> (Emphasis added.)

97 The words "needs to be tested" in the penultimate sentence of this passage provided a focus of attention for the patentee (Merck) which argued at trial, purportedly on the authority of *BMS v Faulding*, that "something that needs to be tested is not to anticipate that which is suggested". The trial judge dealt with that contention by reference to the passage from *BMS v Faulding* at [67], which we have quoted at [88] above. Specifically, the trial judge said:

> 107 … That statement of principle was based upon a review of certain of the authorities. Those authorities stand for the proposition that the claimed invention must be disclosed as such and not simply as a possibility. If the Lunar News article had said 'in view of these problems a continuous dosing schedule with various intervals greater than one day should be tested' it would not anticipate claim 3, even though a weekly dosage interval would be both technically and practically contemplated by that suggestion. On the contrary, here, the disclosure is quite precise and accords with the gist of the claimed invention. I do not accept the submission on behalf of Merck that the passage in question from *Faulding* adds an additional requirement for anticipation, namely that the publication should recommend the use of the invention as disclosed. That is not what the passage from *Faulding* says and it does not follow from the authorities analysed in that judgment. The essential difference in the treatment of the prior publications in *Faulding* lay in the view that one publication pointed clearly to one solution which was the invention rather than other publications which did not so point. That was a factual rather than a legal judgment and cannot be translated to the present circumstances.
>
> 108 In my opinion, the mere fact that a test of a defined solution to a problem is suggested does not avoid the disclosure being an anticipation. A drawing of a mechanical device with a caption 'should be tested for speed' would be an anticipation of a claim for that mechanical device. This point has particular cogency in relation to the present field. No invention can be used in the treatment of humans without extensive testing. In the present case, the patent was applied for before that testing had even commenced. The same reasoning

> is an answer to the argument advanced on behalf of Merck that the disclosure could not amount to an anticipation as no sensible medical practitioner would have acted upon it without adequate testing for safety. Even if that were correct (and it is contrary to some of the expert evidence led on behalf of Arrow) it would not affect the fact of disclosure having been made and being publicly available.

98 On appeal, Merck raised two contentions. First, the information in the articles in *Lunar News* did not form part of the prior art base because, in the language of s 7(1)(a) of the Act, they were not "publicly available". For the purposes of this appeal, that contention can be put to one side. Secondly, Merck contended that the articles did not provide a sufficient disclosure of the invention that was claimed in the relevant claims.

99 As to this matter (the sufficiency of the disclosures), the Full Court said (at [104]) that the contemplation of further experiments and testing was not necessarily fatal to a finding of anticipation. Their Honours also noted that Merck had approached the appeal by relying, by way of analogy, on a detailed examination of the various publications which the Full Court in *BMS v Faulding* held to be or, perhaps more importantly, held not to be, anticipations. As to this, the Full Court said:

> 109 Merck's argument sought to rely by way of analogy on a detailed examination of the various publications which the Full Court in *Faulding* held were or were not anticipations. But, as the primary judge in the present case pointed out, these were questions of fact. We do not read *Faulding* as support for any proposition of law that, in the case of pharmaceutical patents, no publication can amount to an anticipation unless clinical trials have been actually conducted.
>
> 110 In any event, *Faulding* at [67] speaks of a requirement that an alleged anticipation 'teach', in the sense of 'direct, recommend or suggest', that which is claimed. So a characterisation of an alleged anticipation as suggestion is not necessarily fatal to a novelty argument. Nor is it necessary that a reader, or even all readers, agree with the suggestion. Thus the fact that a Merck medical witness said that he would not have followed the Lunar News article for fear of side effects, does not if itself mean that disclosure was insufficient.

100 Importantly, the Full Court added:

> 111 As *Hill v Evans* … long ago established, equality of disclosure, anticipation as against patent, is the essential element …

101 The Full Court explained (at [112]) that the claimed method was "clearly conveyed" in the *Lunar News* articles and that "nothing additional" was required in order to deprive the invention of novelty.

102 The Full Court's understanding of *BMS v Faulding* accords with our own understanding. We do not accept, therefore, that *Merck v Arrow* was wrongly decided. *BMS v Faulding* was a case

dealing with the sufficiency of particular disclosures as anticipations of the invention that was claimed. It turned on an evaluation of the facts of the case, not (as we have said) on any new or modified principle of anticipatory disclosure. We read both cases as proceeding on the acceptance and application of well-established principles that are not in doubt.

103 As we have noted, the substance of Mylan's submission in this appeal is that the ACCORD Protocol could not anticipate the invention as claimed because it advanced no more than a reasoned hypothesis for treatment, not a method of treatment as such.

104 We do not accept that a documentary disclosure containing an hypothesis cannot be an anticipatory disclosure that deprives an invention of novelty. In such a case the question, simply put, remains: what does the prior document disclose? The occasion on which, or the context in which, a particular documentary disclosure is made may well inform the interpretation of the document's content. But if, as a matter of interpretation, the document nonetheless discloses that which is later claimed as an invention, that disclosure will anticipate the invention and deprive it of novelty.

105 Having reviewed previous clinical data, the authors of the ACCORD Protocol arrived at the primary hypothesis that a therapeutic strategy that uses a fibrate to lower triglyceride levels and raise HDL-C levels in patients already receiving a statin drug for treatment of LDL-C levels *will* reduce the rate of development or progression of diabetic retinopathy compared to a strategy in which a statin alone is used. It is, of course, true that a study based on the ACCORD Protocol was to be conducted to test the hypothesis. But it is equally true that, by proposing the study, according to the Protocol and its hypothesis, there was a disclosure that fenofibrate was to be deliberately administered with a statin with the aim of preventing or treating diabetic retinopathy in patients in need of such treatment. That is, plainly, the method of treatment that the ACCORD Protocol instructed practitioners participating in the study to carry out. Equally clearly, that was a method of treatment claimed in claim 7 and, more specifically, the method of treatment claimed in claim 10 of the 711 patent. It was also a method of treatment claimed in claim 11 of the 711 patent (there being no issue taken on appeal that the ACCORD Protocol also disclosed one of the particular dosages referred to in that claim). Therefore, the ACCORD Protocol disclosed the claimed method. Nothing additional was required in order for the Protocol to function as an anticipatory disclosure. The disclosure of the Protocol's instruction to carry out the purposeful administration of fenofibrate at the

claimed dosages and with a statin was not diminished because a trial to validate the hypothesis was in contemplation.

106 It is important to stress that validation of the ACCORD Protocol's hypothesis was certainly not required in order to achieve the equality of disclosure referred to in *Hill v Evans*. Looked at from a different perspective, it is not a requirement for a patentable invention that the invention, as claimed, be based on scientific proof or substantiation: *Generic Health Pty Ltd v Bayer Pharma Aktiengesellschaft* [2018] FCAFC 183; 267 FCR 428 at [135]. That being so, no greater requirement is imposed on a prior documentary disclosure in order for it to be anticipatory. What is required is that the prior document discloses that which is subsequently claimed as an invention. If that is disclosed, the invention cannot be new. If it should also be proved that the invention is not useful (for example, a claimed method of medical treatment is wholly or partly ineffective), then the patent can be challenged on that basis as well. But that raises a separate and distinct ground of invalidity.

107 Here, the method of treatment claimed in claims 7, 10 and 11 was not new because the prior-published ACCORD Protocol disclosed it. We mention claim 7 because, even though Mylan does not seek to support claim 7 under these grounds of appeal, the method of treatment claims it does seek to support—claims 10 and 11—are dependent on claim 7. Mylan does not suggest that the other claim it seeks to support under these grounds—claim 5 (the Swiss type claim)—should be treated differently from claims 10 and 11 in this respect.

108 As we have noted, Mylan called in aid the analysis in *InterPharma*, which found that the patient consent form used in Phase II trials—the 249 Form—was not an anticipatory disclosure of the use of dexmedetomidine to sedate a patient in an ICU. There are certainly passages in that analysis which support the way in which Mylan couched its submissions in this case. For example, the trial judge in that case referred (at [419]) to the fact that the 249 Form recorded a proposal for a trial to evaluate an hypothesis, namely whether use of dexmedetomidine in ICU sedation was safe, effective and dose titratable. The trial judge also referred (at [422]) to the fact that the 249 Form disclosed only the possibility of the use of dexmedetomidine as an ICU sedative and that a study was to be conducted to evaluate that possibility. The trial judge considered the disclosures of the 249 Form to be different in substance, and hence in legal effect, from the disclosures in *BMS v Faulding* and *Merck v Arrow* that were found to be anticipations. The correctness of that factual conclusion is not before us.

109 While comparisons with other case examples can be instructive, at root is the evaluation of particular evidence, and the consequent findings of fact based on that evidence, in each case. For the reasons we have given, we are not persuaded that the primary judge erred in the conclusion to which he came as to the substance and legal effect of the disclosures in the ACCORD Protocol. Therefore, Grounds 5 – 7 of the appeal fail.

110 Before departing from these grounds of appeal, we record that, in the course of oral argument, and after inquiry by the Full Court, Mylan also referred to two United Kingdom authorities which, it submitted, supported its position that the ACCORD Protocol could not anticipate the invention as claimed because it advanced no more than a reasoned hypothesis for treatment, not a method of treatment as such: *Regeneron Pharmaceuticals Inc v Genentech Inc* [2012] EWHC 657 (Pat); *Hospira UK Limited v Genentech Inc* [2015] EWHC 1796 (Pat); [2016] RPC 1. Mylan's written submissions also referred to *Hospira UK Ltd v Genentech Inc* [2014] EWHC 1094 (Pat). Leave was granted to the parties to file written submissions dealing with these cases following the hearing of the appeal.

111 These cases do provide some broad support for Mylan's position in that they accept that, in the case of Swiss type claims and purpose-limited product claims allowed under the European Patent Convention 2000, novelty will not be destroyed merely by a prior disclosure that a pharmaceutical compound (or combination of compounds) might have the therapeutic effect that the patent in suit claims for that compound or combination. In each case, anticipation was not established because the prior disclosure did not also disclose that the therapeutic effect *would* be achieved. However, in reasoning to that conclusion, it is important to note that, in each case, the court proceeded on the case law of the Boards of Appeal of the European Patent Office, which holds that the actual achievement of the therapeutic effect is a functional technical feature of the claim, as opposed to a mere statement of purpose or intention. In other words, the claim is read as *achieving* the therapeutic effect. The claim thus imports an element of established efficacy. Building on this, the case law further holds that, in order to anticipate, the prior art must disclose the achievement of the therapeutic effect itself or a pharmacological effect directly and unambiguously underlying that therapeutic effect. It is apparent, therefore, that the principles on which the court proceeded in each case are not the principles developed under Australian case law as applied in *BMS v Faulding* and *Merck v Arrow*.

THE 711 PATENT: GROUNDS 10 – 15

The primary judge's reasons

112 The primary judge found:

> 248 In my opinion, the notional skilled team would have been directly led by ETDRS 22 to try fenofibrate (because of its effectiveness in reducing elevated triglyceride levels and increasing HDL cholesterol levels) in combination with statins (because of their effectiveness in reducing elevated LDL cholesterol levels) in the expectation that this might well prevent or slow the development or progression of retinal hard exudates.

113 This finding was an application of the reformulated "Cripps question" referred to and accepted in *Aktiebolaget Hässle v Alphapharm Pty Ltd* [2002] HCA 59; 212 CLR 411 (***Hässle v Alphapharm***) at [53]. The specific question that the primary judge posed in that regard was:

> 194 Would the notional team at the relevant date, in all the circumstances, which include a knowledge of all the relevant prior art, directly be led as a matter of course to try fenofibrate (whether alone or combination with a statin) as a medicament for use in the prevention or treatment of diabetic retinopathy in the expectation that it might well produce a useful or better alternative to other therapies used for that purpose?

114 In arriving at his finding, the primary judge noted that ETDRS 22 provided support for the hypothesis that the use of a lipid-lowering agent for the treatment of hyperlipidaemia may well prevent or slow the development or progression of retinal hard exudates. The primary judge accepted that ETDRS 22 was an observational study that was not designed to evaluate the effectiveness of any relevant pharmacological treatment on hard exudates or diabetic retinopathy more generally. But, the primary judge said, it still provided clinically important evidence pointing to an association between lipid levels and hard exudates. The primary judge accepted that, as at 10 November 2005, statins were the preferred and most widely prescribed lipid-lowering agents. However, as at 10 November 2005, fenofibrate was a well-known lipid-lowering agent that was well-suited for use in the treatment of patients with elevated triglycerides and low HDL-C levels. It was also part of common general knowledge that fenofibrate was an effective cholesterol lowering drug that was approved for use in Australia for the treatment of hypercholesterolaemia.

115 At trial, Mylan submitted that the reformulated Cripps question should be answered negatively. It argued that the person skilled in the art would discount an association between elevated triglyceride levels and hard exudates. This submission was based on the following argument. According to Mylan, ETDRS 22 had reported that triglyceride levels were not associated with the presence of obvious retinal hard exudates in patients enrolled in the ETDRS at the

commencement of the study (baseline). Further, the person skilled in the art would understand from ETDRS 22 that serum lipid levels of patients enrolled in the study were only collected at its commencement. Therefore, the person skilled in the art would not know whether the development of retinal hard exudates in patients over the course of the study was related to other factors that occurred during the study period, such as poor glycaemic control.

116 Mylan also submitted that the person skilled in the art would not consider that the association between lipid values collected at the commencement of the study and the development of retinal hard exudates over the course of the study were reliable. According to Mylan, at most the person skilled in the art would focus on associations between hard exudates, total cholesterol and LDL-C levels because those lipid fractions were known to fluctuate less with poor glycaemic control than triglycerides.

117 Mylan further submitted that, even if the person skilled in the art had considered it worthwhile to reduce serum lipid levels on the basis of what was stated in ETDRS 22, that person would have been directly led to use statin therapy, not fibrate therapy; even then, based on common general knowledge as at 10 November 2005, the person skilled in the art would not have had the requisite expectation of success that administering a statin would have a beneficial effect on the prevention or treatment of diabetic retinopathy. If the person skilled in the art had been directly led to use fibrate therapy, the expectation of success would have been even lower than for statins.

118 The primary judge rejected these submissions. He noted that the methodology employed in the study, which required adjustments for certain variables, might make it difficult to identify the existence of an independent association between triglyceride levels and hard exudates in circumstances where blood lipid levels were only measured at the commencement of the study. However, the primary judge accepted evidence given by Professor Carter, a consultant endocrinologist with particular expertise in the diagnosis and management of diabetes, that ETDRS 22 showed a significant association between high triglycerides at baseline and the development of hard exudates during the study. We note, parenthetically, that the passage from ETDRS 22 we have quoted at [54] above makes clear the authors' conclusion that patients with elevated serum triglyceride levels, who did not have obvious retinal hard exudates at baseline, were at increased risk of developing hard exudates during follow-up. We also note that, contrary to Mylan's submission, the authors of ETDRS 22 did not state that elevated triglyceride levels were not associated with the presence of obvious retinal hard exudates at the

commencement of the study. What the authors did state was that those patients who had elevated serum total cholesterol or elevated LDL-C levels were more likely to have retinal hard exudates at the commencement of the study, based on a regression analysis that had been undertaken which showed that, at baseline, only total cholesterol and LDL-C levels were statistically significantly associated with the presence of hard exudates.

119 The primary judge reasoned that, while the methodology of ETDRS 22 was less than perfect, Mylan had overstated the significance of any methodological shortcomings. Apart from Professor Carter's evidence, the primary judge noted the evidence given by Dr Beaumont, a consultant ophthalmologist, that the observations in ETDRS 22 were highly credible; the evidence given by Professor O'Brien, an endocrinologist, that ETDRS 22 was clinically important; and the evidence given by Professor Mitchell, an ophthalmologist, that, based on ETDRS 22, it would be reasonable to think that fenofibrate "could have benefit for the eye in people with diabetic retinopathy" and that practitioners prescribing fenofibrate for the purpose of lowering lipids could reasonably do so in the belief that this may also help to preserve a patient's vision.

120 The primary judge also rejected a submission by Mylan that, at 10 November 2005, the person skilled in the art would have been deterred from using fibrates in combination with statins because of a concern about interactions between the two. In this connection, the primary judge noted that guidelines issued by the National Health and Medical Research Council (**NHMRC**) in 2004 for the management of type 2 diabetes specifically sanctioned treatment using a statin and fibrate in patients with moderate to marked elevation of both LDL-C and triglycerides. The guideline did refer to an increased risk of myositis (inflammation of the muscles) with this treatment, but the primary judge noted that this did not deter either Professor Carter or Professor O'Brien from prescribing combination therapy where appropriate.

121 As to Mylan's submission that, if the person skilled in the art considered it worthwhile to reduce serum lipid levels in order to prevent or slow the development of hard exudates statins would have been used, the primary judge noted that there were patients who were intolerant of statins (in circumstances where statin therapy was the first line of treatment for elevated cholesterol levels). As we have noted, it was common general knowledge, as at 10 November 2005, that fenofibrate was also an effective cholesterol-lowering drug that had been approved for use in Australia for the treatment of hypercholesterolaemia. The primary judge noted that it was no answer to argue that the person skilled in the art might first have gone down the pathway of

trying statins rather than fibrates. This did not mean that it would not have been worthwhile to conduct a trial using fibrates.

122 Finally, the primary judge said that Professor O'Brien had given evidence that, in his assessment, the prospect of fenofibrate proving effective in the treatment of diabetic retinopathy was "no better than fifty – fifty". The primary judge noted that this statement seemed to imply that there was no support at all in ETDRS 22 for the hypothesis that the use of a lipid-lowering agent in patients with elevated serum lipid levels would prevent or slow the development or progression of retinal hard exudates. The primary judge noted that this is not what ETDRS 22 disclosed and that the reformulated Cripps question could receive an affirmative answer even if the person skilled in the art assessed the prospects of success at less than "fifty – fifty".

The appeal

123 In oral submissions, Mylan summarised Grounds 10 – 15 as addressing two broad contentions. The first was that the primary judge misconstrued the evidence on which he relied to support his finding of lack of inventive step. This contention is covered by Grounds 11, 12 and 13 of the notice of appeal. Ground 11 seizes on various findings made by the primary judge (a number of which Mylan considered to be positively supportive of its case) to allege that his Honour erred in finding that the person skilled in the art would have been directly led by ETDRS 22 to try fenofibrate in combination with statins in the expectation that this might well prevent or slow the development or progression of retinal hard exudates. In summary, those findings are:

(a) It was not common general knowledge that lipid-lowering agents had a beneficial effect on the underlying causes of diabetic retinopathy (at [221]).

(b) As at 10 November 2005, fibrates, including fenofibrate, were not prescribed for the treatment of hypercholesterolemia if target lipid levels could be achieved by the use of a statin unless there were some other reason why a patient's elevated lipid levels could not be treated with a statin (for example, because of side-effects) (at [222]).

(c) ETDRS 22 did not, and was not designed to, determine whether lipid-lowering agents could be used to reduce the risk of the development or progression of hard exudates or diabetic retinopathy more generally; nor did it demonstrate a

causative link between blood lipid levels in the development or progression of hard exudates (at [228]).

(d) ETDRS 22 was an observational study that was not designed to evaluate the effectiveness of any relevant pharmacological treatment on hard exudates or diabetic retinopathy more generally (at [231]).

(e) As at 10 November 2005, statins were the preferred, and most widely prescribed, lipid-lowering drugs (at [231]).

(f) There were no pharmacological treatments that had been shown to prevent or slow the development of hard exudates or diabetic retinopathy more generally (at [231]).

(g) The authors of ETDRS 22 adjusted for certain variables. This was necessary given the data they had, but which was less than perfect, particularly if they were seeking to determine whether there was an association between elevated levels of triglycerides and retinal hard exudates that is independent of blood glucose levels. Patients with high triglyceride levels generally have high blood glucose levels (known to be causally related to diabetic retinopathy) which may make it difficult to identify the existence of an independent association between triglyceride levels and hard exudates in circumstances where blood lipid levels were only measured at the commencement of the study (at [236]).

124 Ground 12 is largely to the same effect as Ground 11: the primary judge erred in relying on ETDRS 22 as evidencing that the person skilled in the art would have expected that fenofibrate, alone or with a statin, might well produce a useful or better alternative than other therapies to prevent or treat diabetic retinopathy. Ground 13 alleges that the primary judge gave "improper weight" to the evidence given by Dr Beaumont and Professor Carter.

125 The second contention was that the primary judge misunderstood the expectation of success expressed in the reformulated Cripps question. This contention is covered by Grounds 14 and 15 of the notice of appeal. Ground 14 challenges the primary judge's finding that the reformulated Cripps question may receive an affirmative answer if the person skilled in the art "has prospects of success that are less than fifty – fifty". Ground 15, relatedly, alleges that, in answering the reformulated Cripps question, the primary judge gave no or insufficient weight to Professor O'Brien's evidence that the prospect of fenofibrate proving effective in the treatment of diabetic retinopathy was "no better than fifty– fifty".

126 For completeness we note that Ground 10 of the notice of appeal (not specifically referenced by Mylan to either contention) simply alleges that the primary judge erred in finding that the relevant claims of the 711 patent were invalid for lack of inventive step in light of the common general knowledge. It can be taken that Grounds 11 – 15 provide the particulars for Ground 10.

127 Although addressing both contentions, Mylan developed its submissions around the second contention. With reference to *Hässle v Alphapharm*, it submitted that the requisite expectation of success, expressed through the reformulated Cripps question, is not met by acknowledging the existence of "possibilities". Rather, a probability of success is required. Mylan submitted that the primary judge had made a "crucial" error of law in his application of the reformulated Cripps question by proceeding on the basis of "possibilities" alone.

128 Mylan submitted that this crucial error was compounded by errors in fact-finding. One area of focus for Mylan in this regard was the primary judge's finding (at [221] and [242]) that Professor O'Brien, who had been called by Mylan, had accepted that the results presented in ETDRS 22 were statistically significant and clinically important. The following findings (at [249]) provided another area of focus:

> 249 I should add that Professor O'Brien said in his oral evidence that, in his assessment, the prospect of fenofibrate proving effective in the treatment of diabetic retinopathy was "no better than fifty-fifty". That statement seems to imply that there was no support at all in ETDRS 22 for the hypothesis that the use of a lipid-lowering agent in patients with elevated serum lipid levels would prevent or slow the development or progression of retinal hard exudates. For the reasons I have given I do not think this is correct. Nor do I think the use of a percentage based analysis is useful in this case especially when it is expressed in terms of "no better than fifty-fifty". The modified Cripps question may receive an affirmative answer even if the hypothetical person (or team) skilled in the art has prospects of success that are less than fifty-fifty. Whether or not it does so must depend on the circumstances of each case.

129 Mylan referred to a number of passages in the oral evidence given concurrently by Professor O'Brien and Professor Carter (who had been called by Sun Pharma) to advance the proposition that Professor O'Brien's acceptance that ETDRS 22 was statistically significant and clinically important was made with reference to its disclosure concerning the lowering of total cholesterol, not the lowering of triglycerides. In Mylan's submission, the same was also true of Professor O'Brien's assessment of the chance (no better than "fifty-fifty") that lowering serum lipids would prevent or slow the development or progression of retinal hard exudates. According to Mylan, Professor O'Brien's evidence in this regard was directed to the possible

effects of lowering total cholesterol not, once again, to the possible effects of lowering triglycerides. Mylan also submitted that Professor O'Brien's evidence must be understood in light of the extent, limitations and shortcomings of the disclosures made in ETDRS 22.

130 The thrust of these submissions was that, properly understood, ETDRS 22 may have disclosed a possible association between elevated serum total cholesterol and the development or progression of hard exudates. However, according to Mylan, there were "difficulties in relation to the assessment on triglycerides". These difficulties stemmed from two matters.

131 The first matter was that patients who present with high triglycerides may have poor diet control, thereby indicating likely poor glycaemic control. Poor glycaemic control is the most critical risk factor for the development and progression of diabetic retinopathy. ETDRS 22 was conducted over seven years with serum lipids measured at baseline but without knowledge of the patients' glycaemic control during that time. For Professor O'Brien (although not for Professor Carter), this meant that the strength of the association drawn by the authors of ETDRS 22 between high triglycerides and the development of hard exudates, was significantly undermined.

132 The second matter was what Mylan called, in oral submissions, the "inconsistency" between "the baseline hard exudate existence" and the later development of hard exudates, during the course of the study, with patients presenting with elevated serum triglycerides. As we have noted, ETDRS 22 found that only total cholesterol and LDL-C levels were statistically significantly associated with the presence of hard exudates at baseline. Mylan argued that, consequently, the person skilled in the art would have considered the association between elevated serum triglycerides and the development of hard exudates to be weaker because of these findings. Mylan submitted that, although the primary judge considered the first matter when addressing the methodological difficulties of ETDRS 22, his Honour did not address the "inconsistency" presented by the second, related matter.

133 In its written submissions, Mylan put the matter slightly differently, although substantively to the same effect. It argued that the only "consistent" association identified in ETDRS 22 was between increased levels of total cholesterol and LDL-C, and the existence of hard exudates—"consistent", it would seem, because the associations were observed at baseline and at follow-up. On the other hand, ETDRS 22 disclosed no association between HDL-C and hard exudates, and an association between elevated triglycerides and hard exudates only at follow-up, not at baseline.

134 It will be apparent that these submissions reflect, in large measure, the case which Mylan advanced at trial, but which the primary judge rejected, on the interpretation of ETDRS 22.

135 In addition, Mylan submitted that the primary judge's reliance on Professor Carter's evidence was misplaced. At [237], the primary judge referred to the fact that Professor Carter had acknowledged that there were difficulties with the "ETDRS 22 methodology", but recorded Professor Carter's statement that one could not get away from the fact that ETDRS 22 recorded a significant association between high triglycerides at baseline and the development of hard exudates during the study. In Mylan's submission, Professor Carter's opinion on this score was affected by other knowledge he had gained of previous work that was not part of the common general knowledge. The primary judge acknowledged this possibility (at [239]):

> 239 It is apparent that Professor Carter's thinking was very much informed not only by ETDRS 22, but also by various articles none of which was suggested to form part of the common general knowledge, a point that was understandably seized upon by the applicants in their submissions. However, that is not a basis for rejecting Professor Carter's view that ETDRS 22 showed a significant association between high triglycerides at baseline and the development of hard exudates.

136 However, Mylan submitted that, in making that finding, the primary judge did not properly deal with reservations that Professor Carter either had, or ought to have had, in light of Professor O'Brien's evidence. Mylan submitted that, overall, it was not open to the primary judge to "downplay the evidence of Professor O'Brien and rely on Professor Carter in the way he did".

137 Mylan also criticised the primary judge's reliance on Professor Carter's evidence concerning the theoretical basis on which the association reported in ETDRS 22 could be supported. Professor Carter's theoretical basis was that if retinal hard exudates are lipids which have leaked into the macula, a beneficial effect might be achieved by reducing lipid levels in the patient's blood, particularly with respect to elevated triglyceride levels. At [240], in apparent acceptance of this theoretical underpinning, the primary judge referred to Professor Carter's reasoning as "simple". Mylan submitted that Professor Carter's reasoning was "simplistic" and not shown to be part of common general knowledge. Moreover, his theoretical basis was not referred to in ETDRS 22.

138 Mylan also submitted that the primary judge had made an error in fact-finding at [241] in stating:

> 241 ETDRS 22 showed a relationship between progressive high risk proliferative

> diabetic retinopathy over five years and baseline serum triglycerides in the age group 50-69, which is no doubt an important age group in the context of type 2 diabetes and diabetic retinopathy. It provided a reasonable basis to hypothesize that a reduction in elevated serum triglyceride levels achieved through the use of fenofibrate would reduce the risk of diabetic retinopathy at least in this age group.

139 Mylan submitted that ETDRS 22 did not make this disclosure, arguing that the primary judge probably confused ETDRS 22 with the ACCORD Protocol, where that statement can be found.

140 As to the primary judge's reliance on Professor Mitchell's evidence, Mylan submitted that Professor Mitchell had expressed his view after a series of questions in relation to materials that were not common general knowledge. In short, Professor Mitchell's evidence was not based on ETDRS 22 alone. Mylan also submitted that Professor Mitchell's evidence in this regard did not rise above mere assertion.

141 As to the primary judge's reliance on Dr Beaumont, Mylan submitted that Dr Beaumont's (and Professor Carter's) understanding that the observations in ETDRS 22 were highly credible, "simply confirmed their preconceived bias in favour of the view that fenofibrate could be used to treat diabetic retinopathy". This submission was not developed in any way. Mylan submitted further that Professor Carter's and Dr Beaumont's opinions could not assist in any event. The primary judge had found (at [197]) that Dr Beaumont was not a particularly good proxy for a consulting ophthalmologist in the notional "team" (representing the person skilled in the art) because he was particularly creative and an independently-minded thinker who was the antithesis of the non-inventive worker in the field. The primary judge had found (at [230]) that Professor Carter was not someone who could be considered to be uninventive.

142 In summary, Mylan submitted that, at best, the person skilled in the art, on reading ETDRS 22, would see that there was an association between total cholesterol and hard exudates at baseline, but no such association between triglycerides and hard exudates. The person skilled in the art would consider there to be an "inconsistent association" between triglycerides and the development of hard exudates and would note that levels of glycaemic control were not measured over the period of the study. For those reasons, the person skilled in the art would not be concerned about the observations recorded with respect to elevated serum triglycerides and hard exudates. The person skilled in the art would be more concerned with the association between serum total cholesterol and the development of hard exudates, but even then would not be directly led to try even statins to prevent vision loss associated with retinal hard exudates, with the requisite expectation of success. Once again, Mylan referred to Professor O'Brien's

evidence. At the time that ETDRS 22 was published, patients with elevated lipid levels with diabetes were already being treated with lipid-lowering agents to reduce their risk of cardiovascular disease. Professor O'Brien had given evidence that, despite having "excellent lipid control", a significant number of his patients still developed diabetic retinopathy. Mylan submitted that the person skilled in the art would not consider the use of fenofibrate as anything more than "worth a try" and, indeed, would not even consider it "worth a try" where a statin was already being used because (according to Mylan) lipid-lowering would already have failed to prevent the development of diabetic retinopathy and fenofibrate would not be expected to provide any additional benefit over a statin.

Discussion

143 The primary judge's consideration of whether the claims in suit lacked an inventive step was based on the disclosures of ETDRS 22 and, as we have noted, an application of the reformulated Cripps question.

144 There can be no doubt that ETDRS 22 reported an association between the elevated serum triglyceride levels of patients participating in the study and the increased risk of those patients developing retinal hard exudates during follow-up over the course of the study. What was in contention between the parties was not the fact that that disclosure had been made but, rather, the nature and strength of that association as reported in ETDRS 22 and seen through the eyes of a person skilled in the art as at the priority date (10 November 2005), and whether that association was such that the person skilled in the art (represented by a notional team) would have been directly led as a matter of course to try fenofibrate (either alone or in combination with a statin) as a medicament for use in the prevention or treatment of diabetic retinopathy, in the expectation that it may well produce a useful or better alternative to other therapies used for that purpose. This was the question posed by the primary judge at [194], which we have also quoted above. It is to be remembered that, for the purposes of the 711 patent, the prevention of diabetic retinopathy included preventing the development or progression of hard exudates—hence, the significance of ETDRS 22 to the primary judge's ultimate answer to the question.

145 At trial, much of this debate centred on the concurrent evidence given by Professor O'Brien and Professor Carter. In making this observation, we do not ignore the evidence given by other witnesses, namely Professor Mitchell and Dr Beaumont. But the primary judge's reasons show that the evidence of Professor O'Brien and Professor Carter had the greatest influence on his

Honour's understanding of the significance of ETDRS 22 to the question he had posed. As the High Court observed at [52] in *Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 2)* [2007] HCA 21; 235 CLR 173 (quoting Lord Greene MR in *Raleigh Cycle Co Ltd v H Miller & Co Ltd [No 1]* (1946) 63 RPC 113 at 136) (***Lockwood No 2***), an inventive step is often an issue borne out by the evidence of experts.

146 There are some submissions advanced on appeal which we should address at the outset.

147 First, we do not accept that the primary judge misunderstood the reformulated Cripps question as one addressing the existence of mere possibilities. To address mere possibilities would be tantamount to accepting the approach, rejected in *Hässle v Alphapharm* (see at [66] – [76] and [78]), of determining the question of obviousness by asking whether a given step or given steps were "worth a try" or "well worth trying out" or "trying out various known possibilities". The fact that the primary judge did not adopt this approach is made abundantly clear by the terms in which his Honour posed the question at [194] (which Mylan does not criticise) and then answered it at [248]. Both passages specifically refer to the requirement of an expectation of success. Indeed, at [189], the primary judge expressly noted that a claimed invention is not obvious according to the legal standard expressed in s 7(2) of the Act merely because the person skilled in the art would consider that it was "worthwhile to try". Thus, the primary judge did not commit the "crucial" error of law that Mylan attributed to him.

148 Secondly, and relatedly, the primary judge did not err by eschewing a percentage-based analysis in reaching a view as to whether an appropriate expectation of success was established on the evidence before him. An invention claimed in a standard patent is to be taken to involve an inventive step unless the invention would have been obvious to the person skilled in the art, in light of the common general knowledge considered separately or, where permitted by s 7(3) of the Act, with certain prior art information: s 7(2). In the context of s 7(2) of the Act, the legal standard, expressed by the word "obvious", is a flexible and indeterminate standard which poses a question of fact to which there is often, perhaps usually, no single, right answer: *Hässle v Alphapharm* at [90] per McHugh J. Thus, in answering the question whether an invention is obvious, an evaluative judgment is called for and, in order to answer the question affirmatively, the Court must be persuaded that the invention, as it is claimed, is indeed obvious. As a general proposition, reasoning to such a conclusion is not assisted by a percentage-based analysis. The reformulated Cripps question is but an aid to answering the statutory question posed by s 7(2): *Generic Health Pty Ltd v Bayer Pharma Aktiengesellschaft* [2014] FCAFC 73; 222 FCR 336

at [71]. It cannot be considered in isolation from the ends it is designed to serve. It, too, involves the exercise of an evaluative judgment. With this function in mind, we are not persuaded that, when answering the question he had posed, the primary judge erred in concluding that a percentage-based analysis was not useful, especially when expressed in terms of "no better than fifty-fifty".

149 Thirdly, we are not persuaded that the primary judge erred in finding that Professor O'Brien had accepted that the results presented in ETDRS 22 were statistically significant and clinically important. This proposition was accepted by Professor O'Brien in cross-examination. Having considered the line of questioning which elicited this evidence, we are not persuaded that Professor O'Brien confined his acceptance of the proposition to only those findings in ETDRS 22 concerning subjects who, at baseline, presented with elevated levels of serum total cholesterol and LDL-C. That said, we accept that when Professor O'Brien proffered the opinion as to his expectations of success, it was with respect to an expectation that lowering of cholesterol would be useful in preventing the development of hard exudates. For example, Professor O'Brien gave this evidence:

> … The very strong predictor in the ETDRS was, in fact, cholesterol. It wasn't triglycerides. They were only significant for progression, and I've already mentioned my concerns about possible confounders, whereas I think the data supporting cholesterol is stronger than triglycerides. Clearly, if I were going to take a hypothesis from that trial, it would be that I would use a cholesterol-lowering drug, not a triglyceride-lowering drug to prevent the condition.

150 Professor O'Brien was then immediately asked to "give that hypothesis a level of expectation". He answered:

> Well, I mean, it would still be no better than fifty-fifty.

151 Earlier in his evidence, Professor O'Brien said:

> … My hypothesis would be that cholesterol-lowering might have a beneficial effect in diabetic retinopathy if it was confirmed that there was this association between cholesterol and hard exudates or retinopathy that was seen in the [ETDRS 22] study.

152 Once again, Professor O'Brien was asked to express his degree of expectation about that hypothesis proving to be true. He said:

> I would have a low expectation based on – I mean, I don't think this data is strong enough for me to have a high expectation. Expect – you know, you asked me do I expect something, then I would have to say it's more than 50 per cent likely that that would happen. I would not draw that that conclusion from that data.

153 We understand from this last answer that Professor O'Brien understood the word "expect" to require a likelihood expressed as greater than a fifty per cent chance and that he did not have that expectation with respect to the hypothesis he was asked about.

154 The primary judge said:

> 249 I should add that Professor O'Brien said in his oral evidence that, in his assessment, the prospect of fenofibrate proving effective in the treatment of diabetic retinopathy was "no better than fifty-fifty". That statement seems to imply that there was no support at all in ETDRS 22 for the hypothesis that the use of a lipid-lowering agent in patients with elevated serum lipid levels would prevent or slow the development or progression of a retinal hard exudates. For the reasons I have given I do not think that this is correct. …

155 We accept that the primary judge erred in his understanding of Professor O'Brien's evidence in this particular respect. Professor O'Brien was not expressing a view about the prospect of fenofibrate proving effective in the treatment of diabetic retinopathy. Rather, he was expressing a view about whether the lowering of cholesterol might have a beneficial effect in preventing the formation or progression of hard exudates. Further, he saw fenofibrate as a drug whose predominant therapeutic effect was to lower triglycerides, not cholesterol (although, as we have observed, fenofibrate was listed and also used as a cholesterol-lowering drug).

156 Notwithstanding this error, the focus of the primary judge's comment at [249] was whether, based on Professor O'Brien's evidence, it could be said that ETDRS 22 provided "no support at all" for the hypothesis that the use of a lipid-lowering agent in patients with elevated serum lipid levels would prevent or slow the development or progression of retinal hard exudates. The primary judge rejected the proposition that there was no support, if in fact that proposition was being advanced. We are not persuaded that his Honour erred in doing so, for the following reasons.

157 ETDRS 22 expressly states that the data obtained from the study suggested that a reduction of elevated serum lipid levels may help prevent vision loss associated with retinal hard exudates and that this may be an additional motivating factor for lowering serum lipid levels in persons with diabetes presenting with elevated serum lipids. Should there be any doubt about that matter, there was abundant evidence before the primary judge to support this reading of ETDRS 22. We do not think, however, that there is any doubt about what ETDRS 22 said. Indeed, Professor O'Brien did not dispute that matter. Professor O'Brien's evidence about his expectation of success, expressed as a percentage, was directed to his assessment of the strength of the association which ETDRS 22 reported with respect to patients with elevated serum total

cholesterol and LDL-C at baseline. Further, his evidence was that this association was stronger (albeit, no better than "fifty-fifty") than the association reported for patients who presented with elevated serum triglycerides at baseline and developed hard exudates at follow-up. This was because the development of hard exudates in these patients might be explicable by other means, namely poor glycaemic control. As we have said, the focus of the primary judge's comment at [249] was whether it could be said that ETDRS 22 provided no support for the broader hypothesis that the use of a lipid-lowering agent in patients with elevated serum lipid levels would prevent or slow the development or progression of retinal hard exudates. Therefore, when seen in its context, we are not persuaded that the erroneous attribution which the primary judge made in the first sentence of [249] of his reasons is material.

158 Fourthly, we are not persuaded that the primary judge did not consider Mylan's argument concerning the "inconsistency" between "the baseline hard exudate existence" in the later development of hard exudates, during the course of the study, for patients presenting with elevated serum triglycerides at baseline. So much is clear from the following passages of the primary judge's reasons:

> 233 The applicants submitted that the modified Cripps question should be answered in the negative for a number of reasons. The applicants submitted that although ETDRS 22 reported an association between elevated total cholesterol levels, LDL-C levels and triglyceride levels with the development of obvious retinal hard exudates in patients enrolled in the ETDRS over the course of the study, the notional team would discount the association with triglyceride levels because:
>
> (a) This association was inconsistent, in that triglyceride levels were not associated with the presence of obvious retinal hard exudates in patients enrolled in the ETDRS at the commencement of the study;
>
> (b) The notional team would understand from ETDRS 22 that the blood lipid levels of the patients enrolled in the study were only collected at the commencement of the study, and the associations reported in ETDRS 22 were only corrected (ie. adjusted) using blood glucose levels collected at the commencement of the study; and
>
> (c) The notional team would not know whether the development of retinal hard exudates in patients over the course of the study was related to other factors that occurred during the study period, such as poor glycaemic control.
>
> 234 According to the applicants' submission, the notional team would not consider that the association between lipid values collected at the commencement of the study and the development of retinal hard exudates over the course of the study were reliable. It was submitted that the notional team would (at most) focus on associations between hard exudates, total cholesterol and LDL-C levels, because those lipid fractions were known to fluctuate less with poor glycaemic control than triglycerides. This submission was essentially directed to the

> quality of the methodology used in the ETDRS 22 study and, in particular, its ability to reliably detect an association between retinal hard exudates and elevated levels of serum triglycerides against which fibrates were known to be particularly effective.

159 Consistently with this summary of Mylan's submissions, the succeeding paragraphs of the primary judge's reasons ([236] – [239]) address the association between elevated serum triglycerides at baseline and the *development* of hard exudates. Thus, the primary judge was well-seized of the fact that one of the planks in Mylan's case was that elevated serum triglyceride levels were not associated with the presence of obvious retinal hard exudates in patients enrolled in ETDRS 22 at the commencement of the study.

160 Fifthly, we do not accept that the primary judge's reliance on Professor Carter's evidence was misplaced. It is clear that the primary judge gave special attention to the fact that Professor Carter—who expressed the opinion that ETDRS 22 showed a significant association between high triglycerides at baseline and the development of hard exudates during the study— had given oral evidence about other observational studies that had shown a significant association between lipids and retinopathy. However, the primary judge was not persuaded that Professor Carter's view about what ETDRS 22 itself showed, should be rejected because he had also given evidence about other studies showing a significant association between lipid levels and retinopathy. The primary judge did not err in treating Professor Carter's evidence in that way. Moreover, we do not accept Mylan's related submission that the primary judge "played down" Professor O'Brien's evidence and placed undue reliance on Professor Carter's evidence. There is nothing in the expression of the primary judge's reasons, considered against the backdrop of the extensive passages in the transcript to which we were taken, that would lend support to that submission.

161 Sixthly, we are not persuaded that the primary judge erred by referring, at [240] of his reasons, to the theoretical basis that informed Professor Carter's reasoning (namely, if retinal hard exudates are lipids which have leaked into the macula, a beneficial effect might be achieved by reducing lipid levels in the patient's blood). Mylan's criticism of the primary judge for referring to this evidence is misplaced. As we read the primary judge's reasons, his Honour was doing no more than alluding to an apparently plausible, albeit simple, explanation for the association between elevated serum lipids and the development or progression of hard exudates reported in ETDRS 22, which was an element of Professor Carter's thinking. The primary judge was not seeking to suggest that Professor Carter's thinking, in this regard, was part of

the common general knowledge or that ETDRS 22 propounded a theoretical basis for the association that was observed.

162 In the last sentence of [240], the primary judge said:

> … The publication of ETDRS 22 raises the same question, particularly with respect to elevated triglyceride levels.

163 We accept that, in this sentence, the primary judge gave some prominence to the association drawn with respect to elevated serum triglyceride levels and that the use of the word "particularly" might not be apt. But we do not think that this bespeaks appealable error on the part of the primary judge. Overall, we think that Mylan has placed too much significance on this paragraph in the primary judge's reasoning.

164 Seventhly, we see no error in the primary judge's reliance on Professor Mitchell's evidence and Dr Beaumont's evidence. As we have noted, Mylan advanced a submission that Professor Mitchell's evidence was not based on ETDRS 22 alone and did not rise above mere assertion. We do not accept that submission. It is not supported by the passages of the transcript of Professor Mitchell's evidence to which we were taken in submissions. As to Dr Beaumont's evidence, and the contention that it was the product of preconceived bias in favour of the view that fenofibrate could be used to treat diabetic retinopathy, we simply repeat our earlier observation that Mylan's submission was not developed in any way. At [203] – [208], the primary judge referred to, and discussed, Dr Beaumont's evidence that he was prescribing fenofibrate before 10 November 2005 for the treatment of diabetic retinopathy. In these paragraphs, the primary judge also referred to Dr Beaumont's evidence that he was prescribing another fibrate (clofibrate) and other lipid-lowering drugs to slow or prevent the formation of retinal hard exudates. However, we were not taken to any particular passage in Dr Beaumont's evidence regarding the disclosures in ETDRS 22. No error has been demonstrated in the primary judge's finding (at [242]) that Dr Beaumont thought that the observations in ETDRS 22 were highly credible, notwithstanding any shortcomings in the methodology employed in the study. We would add that even Professor O'Brien considered ETDRS 22 to have been a well-conducted study which, as we have said, yielded results that were clinically important and statistically significant.

165 In the end, the primary judge did not accept Mylan's submission as to how the person skilled in the art would read and understand ETDRS 22 as at the priority date. Central to Mylan's case, both below and on appeal, was the contention that the person skilled in the art would not

be concerned about the observations recorded on ETDRS 22 with respect to the association between elevated serum triglycerides and the development of retinal hard exudates. There was clearly disagreement between Professor O'Brien and Professor Carter on that question. Despite Professor O'Brien's concerns about the study's methodology, and his lack of persuasion that ETDRS 22 supported a convincing basis to think that reducing serum triglycerides might prevent the development of retinal hard exudates, the primary judge was persuaded, on the basis of all the evidence before him, but with particular reference to Professor Carter's evidence, that the person skilled in the art would read ETDRS 22 as providing support for the hypothesis that the use of lipid lowering agents for the treatment of hyperlipidaemia may well prevent or slow the development or progression of retinal hard exudates and that this hypothesis would include the lowering of elevated serum triglyceride levels. In coming to that conclusion, the primary judge did not err by not attributing to the hypothetical person skilled in the art the particular concerns that Professor O'Brien actually had or the lack of persuasion he actually felt.

166 There is, however, one material finding in the primary judge's reasons which we accept was made in error. As we have noted, at [241] the primary judge found that ETDRS 22 showed a relationship between progressive high risk proliferative diabetic retinopathy over five years and baseline serum triglycerides in the age group 50 – 69, which his Honour found would have provided a reasonable basis to hypothesise that a reduction in elevated serum triglyceride levels achieved through the use of fenofibrate would reduce the risk of diabetic retinopathy, at least in that age group. We accept that ETDRS 22 made no such finding. Such a finding was reported in the ACCORD Protocol with reference to ETDRS 18, not ETDRS 22:

> The ETDRS has shown a relationship between progression to high risk proliferative DR over 5 years and baseline serum triglycerides in the age group 50-69. Progression was 23% higher in those with serum triglycerides > 190mg/dl versus those whose serum triglycerides were normal, after adjustment for 11 significant covariates. It might be noted parenthetically that in the type 1 diabetes DDCT Trial, although reduction in A1C levels appeared to be the major mechanism for the decrease in retinopathy produced by intensive glycemic management, the latter treatment also produced a significant decrease in serum triglyceride levels over the 6.5 years of follow-up. It is therefore reasonable to hypothesize that fibrate therapy which decreases serum triglycerides will reduce the risk of DR.

167 This error is material because the primary judge relied on the above passage as demonstrating a relationship, not merely an association, between progressive high risk proliferative diabetic retinopathy and elevated serum triglyceride levels. It is also clear that the primary judge acted on the express statement that it was reasonable to hypothesise that fibrate therapy which

decreases serum triglycerides will reduce the risk of diabetic retinopathy. This statement, linked with the stated relationship on which it is based, goes somewhat further than the disclosures made in ETDRS 22. Put simply, in his fact-finding the primary judge attributed to ETDRS 22 a disclosure which it did not make, which appears to have contributed to the ultimate finding that his Honour made at [248] of the reasons, when answering the question he had posed at [194].

168 We are satisfied, therefore, that Mylan has established appealable error with respect to the primary judge's finding at [241] of the reasons. The consequence is that we must decide the question of obviousness for ourselves. In undertaking that task, two preliminary observations should be made. First, although the primary judge was under a misapprehension as to one aspect of the evidence, it does not follow that the answer his Honour gave at [248] of the reasons was necessarily wrong. Secondly, the primary judge's other findings of fact remain. Those findings should not be ignored, particularly when made with the advantage of witnessing the development of the evidence on this topic through the dynamic process of experts giving their evidence, and exchanging their opinions, concurrently—an advantage not readily enjoyed by simply reading the transcript of the evidence. Therefore, due weight must be given to those findings. That said, it falls to the Full Court, acting as the appeal court, to make up its own mind as to whether, on the evidence, the invention as claimed is obvious and, therefore, lacks an inventive step: *Branir Pty Ltd v Owston Nominees (No 2) Pty Ltd* [2001] FCA 1833; 117 FCR 424 at [28] – [29]; *Optical 88 Ltd v Optical 88 Pty Ltd* [2011] FCAFC 130; 197 FCR 67 at [33]; *Aldi Foods Pty Ltd v Moroccanoil Israel Ltd* [2018] FCAFC 93; 133 IPR 375.

169 As we have noted, ETDRS 22 expressly states that the data obtained from the study suggested that a reduction of serum lipid levels may help prevent vision loss associated with retinal hard exudates and that this may be an additional motivating factor for lowering serum lipid levels in persons with diabetes in whom those levels are elevated. Indeed, ETDRS 22 stressed that the association observed may have important clinical implications, in circumstances where a clinical trial designed to evaluate the effects of lipid-lowering on retinal hard exudates or visual acuity was unlikely because lipid-lowering was already the standard care for persons with elevated serum lipid levels, with or without diabetes.

170 Although these observations were expressed in terms of elevated serum lipid levels, ETDRS 22 evaluated and reported on serum total cholesterol, LDL-C, HDL-C and triglyceride levels separately for association with the presence of hard exudates. Once again, ETDRS 22 reported

that patients with elevated serum total cholesterol, LDL-C *or* triglyceride levels, who did not have obvious retinal hard exudates at baseline, were at an increased risk of developing retinal hard exudates during follow-up.

171 The inclusion in this disclosure of patients with elevated serum triglycerides at baseline was not only express and separately reported, but of some importance. The evidence before the primary judge was that, as at 2004 (immediately before the priority date of the claims in suit), lipid abnormalities in patients with type 2 diabetes were characterised by raised fasting triglycerides and lowered HDL-C (i.e., hyperlipidaemia, not hypercholesterolaemia). The NHMRC's *National Evidence Based Guidelines for the Management of Type 2 Diabetes Mellitus – Part 7 Lipid Control in Diabetics* dated 16 September 2004 recommended that the first line therapy for patients with predominantly elevated triglycerides and low HDL-C was treatment with fibrates. It recommended that treatment with statins and fibrates should be considered in patients with moderate to marked elevation of both LDL-C and triglycerides. The primary judge made specific reference to this evidence at [246] of his reasons when rejecting Mylan's submission that, at the priority date, the person skilled in the art would have been deterred from using statins and fibrates in combination.

172 These facts support the primary judge's finding at [230] that ETDRS 22 not only pointed to an association between lipid levels and diabetic retinopathy, but provided support for the hypothesis that the use of a lipid-lowering agent for the treatment of hyperlipidaemia may well prevent or slow the development or progression of retinal hard exudates. As ETDRS 22 pointed out, this may be an additional motivating factor for lowering serum lipid levels in patients with diabetes. And, as we have remarked on a number of occasions, the evidence before the primary judge was that ETDRS 22 was not only common general knowledge, but a well-conducted study whose results were clinically important and statistically significant.

173 Thus, putting aside the primary judge's misplaced attribution to ETDRS 22 of the observations made in the ACCORD Protocol with reference to ETDRS 18, there was a substantial basis for concluding, as his Honour did at [248], that the notional skilled team (i.e., the person skilled in the art) would have been directly led by ETDRS 22 to try fenofibrate in combination with statins in the expectation that this might well prevent or slow the development or progression of retinal hard exudates. This is particularly so given (as the primary judge found at [222]) that fenofibrate was not only effective in reducing elevated triglyceride levels and increasing HDL-C levels, but was also an effective cholesterol-lowering drug (approved for use in Australia as

such as at the priority date) that was considered to be more effective at lowering cholesterol than other fibrates. Further, the primary judge's finding at [248] was supported by the expert evidence before him, notwithstanding the lack of support expressed through Professor O'Brien's concerns and reservations about the association that ETDRS 22 reported. As we have said, the primary judge did not err by not attributing to the hypothetical person skilled in the art Professor O'Brien's actual concerns and lack of persuasion.

174 Therefore, in light of all the evidence, we are persuaded that the primary judge's conclusion at [248] was correct and that his finding at [250] that the claims in suit were invalid for lack of inventive step, should stand. For these reasons, Grounds 10 – 15 of the appeal fail.

THE 711 PATENT: GROUNDS 1 – 4

The primary judge's reasons

175 The primary judge was not satisfied that the evidence supported a finding that the Swiss type claims in suit—claims 1, 5 and 6—would be infringed, assuming them to be valid.

176 Two issues were raised in Mylan's case in respect of the Swiss type claims. The first issue was whether a Swiss type claim can be infringed by the importation and supply in the patent area of a medicament that is manufactured outside the patent area. Mylan had submitted that such a claim could not be infringed in those circumstances. The primary judge rejected that submission, relying on the construction of the word "exploit" in s 13(1) of the Act, as found in *Apotex Pty Ltd v Warner-Lambert Company LLC (No 2)* [2016] FCA 1238; 122 IPR 17 at [296] – [298] and, on appeal, *Warner-Lambert Company LLC v Apotex Pty Ltd (No 2)* [2018] FCAFC 26; 129 IPR 205 at [167] – [168]. There is no appeal from that finding.

177 The second issue was whether a Swiss type claim can be infringed if the manufacturer has prepared the relevant medicament knowing that it is suitable for use in the treatment of the condition specified in the claim. Mylan had submitted that such a claim would be infringed in those circumstances. It said that the manufacturer's actual intention in making the medicament was irrelevant. In advancing that submission, Mylan relied on an observation made by Yates J in *Otsuka Pharmaceutical Co. Ltd v Generic Health Pty Ltd (No 4)* [2015] FCA 634; 113 IPR 191 (***Otsuka***):

> 172 For the purpose of determining infringement of a Swiss type claim, does it matter that the alleged infringer does not actually advertise or promote the medicament specifically for the therapeutic use defined in the claim? I do not think it necessarily does. The question is whether, objectively ascertained, the medicament that results from the claimed method or process is one that has the

> therapeutic use defined in the claim. The question is not really about how the alleged infringer markets its product, although, plainly, its conduct in that regard may well assist in determining, objectively, whether the accused product has the claimed therapeutic use.

178 The primary judge rejected that submission. First, his Honour noted that the passage in *Otsuka* on which Mylan relied was not addressing the question of the manufacturer's purpose or intention in making the medicament, albeit it was talking about the suitability of the medicament for a particular therapeutic use. Secondly, suitability for use, alone, could not be determinative of the question of infringement. The primary judge explained:

> 101 Suitability for use cannot be determinative of the question of infringement of a Swiss-style claim. If it were, it would render a person liable for infringement who manufactured a medicament for the purpose of using it to treat an indication which it had been used to treat before the priority date of the Swiss-style claim merely because the medicament might also be used for the purpose of treating a second indication that provided the novelty-conferring subject matter of the claim. If the applicants' submission is correct, there would be an infringement even if the manufacturer took steps to ensure that the product was not used to treat the designated condition, and had no reason to believe that it would be so used. I do not think there is any doubt that this would be an absurd result, and contrary to the policy behind modern patent legislation.

179 The primary judge said (at [102]) that the crucial question concerning the infringement of a Swiss type claim was whether the manufacturer had made or will make the medicament with the intention that it be used in the treatment of the designated condition. His Honour considered that that question was to be determined objectively in light of all the relevant facts and circumstances, including the medicament's approved product information and its labelling, and the pertinent characteristics of the market into which the medicament is to be sold. His Honour said:

> 103 … The fact that it may be reasonably foreseeable or even likely that a substantial portion of the product manufactured will be used to treat that condition is certainly not determinative at least not where the product is also used extensively in the treatment of other non-designated conditions.

180 As to the facts of the case before him, the primary judge noted that the Ranbaxy Products had been approved, originally, for the same indications as Mylan's fenofibrate (Lipidil) product—namely, the reduction in the progression of diabetic retinopathy in patients with type 2 diabetes and existing diabetic retinopathy. The product information for the Ranbaxy Products was subsequently amended to remove reference to diabetic retinopathy. The amended product information stated that fenofibrate was indicated as an adjunct to diet in the treatment of hypercholesterolaemia, and various types of dyslipidaemia, including that associated with type 2 diabetes.

181 Mylan had submitted that, even so, there were three matters that demonstrated that there was a sound medical basis for considering that the Ranbaxy Products were suitable to be administered for the prevention and/or treatment of retinopathy, in particular diabetic retinopathy (as specified in the claims in suit). First, the amended product information for the Ranbaxy Products said that those products were bioequivalent to Lipidil. Secondly, the product information for Lipidil stated that it was indicated for reducing the progression of diabetic retinopathy, and included details of the ACCORD Study and the FIELD Study. Thirdly, the product information for the Ranbaxy Products did not assert that those products were not indicated for diabetic retinopathy or were not bioequivalent to Lipidil for that purpose.

182 The primary judge accepted those facts but, for the reasons he had given earlier, did not consider that they addressed the point in issue. Further, they did not indicate that the Ranbaxy Products had been or would be made for the purpose of being used for the prevention or treatment of diabetic retinopathy. The primary judge concluded, therefore, that the infringement case based on the Swiss type claims must fail.

183 Because of its significance to one of Mylan's grounds of appeal (Ground 4), we note that the primary judge was satisfied that Mylan had established that the method of treatment claims in suit—claims 7, 10, 11 and 12—would be indirectly infringed by Sun Pharma supplying the Ranbaxy Products in the patent area, having regard to the operation of s 117(1) of the Act. This was because Sun Pharma had reason to believe that a significant portion of the Ranbaxy Products it proposed to supply would be used in a manner that would infringe those claims (i.e., for the prevention and/or treatment of retinopathy): see s 117(2)(b) of the Act.

184 In considering the question of infringement, the primary judge referred to the decision of the United Kingdom Supreme Court in *Generics (UK) v Warner-Lambert Company LLC* [2018] UKSC 56; [2018] RPC 21 (***Generics (UK) v Warner-Lambert***). His Honour observed:

> 96 … At the hearing of the appeal before the Supreme Court, the parties conceded that, as a matter of construction, a Swiss-style claim required a "mental element" in the sense that the manufacturer must have manufactured the relevant medicament with the intention that it would be used to treat the medical condition designated in the claim. The judgments given make clear that all members of the Supreme Court considered that this concession was rightly made. The crux of the debate before their Lordships was whether the mental element involved an objective or a subjective intention. The majority held that, properly construed, a Swiss-style claim requires that the manufacturer who makes the relevant medicament do so with the objective intention that it be used to treat the medical condition designated in the claim.

The appeal

185 Ground 1 of the notice of appeal simply alleges that the primary judge erred in finding that the Swiss type claims had not been infringed.

186 Ground 2 challenges the primary judge's finding that infringement of a Swiss type claim imports an "objective intention" on the part of the manufacturer of the medicament. In substance, this ground repeats the case on infringement which Mylan unsuccessfully advanced below.

187 Ground 3 alleges that, if the manufacturer's objective intention is required to be established, then the primary judge erred in finding that that intention had not been established in the present case.

188 Ground 4 relies on the finding which the primary judge made with respect to infringement of the method of treatment claims. Under this ground, Mylan contends that if the primary judge was satisfied that Sun Pharma had reason to believe that a significant portion of the Ranbaxy Products it proposed to supply in the patent area would be used in a manner that would infringe claims 7, 10, 11 and 12, then his Honour should have been satisfied that the manufacturer of the Ranbaxy Products made those products with the objective intention that they be used for the prevention or treatment of diabetic retinopathy.

189 As we have noted, in this appeal Mylan only seeks to advance infringement under claim 5, not the other Swiss type claims in contest below.

190 The decision of the Supreme Court in *Generics (UK) v Warner-Lambert* was front and centre of Mylan's presentation of this aspect of its appeal. We discuss that decision below. While submitting that the Full Court should be cautious in adopting the reasoning in that case (because it involved the application of the Protocol on the Interpretation of Article 69 of the European Patent Convention (the **Protocol**)), Mylan nevertheless submitted that certain parts of the Supreme Court's reasoning were of assistance in determining the correct approach to be applied under Australian law with respect to the infringement of Swiss type claims.

191 Mylan also submitted that the primary judge erred in his understanding of the decision: a majority did not import any mental element for the purpose of determining infringement but, rather, adopted an "outward presentation test"; no member of the Supreme Court imported an objective intention test; and, in any event, an objective intention test is determined by reasonable foreseeability.

192 Underlying Mylan's submissions was the question whether, as a matter of claim construction, a Swiss type claim imports a mental element with respect to the manufacturer's intention. If such an element is not imported then, in Mylan's submission, the question of infringement should be determined by an "outward presentation test" of the kind referred to in *Generics (UK) v Warner-Lambert*. It would be fair to say that this was Mylan's primary position in the appeal. It supported that position by arguing that intention is not an element of infringement; liability for infringement is strict. However, if such an element is to be imported, then Mylan submitted that infringement is to be determined by a "reasonable foreseeability" test which, on the evidence, would be satisfied in any event. Mylan submitted that the primary judge had noted, with reference to *Generics (UK) v Warner-Lambert* that an objective intention was to be determined by reference to a reasonable foreseeability test. It submitted that, inconsistently, his Honour did not apply that test.

Discussion

193 The Act classifies inventions as falling into one of two broad classes: inventions that are products, and inventions that are methods or processes. Swiss type claims are properly characterised as method or process claims. They are not product claims: *Otsuka* at [120].

194 As explained in *Otsuka* at [100] – [115], Swiss type claims derived from the need to accommodate and satisfy particular requirements for patentability which, formerly, applied under the European Patent Convention. These particular requirements are not, nor have they been, part of the Australian legal landscape. Nevertheless, patentees have sought Swiss type claims in their Australian patents. They have, perhaps, been motivated to do so because such claims provide an avenue, in addition to indirect infringement under s 117(1) of the Act, for suing to restrain the supply of competitive pharmaceutical products rather than seeking to restrain medical practitioners who prescribe, and patients who use, those products for medical treatment.

195 It is also important to bear steadily in mind that, while Swiss type claims are method or process claims, they are not method of treatment claims. The monopoly obtained through a Swiss type claim is in respect of the method or process of making a medicament. That process is complete upon manufacture. A Swiss type claim does not, in and of itself, create a monopoly that extends to a method of treatment using, for example, the medicament once made. This is the province of method of treatment claims.

196 Further, Swiss type claims are purpose-limited claims in the sense that the medicament resulting from the method or process is characterised by the therapeutic purpose for which it is manufactured, as specified in the claim. Claim 1 of the 711 patent is typical of such claims. It claims the use of fenofibrate (or a derivative thereof) for the manufacture of a medicament *for* the prevention and/or treatment of retinopathy, in particular diabetic retinopathy: see [37] above.

197 The specification of a therapeutic purpose imposes an important limitation on the scope of the claim. In theory, it is this limitation which supports the novelty, and hence the patentability, of the invention. Without this limitation, the claim would be invalid because its scope would be broadened to include old subject matter (bearing in mind that Swiss type claims are directed to methods or processes whose products are for second or later therapeutic uses). It is appropriate, therefore, to consider this purpose as one that confines the use of the method or process to the achievement of one end and one end only—a medicament for the specified therapeutic purpose; not a medicament for any other therapeutic purpose. Put another way, a Swiss type claim does not claim the invention in terms of a medicament that is useful for, or can be used for, the specified therapeutic purpose and other therapeutic purposes. In order to support its patentability, and preserve its validity, the invention, as claimed through a Swiss type claim, is necessarily more limited in scope.

198 The characterisation of the medicament by specification of the therapeutic purpose is, therefore, an essential feature of the invention as claimed. Like any other essential feature, it must be proved in order for infringement of the claimed method or process to be established.

199 The Supreme Court's decision in *Generics (UK) v Warner-Lambert* concerned the infringement of Swiss type claims for a second medical use of pregabalin (namely, for the treatment of pain, including inflammatory pain and neuropathic pain). Pregabalin was also supplied for non-patented indications (namely, for the treatment of general anxiety disorder (**GAD**) and epilepsy) for which there was a real and substantial market.

200 The appeal to the Supreme Court raised issues of validity (sufficiency of disclosure/plausibility) and infringement. The claims in suit were found to be invalid. Therefore, the question of infringement was, ultimately, moot (as happens to be the case here). Nevertheless, because of its importance, the question was considered by the Supreme Court.

201 Noting that Swiss type claims are purpose-limited claims, the parties presented their respective cases on the basis that infringement involves a particular mental element which is either actual or imputed. As initially presented on the appeal, the alleged infringer argued that the test of purpose was the manufacturer's subjective intention in making the medicament: did the manufacturer subjectively intend to target the patent-protected market? The patentee said that the test of purpose was an objective test, based on reasonable foreseeability: the manufacturer must be taken to intend the foreseeable consequences of its actions.

202 During the course of the appeal hearing, the parties altered their positions in various ways. But it was the broad dichotomy of actual intention versus imputed intention that formed the framework for the Supreme Court's consideration of the question.

203 The dictates of the Protocol were also relevant to the Supreme Court's consideration. To explain, s 125(1) of the *Patents Act 1977* (UK) (the **UK Act**) provides that a claim must be:

> … interpreted by the description and any drawing contained in [the] specification, and the extent of the protection conferred by a patent or application for a patent shall be determined accordingly.

204 Section 125(3) of the UK Act provides that the Protocol, as in force from time to time, applies for the purposes of s 125(1).

205 The Protocol is directed to Art 69 of the European Patent Convention. Article 69(1) states:

> The extent of the protection conferred by a European patent or a European patent application shall be determined by the claims. Nevertheless, the description and drawing shall be used to interpret the claims.

206 The Protocol states:

> Article 69 should not be interpreted as meaning that the extent of the protection conferred by a European patent is to be understood as that defined by the strict, literal meaning of the wording used in the claims, the description and drawings being employed only for the purpose of resolving an ambiguity found in the claims. Nor should it be taken to mean that the claims serve only as a guideline and that the actual protection conferred may extend to what, from a consideration of the description and the drawings by a person skilled in the art, the patent proprietor has contemplated. On the contrary, it is to be interpreted as defining a position between these extremes which combines a fair protection for the patent proprietor with a reasonable degree of legal certainty for third parties.

207 Lords Sumption, Reed, Hodge and Briggs held that, had the claims been valid, they would not have been infringed. However, they differed as to their reasons.

208 Lords Sumption and Reed held that the intention of the manufacturer was irrelevant, whether actual or imputed. The sole criterion of infringement was whether the product, as it emerged from the manufacturing process (including its labelling and accompanying leaflets), was presented as suitable for the use claimed in the patent. This is the "outward presentation test" referred to by Mylan, which it advocated in the present appeal. In *Generics (UK) v Warner-Lambert* it had been found at trial that the accused product was sold with patient information leaflets to the effect that it was for the treatment of seizure disorders and GAD. Therefore, on this basis, infringement was not established.

209 Lord Sumption (with whom Lord Reed agreed) discussed the competing views advanced by the parties as to the test to be applied to prove the manufacturer's intention. His Lordship noted difficulties in proof and policy should either the subjective intention test or objective (reasonable foreseeability) test be adopted: see at [74] – [81]. He also accepted that an outward presentation test was imperfect, but less imperfect than applying the other tests. His Lordship reasoned (at [86]) that an outward presentation test best served the application of the Protocol. Further, the imperfect nature of the protection conferred by the outward presentation test arose from the limitation inherent in the Swiss type claim:

> 86 … A person's exposure to liability for infringement depends on the purpose for which the patent-protected product was manufactured. The patentee's protection is therefore necessarily incomplete. A test which treated the claim as extending to the promotion of the product after its manufacture appears on the face of it to ignore the limitation. …

210 We understand his Lordship's reference in this passage to the "patent-protected product" as an intended reference to the medicament as a product that results from the patent-protected process.

211 Lords Hodge and Briggs held that infringement depended on the manufacturer's subjective intention: did the manufacturer of the medicament intend to target the patent-protected market? At trial, it had been found that this intention had not been established. Therefore, on this basis, infringement was also not established.

212 Lord Briggs reasoned that the simple foreseeability test primarily contended for by the patentee would not strike the correct balance required by the Protocol: see at [156] – [161]. But his Lordship was not persuaded that it would be appropriate to "abandon the search for an appropriate mental element altogether" by treating the purposive element of a Swiss type claim as conclusively determined by a review of the fully-manufactured product itself (including its

packaging, labelling and enclosed patient instructions) on the conceptual basis that the relevant purpose was an aspect of the physical characteristics of the product emerging from the manufacturing process: see at [163] – [171]. Foremost amongst Lord Briggs' reasons was the fact that a Swiss type claim necessarily involves a mental element of some kind. His Lordship said:

> 165 … When we speak of someone making something "for" a particular use, and conclude as we must that "for" means something more than "suitable for", it must point to something in the mind of the manufacturer. Even if the manufacturer is a corporation using a factor entirely staffed by robots, if the manufacturing process is only protected by the patent if it is carried out for a particular purpose, the requirement to identify a mental element on the part of the manufacturer is simply inescapable. The court is well versed in identifying the governing mind of a corporation and, when the need arises, will no doubt be able to do the same for robots.

213 Lord Briggs concluded that a subjective intention test should be applied. His Lordship said:

> 172 The so-called subjective intent test … would I think accommodate all forensic means whereby a purpose of the generic manufacturer to serve (and profit from) the market for neuropathic pain could be proved, including but not limited to the packaging on the product. Anything from which the court could properly find that the manufacturer had such a purpose could be relied upon, including targeted disclosure, during litigation, of documentary records of the manufacturer's decision-making processes. I call it a "so-called" subjective test because a person's intention is as much a matter of fact as the state of his digestion, and this is true of corporate persons as much as of individuals. It may be proved objectively by words, conduct and even inactivity, and the court is well versed in treating a decision not to enquire about something suspected as probative of blind-eye knowledge.

214 After acknowledging that this solution was itself a compromise that fell short of providing complete protection for a patentee, Lord Briggs continued:

> 174 It was submitted [for the alleged infringer] that to the extent that their proposed test for the mental element fell short of providing full protection to patentees, this should be regarded as a necessary consequence of the judicial fudge constituted by the recognition of Swiss-form patents in the first place. There is something in this point, but it does not absolve the court from seeking a construction of the purpose limitation which strikes as fair a balance as possible. Nor do policy considerations mean that the court can do otherwise than choose between available meanings of the claim as a matter of construction. The claim cannot just be re-written. But I consider that a test for the manufacturer's purpose based upon determining his intent, in the matter described above, is well within the ambit of legitimate construction. That is the construction which I consider to be correct.

215 Lord Hodge also rejected the foreseeability test, and agreed with Lord Briggs' approach, in preference to Lord Sumption's approach, saying:

> 188 … The disagreement between Lord Sumption and Lord Briggs is whether, as Lord Sumption advocates, to adopt an approach, which has (at least until recently) found favour in the German courts, confining evidence of the purpose of an alleged infringing manufacturer's process to the outward manifestation of that purpose on the product itself, including its packaging, labelling or in an accompanying patient information leaflet, or, as Lord Briggs suggests, to assess that manufacturer's actual intention in producing the medicament by taking account also of other manifestations of that manufacturer's purpose. The approach of the German courts has the serious disadvantage of giving inadequate protection to the patentee of the Swiss-form patent against a generic manufacturer who uses "skinny labels" and patient information as a charade behind which it exploits the second use market. The approach which Lord Briggs favours may expose dealers in the generic product and dispensing pharmacists to strict liability for infringement as a result of matters over which they may have neither knowledge nor control. Both approaches are far from perfect. I confess to having been strongly attracted by the tidiness and consistency with the principles of tort law which Lord Sumption's approach involves. That approach also reduces the risk that suppliers and pharmacists will decline to deal in generic products after a patent has expired if there is a second medical use patent. But in my view Lord Brigg's approach creates a fairer balance between the central policy objectives which he sets out in … his judgment. Principally, for that reason but also for the other reasons which he advances, I agree with Lord Brigg's judgment on this matter. If, on this approach [the relevant statutory provision] were to cause serious problems to operators in the downstream market for generic products or to pharmacists, which in turn cause them to refuse to handle such generic products, it will be for the legislature to address those problems.

216 Lord Mance held that the test for infringement depended on the objective appearance and characteristics of the product as presented and put on the market. He considered it to be unsatisfactory that patent infringement should depend on an investigation of a subjective intention internal to the manufacturer, because this would leave open the possibility of entirely blameless pharmacists and end users being liable for the disposal or use of generic product made by a manufacturer whose subjective intentions they could not gauge. Whilst propounding an objective appearance and characteristics test, Lord Mance left open the possibility that, in given contexts, it may be that the objective appearance and characteristics of the product should not be taken at face value: see at [204]. Further, his Lordship reasoned that there may be circumstances in which, in order to avoid infringement, a generic manufacturer should positively exclude use of the product for the purpose protected by the patent: see at [216].

217 What emerges from *Generics (UK) v Warner-Lambert* is that the Supreme Court effectively rejected an objective test of purpose satisfied by the standard of reasonable foreseeability. However, the outward presentation of the medicament, as a product emerging from the process of manufacture, was an important indicator of the purpose for which the medicament was made. For Lords Sumption and Reed it was the determinative test of purpose; an inquiry into the

manufacturer's intention, either subjective or objective (by the standard of reasonable foreseeability) was simply irrelevant. Lord Mance's position was broadly aligned to Lord Sumption's and Lord Reed's position, based on his preferred construction of a Swiss type claim in which the second use of the word "for" attaches to the pharmaceutical composition or product as presented and put on the market: see at [201]. Like Lords Sumption and Reed, Lord Mance appears to have considered that recourse to the manufacturer's subjective intention is an irrelevant inquiry.

218 Lords Hodge and Briggs also accepted that the way the product of the manufacturing process is presented to the market (including through its packaging, labelling and patient information) is important, but as a pathway to determining the manufacturer's subjective intention. As Lord Briggs put it, the packaging, labelling patient information will, in most cases, be the best evidence of the manufacturer's intention: see at [173]. Indeed, his Lordship appears to have accepted (at [167]) that the way the product is presented to the market will often, if not usually, be decisive evidence on such an inquiry.

219 What also emerges from the case is that the Supreme Court analysed the proof of therapeutic purpose as requiring a choice between discrete tests: a subjective intention test; an imputed intention test (based on reasonable foreseeability); or an outward presentation test. While differing views were expressed as to the appropriate test, it seems to us that there was much common ground between their Lordships. Where the reasoning of Lords Sumption and Reed, and Lord Mance, differs from the reasoning of Lords Hodge and Briggs is the rejection of any consideration of the manufacturer's subjective intention. This rejection seems to have been based, in part, on an application of the Protocol as a tool for determining the construction of patent claims (although there were also other reasons expressed by Lord Sumption why an inquiry into subjective intention was inapt: see at [75] – [78]). The Protocol mandates the construction of claims by a process that combines fair protection for a patentee with a reasonable degree of legal certainty for third parties. For Lords Sumption and Reed, and Lord Mance, an inquiry into the manufacturer's subjective intention would not achieve the balance that the Protocol mandates: the manufacturer's subjective intention, as a test of purpose, would not provide legal certainty for those supplying, prescribing or using the medicament in question for a non-patented use, and also (for Lords Sumption and Reed) a test of subjective intention would not protect the autonomy of medical practitioners' clinical judgments.

220 A further matter that emerges from the case is that each of the proffered tests was acknowledged to have shortcomings. What was in contest, therefore, was which test, in those circumstances, should be selected for determining the requisite purpose, exclusive of the other tests, having regard to the requirements of the Protocol.

221 Australian patent law does not provide a fiat by reference to which patent claims are to be construed. Patent claims are construed by reference to common law principles applicable to patent specifications as documents created in a particular setting and serving particular ends. There is no requirement to construe patent claims by reference to stated policy objectives such as those contained in the Protocol.

222 As a matter of claim construction, we do not read Swiss type claims, such as those in this proceeding, as adding a further essential feature to the invention, namely the manufacturer's intention in making the medicament. We disagree, therefore, with the primary judge's finding at [102] that the crucial question for infringement is whether the manufacturer has made (or will make) the relevant medicament with the intention that it be used in the treatment of the specified condition. Infringement arises from the taking of the essential features of the invention as claimed. Therefore, infringement of a Swiss type claim is concerned with what the allegedly infringing manufacturer has done, not what it intended to do. Bearing in mind the limited scope of such claims, a single factual question is presented when considering infringement: as the product of the claimed method or process, is the medicament *for* the specified therapeutic purpose? This question is directed to the characteristics of the manufactured product. It is answered having regard to all the circumstances of the case. We are satisfied that Ground 2 of the notice of appeal is established because the primary judge proceeded on an incorrect basis in addressing the question of infringement by fixing on the manufacturer's intention. As a consequence of this conclusion, Ground 3 of the notice of appeal does not arise.

223 Plainly, one badge of therapeutic purpose (to adopt Lord Sumption's expression) is the physical characteristics of the medicament as it emerges as a product of the manufacturing process, including its formulation and dosage, packaging and labelling, and its patient information. This is a most important consideration. But it does not represent the only evidence that could rationally affect, directly or indirectly, the determination of the question of medicament's therapeutic purpose. Although we do not read the Swiss type claims as adding the manufacturer's intention as an essential feature of the invention, we do not reject the relevance

of direct evidence of the manufacturer's actual intention in making the medicament, where that evidence is available. This is not to say that such evidence would be determinative. If such evidence is available, it would form part of the circumstances of the case to be taken into account with all the other circumstances. Such evidence was not available in the present case.

224 Further, we would not reject consideration of the reasonably foreseeable use or uses to which the medicament would be put after manufacture. Such consideration would also form part of the circumstances of the case. However, we agree with the primary judge that, where a medicament would be used extensively for purposes that fall outside the monopoly of a Swiss type claim, the fact that it is reasonably foreseeable, or indeed likely, that a substantial portion of the manufactured medicament would also be used for the claimed therapeutic purpose will not be determinative of infringement: it might be reasonably foreseeable that a product might be put to a particular use, but it does not necessarily follow that the product, as manufactured, is for that use. Thus, we reject Mylan's submission that the primary judge acted inconsistently by rejecting the case on infringement of the Swiss type claims whilst nevertheless finding infringement under s 117(1) of the Act with reference to s 117(2)(b) in respect of the method of treatment claims. Different considerations inform the question of infringement arising under s 117(1). Ground 4 of the notice of appeal fails.

225 We also agree with the primary judge that mere suitability of a medicament for a claimed purpose cannot be determinative of the question of infringement of a Swiss type claim. We have already touched on this consideration when discussing the limited scope of these claims. The fact that the patent has been granted on the basis of a second or later therapeutic use necessarily means that there are multiple uses to which, potentially, the medicament can be put. Thus, evidence of suitability for use is ambiguous and cannot alone answer the question whether the medicament, as manufactured, is one for the specified therapeutic purpose.

226 Turning to the facts of the present case, there was a substantial therapeutic use for the Ranbaxy Products in the treatment of hypercholesterolaemia, various types of dyslipidaemia, and dyslipidaemia associated with type 2 diabetes. This is how the amended product information, in evidence before the primary judge, presented these products to the market. We accept that it is relevant to consider, as part of the circumstances of the case, the fact that the product information for the Ranbaxy Products refers to them as bioequivalent to Lipidil. It is also relevant to consider that, separately, the product information for Lipidil states that Lipidil is indicated for the reduction in the progression of diabetic retinopathy. But, the conjunction of

these facts does not point persuasively to a conclusion that the Ranbaxy Products are medicaments for the specified therapeutic purpose, especially when it is recognised that the statement that is made with respect to Lipidil in the product information for the Ranbaxy Products is in the context of simply referring to the bioequivalence that has been found in the majority of clinical trials that have been conducted. Mylan's point is diminished further by its acceptance of the primary judge's finding (at [117]) that medical practitioners do not typically read the product information for generic products.

227 The fact that the product information for the Ranbaxy Products does not contain a disclaimer of use for the specified purpose of the claims in suit is also a relevant consideration. But the absence of a disclaimer is hardly proof that, as manufactured, a medicament is one for a therapeutic use that has *not* been disclaimed, when the medicament's therapeutic use *has* been clearly stated. If anything, the making of such a disclaimer might, in a given case, bolster the position of a manufacturer who is alleged to have infringed a Swiss type claim.

228 In the present case, the product information for the Ranbaxy Products states the indications for which they are registered and thus, inferentially, the therapeutic purpose they serve as medicaments. Those indications are hypercholesterolaemia; types II, III, IV and V dyslipidaemia; and dyslipidaemia associated with type 2 diabetes, in each case as an adjunct to diet. The evidence discloses that Sun Pharma applied to the Therapeutic Goods Administration (**TGA**) to amend the product information by adding an express disclaimer that the Ranbaxy Products are not indicated for the prevention or treatment of retinopathy (including diabetic retinopathy) or for the reduction in the progression of diabetic retinopathy in patients with type 2 diabetes. The TGA refused that request because it did not consider that such an amendment would be sanctioned by s 9D(2) of the *Therapeutic Goods Act 1989* (Cth).

229 In oral submissions, Mylan argued that, in the face of that rejection, Sun Pharma might have pursued other avenues to obtain the disclaimers it had sought. The suggestion seems to be that, somehow, Sun Pharma's application to the TGA to amend was made half-heartedly or was, perhaps, a pretence. That seems to be an unlikely interpretation of events. It begs the Court's acceptance of an elaborate feint rather than acceptance of what Sun Pharma's application most obviously was—a request to amend the product information, on which the TGA was asked to act.

230 Mylan also argued that Sun Pharma could have written to medical practitioners and pharmacists asking or instructing them not to prescribe or provide the Ranbaxy Products for the treatment

or prevention of diabetic retinopathy. It submitted that Sun Pharma had proffered undertakings to this effect, but only if it be found at trial that supply of the Ranbaxy Products infringed the 711 patent. No doubt, Sun Pharma could take such steps, independently of the outcome of Mylan's infringement case. But this seems to stray from the question of whether the Swiss type claims are infringed, which focuses on the characteristics of the medicament as it emerges as the product of the claimed method or process. The argument that Mylan raises is one that seems to be more relevant to a consideration of downstream activity, and thus the question of indirect infringement of the method of treatment claims, which the primary judge found would have been infringed by dint of s 117(1) of the Act read with s 117(2)(b), had the method of treatment claims been valid.

231 Had the Swiss type claims been valid—in particular, claim 5 advanced in this appeal—we are not persuaded that the evidence establishes that, as manufactured, the Ranbaxy Products are medicaments for the treatment of retinopathy, in particular diabetic retinopathy. For this reason Ground 1 of the notice of appeal fails. Although Ground 2 of the notice of appeal has been established, it does not lead to the granting of any relief by this Court.

THE 711 PATENT: NOTICE OF CONTENTION

232 As we have noted, the primary judge rejected Sun Pharma's case that the claims in suit were not novel having regard to the conduct of the ACCORD Study and the FIELD Study. We have quoted the primary judge's reasons at [64] above. We note his Honour's observation that this aspect of Sun Pharma's challenge to the novelty of the invention received very little attention in closing submissions.

233 The primary judge's reason for rejecting the conduct of each study as an anticipatory use was that each was conducted as a double-blind study in which neither the investigator nor the participant knew whether fenofibrate or placebo was being administered. By its notice of contention dated 5 March 2019, Sun Pharma seeks to support its challenge to novelty by relying on the conduct of each study.

234 If this aspect of Sun Pharma's challenge to novelty received very little attention at trial, it received even less attention on this appeal. Sun Pharma submitted that the primary judge erred by rejecting the conduct of the trials as anticipatory use on the basis that they were double-blind studies. Sun Pharma submitted that, in the conduct of each study, the investigators and participants knew that fenofibrate was being administered. This was not undone by the fact that some participants received a placebo while other participants received fenofibrate or the

fact that the investigators and participants did not know, in individual cases, whether fenofibrate or placebo was being administered.

235 We are inclined to the view that the challenge to novelty should not fail because each study was a double-blind study. Section 7(1)(b) of the Act provides that novelty can be defeated through prior art information made publicly available through doing two or more related acts if the relationship between the acts is such that the person skilled in the art would treat them as a single source of information. The collective activity of administering fenofibrate or placebo to study participants within the context of a clinical trial whose procedures and objectives are publicly known, including to investigators and participants alike, would arguably constitute the making available of a single source of information for the purposes of s 7(1)(b). We are also inclined to the view that a lack of knowledge of whether, in a given act of administration, fenofibrate or placebo was being administered, would not mean that the requirement of public-availability of the prior art information was not satisfied.

236 However, we refrain from expressing a final view on the matter given the limited attention paid to these grounds of the notice of contention and the fact that we have already concluded that the primary judge did not err in finding that the relevant claims were invalid for lack of novelty, and also for lack of inventive step, in any event.

THE 807 PATENT: BACKGROUND

Introduction

237 On the appeal before us, the only question concerning the 807 patent entitled "Nanoparticulate fibrate formulations" that we need be concerned with concerns the primary judge's finding of a lack of inventive step.

238 His Honour found that all of the asserted claims of the 807 patent were invalid on the basis that the claimed invention in each case would have been obvious to the notional team in light of common general knowledge alone as at the priority date. But his Honour rejected Sun Pharma's case concerning obviousness based upon both common general knowledge as at that date together with the information contained in US patent no 2002/0012704 entitled "Water-insoluble drug particle process" (the **704 patent**).

239 Mylan had submitted before his Honour that the notional team seeking to develop an improved fenofibrate formulation would be faced with a large number of choices and could reasonably pursue many different formulation approaches without the required expectation of success. It

submitted that choices would need to have been made by the notional team in relation to particle size, surface stabilizer, concentration of surface stabilizer and the concentration of fenofibrate. Accordingly, it said that the task would have been complex and detailed, and involved a good deal of trial and error with a significant uncertainty of outcome. It submitted that it would not have been a matter of routine nor would it have been an exercise that could have been embarked upon with the required expectation of success. So according to Mylan, the invention was not obvious. But his Honour rejected that case based upon the foundation of common general knowledge that he had found.

240 At trial, Sun Pharma did not substantively advance a case that the asserted claims lacked an inventive step in light of common general knowledge alone, although such a case was formally pleaded in its amended particulars of invalidity. Rather, Sun Pharma ran a case relying upon both common general knowledge and the 704 patent as s 7(3) information. Although the primary judge rejected such a case, he nevertheless found that all of the asserted claims lacked an inventive step based on common general knowledge alone. In summary, Mylan says that in reaching this conclusion his Honour fell into error in the following key respects.

241 First, Mylan says that his Honour's findings were inconsistent with the evidence of Sun Pharma's experts, Associate Professor Morton and Dr Williams, that they would begin the hypothetical task by finding the 704 patent and then would try to prepare compositions based upon it. Further, it says that there was no evidence that the notional team would have sought to prepare fenofibrate compositions based on common general knowledge alone.

242 Secondly, Mylan says that his Honour erred in finding that the notional team would know of the need for a new fenofibrate formulation suitable for oral administration that eliminated the food effect and that such a problem was common general knowledge. It says that there was no evidence that this problem was common general knowledge.

243 Thirdly, Mylan says that his Honour erred in finding that the notional team would try hydroxypropyl methylcellulose (**HPMC**), which is also known as hypromellose, and sodium lauryl sulfate (**SLS**), both of which were commonly used in the formulation of pharmaceuticals to prevent or reduce particle agglomeration and to assist in dissolution. It says that there was no evidence that the notional team would have sought to prepare smaller fenofibrate particles with this combination of stabilizers based on common general knowledge alone.

244 Fourthly, it says that his Honour erred in finding on the basis of Professor Roberts' evidence that the notional skilled team would have had a reasonable expectation that a formulation that used HPMC and SLS to stabilize nanoparticles of fenofibrate would work. Indeed, according to Mylan, the primary judge proceeded upon an inaccurate characterisation of Professor Roberts' evidence. More generally, it says that the reformulated Cripps test was not satisfied.

245 For the purposes of its appeal Mylan says that no issue concerning the reliability of witnesses arises in relation to the four asserted errors. The first asserted error involves what Mylan says is the unchallenged affidavit evidence of Sun Pharma's experts that they would begin the hypothetical task by finding the 704 patent and then try to prepare compositions based upon it. Further, Mylan says that there was an absence of evidence that the notional team would have sought to prepare fenofibrate compositions based on common general knowledge alone. The second asserted error involves, according to Mylan, the absence of evidence that the notional team would know of the need for a new fenofibrate formulation suitable for oral administration that eliminated the food effect as part of common general knowledge. The third asserted error, according to Mylan, involves the absence of evidence that in formulating fenofibrate the notional team would try HPMC and SLS in light of common general knowledge alone. And the fourth asserted error, according to Mylan, involves a mixed error of fact and law and an inaccurate characterisation of Professor Roberts' evidence.

246 We should say at the outset that, generally speaking, we accept that no question concerning the reliability of witnesses arises. Rather, the question is whether his Honour made an error in his evaluation of the expert evidence in determining the question of obviousness, which process of evaluation we are in many but not all respects in as good a position as his Honour to make. It should not be lost sight of, however, that, as we have previously remarked, his Honour had the advantage that we do not have of participating in the concurrent expert evidence sessions and evaluating the evidence unfolding in real time.

247 For the reasons that follow, we reject Mylan's grounds of appeal. In those circumstances, it is strictly unnecessary for us to deal with Sun Pharma's notice of contention challenging his Honour's rejection of its case based upon both common general knowledge and the 704 patent as s 7(3) information. But in any event we have considered that contention and reject it.

248 We will begin our analysis of this part of the appeal by identifying some features of the complete specification of the 807 patent.

The complete specification

249 The 807 patent is directed to a hypothetical skilled team which would include, as the primary judge explained (at [321]), a pharmaceutical scientist with expertise in particle engineering and a research pharmacist with expertise in pharmacology equipped with the common general knowledge in those fields as at 24 May 2002, being the priority date.

250 The specification describes the field of the invention at p 1 lines 5 to 7 in the following terms:

> The present invention relates to a nanoparticulate composition comprising a fibrate, preferably fenofibrate or a salt thereof. The nanoparticulate fibrate, preferably fenofibrate, particles have an effective average particle size of less than about 2000 nm.

251 Nanoparticulate compositions and prior art methods of making them are then discussed in the section headed "Background Regarding Nanoparticulate Compositions". The specification states at p 1 lines 10 to 19:

> Nanoparticulate compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of a fibrate.
>
> Methods of making nanoparticulate compositions are described in, for example, U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5, 718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

252 Fenofibrate is described in the section headed "Background Regarding Fenofibrate" at p 4 lines 17 to 19 as follows:

> The compositions of the invention comprise a fibrate, preferably fenofibrate. Fenofibrate, also known as 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester, is a lipid regulating agent. The compound is insoluble in water …

253 This is followed by a discussion of other US patents in which fenofibrate is described. Such patents include US patents nos. 6,074,670 and 6,277,405 both for a "Fenofibrate Pharmaceutical Composition Having High Bioavailability and Method for Preparing It", US patent no. 6,074,670 which refers to "immediate-release fenofibrate compositions comprising micronized fenofibrate and at least one inert hydrosoluble carrier", US patent no. 4,739,101 describing a process for making fenofibrate, and US patent no. 6,277,405 directed to micronized fenofibrate compositions having a specified dissolution profile.

254 The specification also refers to two international applications, WO 01/80828 for "Improved Water-Insoluble Drug Particle Process" and WO 02/24193 for "Stabilised Fibrate Microparticles". Both of these publications are said to describe a process for making small particle compositions of poorly water soluble drugs. We note that the primary judge found (at [326]) that both documents were specifically incorporated by reference into the 807 patent.

255 After referring to the processes described in those patents, the specification then states at p 5 lines 12 to 21:

> The process requires preparing an admixture of a drug and one or more surface active agents, followed by heating the drug admixture to at or above the melting point of the poorly water soluble drug. The heated suspension is then homogenized. The use of such a heating process is undesirable, as heating a drug to its melting point destroys the crystalline structure of the drug. Upon cooling, a drug may be amorphous or recrystallize in a different isoform, thereby producing a composition which is physically and structurally different from that desired. Such a "different" composition may have different pharmacological properties. This is significant as U.S. Food and Drug Administration (USFDA) approval of a drug substance requires that the drug substance be stable and produced in a repeatable process.

256 This is followed by a reference to another prior art publication describing compositions of fibrate and vitamin E TGPS, a water soluble derivative of vitamin E, comprising particles the diameters of which are within defined ranges in which the mean diameter is about 100 nm to about 900 nm, with 50% of the particles of each composition below the range 350 nm to 750 nm (D_{50}) and 99% below the range 500 nm to 900 nm (D_{99}). The specification then states at p 6 lines 1 and 2 that that publication "… does *not* teach that the described compositions show minimal or no variability when administered in fed as compared to fasted conditions."

257 Further, as the primary judge explained (at [329]), the specification includes a description of a number of advantages that are said to arise using formulations of the fibrate composition to the invention. Compositions of the invention are said to significantly increase the bioavailability of fenofibrate which can enable the use of a smaller solid dosage size. Compositions of the invention are also said to have an improved pharmacokinetic profile that is not substantially affected by the fed or fasted state of a human to whom such a composition is administered.

258 We pause here to say something about drug absorption. For this purpose it is useful to set out some of the evidence given by Professor Roberts.

259 Oral administration is one of the most common forms of drug delivery. Most drugs that are administered orally, that is, via the gastrointestinal (**GI**) tract, are given for a systemic effect.

In other words, they are delivered to the bloodstream to exert an effect somewhere else in the body after being carried there by the blood.

260 The rate and extent of systemic absorption of a drug administered orally can be affected by inter alia:

(a) the rate and extent of release of the drug from the dosage form in the GI tract after the drug in the dosage form is administered orally;

(b) the drug molecule's behaviour in the GI tract as related to its solubility, potential binding, and stability in the GI tract fluids;

(c) physiological conditions in the GI tract, such as gastric emptying rate or altered pH in the stomach, which may be induced by either co – or prior administration of water or food before taking the oral dose form, and transit time through the intestinal tract;

(d) the drug molecule's ability to cross the epithelial lining of the GI tract into the bloodstream after leaving the stomach; this factor may be affected by the individual's level of blood flow through the GI tract.

261 As has been indicated, the environment in the stomach may have an impact on the rate and extent of absorption, in particular whether the individual has fasted or eaten food just prior to administration of the drug; the type of food may also have an impact. If the presence of food affects the rate or extent of absorption of a drug, then this is referred to as a "food effect".

262 For some drugs, the presence of food can have a substantial effect on the rate and extent of absorption. For instance, it is known that high viscosity food, high and low temperatures of administered water, various sugars and carbohydrates, and also certain fats can slow down gastric emptying. In other cases, the administration of food may lead to an increase in the gastric fluid pH. And the presence of a fatty meal may assist in the dissolution of the drug. In yet other cases, drugs may bind to food being digested in the stomach. For example, the drug griseofulvin is lipid soluble and has a significantly better rate and extent of absorption if taken with food. Contrastingly, tetracycline can bind with divalent cations such as calcium ions and accordingly should not be taken with milk. As a further example, if food is present, then this typically increases the viscosity of the stomach contents and reduces the gastric emptying rate. If no food is present, then the stomach will typically empty quickly which would usually lead

to a faster rate of absorption. The effect of food on the rate of stomach emptying means that food slows down the absorption process.

263 The extent to which drug absorption is affected by food is dependent on the properties of the drug, the dosage form or both. For most orally administered drugs, food does not greatly affect the rate or extent of absorption. It is usually the poorly water soluble drugs in acidic media that have a food effect. In many cases, the food that is administered is fatty and this will facilitate the dissolution of a drug that is soluble in lipids. More generally, given that a drug's water and lipid solubility may influence the food effect, formulation strategies may need to be employed to facilitate an adequate rate and extent of absorption.

264 As his Honour explained (at [330]), the specification asserts that the invention encompasses a fibrate, preferably fenofibrate, composition in which administration of the composition to a subject in a fasted state is bioequivalent to the administration of the composition to a subject in a fed state. In this respect the specification adopts the following measure of bioequivalence at p 16 lines 26 to 30:

> "Bioequivalency" is established by a 90% Confidence Interval (CI) of between 0.80 and 1.25 for both C_{max} and AUC under USFDA regulatory guidelines, or a 90% CI for AUC of between 0.80 to 1.25 and a 90% CI for C_{max} of between 0.70 to 1.43 under the European EMEA regulatory guidelines.

265 Further as to bioavailability, the specification states at p 6 lines 16 to 23:

> Because fibrates, including fenofibrate, are so insoluble in water, significant bioavailability can be problematic. In addition, conventional fibrate, including fenofibrate, formulations exhibit dramatically different effects depending upon the fed or fasted state of the patient. Finally, conventional fibrate, including fenofibrate, formulations require relatively large doses to achieve the desired therapeutic effects. There is a need in the art for nanoparticulate fibrate formulations which overcome these and other problems associated with prior conventional microcrystalline fibrate formulations. The present invention satisfies these needs.

266 The specification includes a number of definitions. According to the specification at p 6A lines 10 to 12, "comprise" and its variants do not exclude other additives, components, integers or steps. We also note that at p 12 lines 3 to 11 there is a definition of "stable":

> As used herein with reference to stable fibrate, preferably fenofibrate, particles, "stable" includes, but is not limited to, one or more of the following parameters: (1) that the fibrate particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly increase in particle size over time; (2) that the physical structure of the fibrate, preferably fenofibrate, particles is not altered over time, such as by conversion from an amorphous phase to crystalline phase; (3) that the fibrate, preferably fenofibrate, particles are chemically stable; and/or (4) where the fibrate has not been subject to a heating step at or above the melting point

of the fibrate in the preparation of the nanoparticles of the invention.

267 The specification sets out a summary of the invention and various embodiments at p 6A line 16 to p 7 line 22:

> The present invention relates to nanoparticulate compositions comprising a fibrate, preferably fenofibrate. The compositions comprise a fibrate, preferably fenofibrate, and at least one surface stabilizer adsorbed on the surface of the fibrate particles. The nanoparticulate fibrate, preferably fenofibrate, particles have an effective average particle size of less than about 2000 nm.
>
> A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized.
>
> Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate fibrate, preferably fenofibrate, composition of the invention. The pharmaceutical compositions comprise a fibrate, preferably fenofibrate, at least one surface stabilizer, and a pharmaceutically acceptable carrier, as well as any desired excipients.
>
> One embodiment of the invention encompasses a fibrate, preferably fenofibrate, composition, wherein the pharmacokinetic profile of the fibrate is not affected by the fed or fasted state of a subject ingesting the composition, in particular as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMEA).
>
> Another aspect of the invention is directed to a nanoparticulate fibrate, preferably fenofibrate, composition having improved pharmacokinetic profiles as compared to conventional microcrystalline fibrate formulations, such as T_{max}, C_{max}, and AUC.
>
> In yet another embodiment, the invention encompasses a fibrate, preferably fenofibrate, composition, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMEA).

268 A number of consistory clauses are then set out. The first consistory clause at p 8A lines 1 to 16 mirrors the language of claim 1. This is then followed by five more consistory clauses that mirror the language of claims 2, 3, 40, 41 and 42. The first three consistory clauses, which mirror claims 1, 2 and 3, refer to compositions. The second three consistory clauses, which mirror claims 40, 41 and 42, refer to methods of treatment.

269 The consistory clauses are followed by a detailed description of the invention including by reference to two graphs, being Figures 1 and 2, which are plots of fenofibric acid concentrations against time, with different time scales used on the x-axis for each graph. For present purposes it is not necessary for us to reproduce these graphs.

270 Then follows a detailed description of the invention. The specification states at p 10 line 16 to p 11 line 16:

> The present invention is directed to nanoparticulate compositions comprising a fibrate, preferably fenofibrate. The compositions comprise a fibrate, preferably fenofibrate, and preferably at least one surface stabilizer adsorbed on the surface of the drug. The nanoparticulate fibrate, preferably fenofibrate, particles have an effective average particle size of less than about 2000 nm.
>
> As taught in the '684 patent, and as exemplified in the examples below, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. It was surprisingly discovered that stable, nanoparticulate fibrate, preferably fenofibrate, formulations can be made.
>
> Advantages of the nanoparticulate fibrate, preferably fenofibrate, formulations of the invention as compared to conventional non-nanoparticulate formulations of a fibrate, particularly a fenofibrate such as TRICOR® (tablet or capsule microcrystalline fenofibrate formulations), include, but are not limited to: (1) smaller tablet or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) increased bioavailability; (4) substantially similar pharmacokinetic profiles of the nanoparticulate fibrate, preferably fenofibrate, compositions when administered in the fed versus the fasted state; (5) improved pharmacokinetic profiles; (6) bioequivalency of the nanoparticulate fibrate, preferably fenofibrate, compositions when administered in the fed versus the fasted state; (7) an increased rate of dissolution for the nanoparticulate fibrate, preferably fenofibrate, compositions; (8) bioadhesive fibrate, preferably fenofibrate, compositions; and (9) the nanoparticulate fibrate, preferably fenofibrate, compositions can be used in conjunction with other active agents useful in treating dyslipidemia, hyperlipidemia, hypercholesterolemia, cardiovascular disorders, or related conditions.
>
> The present invention also includes nanoparticulate fibrate, preferably fenofibrate, compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

271 The specification states at p 24 lines 2 to 8:

> The invention provides compositions comprising fibrate, preferably fenofibrate, particles and at least one surface stabilizer. The surface stabilizers preferably are adsorbed on, or associated with, the surface of the fibrate, preferably fenofibrate, particles. Surface stabilizers especially useful herein preferably physically adhere on, or associate with, the surface of the nanoparticulate fibrate particles but do not chemically react with the fibrate particles or itself. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

272 The specification then goes on to discuss the question of surface stabilizers in considerable detail (pp 26 to 31). We pause here to give some explanation of particle size reduction and surface stabilizers. The following summary is drawn from the evidence of Associate Professor Morton that was adduced before the primary judge and does not appear to have been contentious.

273 Drug particle size has important implications on the bioavailability of many drugs. "Bioavailability" refers to the rate and extent of absorption of a drug following administration.

274 As we have indicated earlier, when a drug is administered orally in solid form, the drug must first dissolve in the fluids present within the lumen of the GI tract and then be absorbed across the GI tract wall to enter the bloodstream, from where drug molecules may be transported to their site of action within the body.

275 As to dissolution, the fluids present in the lumen of the GI tract are aqueous, which means that water forms a significant component of the GI tract fluids. For this reason, one of the factors which influences the rate at which a drug administered orally in solid form dissolves in the GI tract fluid is the drug's aqueous solubility.

276 As to absorption, the wall of the GI tract is lined by cells whose membranes are predominantly composed of lipids, that is, fatty compounds. For many although not all drugs, the rate at which drug molecules traverse the GI tract wall to enter the bloodstream, which is generally referred to as the drug's permeability, depends upon their lipid solubility, that is, the solubility of the drug in a fatty environment.

277 In the case of a drug which has low aqueous solubility and accordingly dissolves slowly in the GI tract but has relatively good permeability, the rate at which drug particles dissolve in the GI tract fluids is likely to be the factor which limits the rate and extent of the drug's absorption into the bloodstream after oral administration.

278 For many such drugs, the rate and extent of drug absorption can be enhanced by reducing the size of drug particles to achieve an overall increase in the ratio of surface area to volume for the drug particles. All else being equal, smaller drug particles generally dissolve faster than larger particles due to the increased total surface area per unit volume of the drug.

279 But when drug particles are reduced in size, the resulting small particles will generally demonstrate an increased tendency to aggregate together to form larger units. Depending upon the circumstances, this process may be referred to by terms including agglomeration and flocculation.

280 In simple terms, small drug particles demonstrate an increased tendency to aggregate together compared to larger drug particles because reducing particle size, and thereby increasing total surface area of the drug particles, increases the free energy of the system. Generally speaking, a collection of drug particles will behave in such a way as to reduce the overall free energy of

the system. And one way in which free energy can be reduced is for small drug particles to aggregate together into larger units. Further, this tendency for small drug particles to aggregate together can also be explained as a competition between forces of adhesion and gravity. As particles become smaller and smaller, the gravitational forces pulling the particles downward, on the one hand, become less and the adhesive interactions pulling the particles together, on the other hand, increase in number.

281 In pharmaceutical preparations involving the use of small drug particles, aggregation of those small particles into larger units is usually undesirable. For example, if drug particle size has been reduced to increase total surface area and thereby increase dissolution rate of a poorly soluble drug, particle aggregation is undesirable because it will reduce the total surface area of the drug particles, leading to reduced dissolution rate, with adverse impacts on the rate and extent of drug absorption.

282 Before the priority date, a primary means to prevent agglomeration of small drug particles was to add materials to the system which would accumulate at the interface of the particles and accordingly impede particle aggregation. Such materials were and still are referred to as surface stabilizers. Surface stabilizers reduce the adhesion between small drug particles and so provide an energy barrier to particle aggregation.

283 In simplified terms, the surface stabilizers which were used before the priority date and indeed after to reduce or prevent aggregation of small drug particles operated on two broad principles. First, one could use substances which accumulated at the surface of drug particles and impeded particle aggregation as a physical barrier. This is referred to as steric hindrance. Secondly, one could use surfactants and surface active agents which impeded particle aggregation by electrostatic or related repulsion forces. Indeed, some surface stabilizers could exert their effects by a combination of these mechanisms.

284 When one refers to surface stabilizers that prevent or reduce particle aggregation by steric hindrance, one is referring to compounds that coat the surface of drug particles (for example, relatively large polymeric molecules that occupy considerable space at the molecular level) to prevent those drug particles from coming into close contact with each other. Before the priority date a variety of polymeric compounds were capable of being used as surface stabilizers for small drug particles, including various derivatives of cellulose such as polyvinylpyrrolidone and, significantly for present purposes, HPMC.

285 When one refers to surfactants, one is referring to amphiphilic molecules which have both a hydrophobic part and a hydrophilic part. Before the priority date, many surfactants were useful for preventing or reducing aggregation of small particles of a hydrophobic drug. When adequately mixed with small particles of a hydrophobic drug, the hydrophobic part of surfactant molecules would orientate towards the surface of the drug particles, whilst the hydrophilic part of surfactant molecules would orientate towards surrounding water molecules and, in this way, reduce the tendency of the hydrophobic drug particles to aggregate together; this is all notwithstanding any potential repulsive forces between the hydrophobic parts of the surfactant molecules and the drug particles.

286 Before and since the priority date, one generally categorised surfactants as non-ionic, cationic or anionic, depending upon whether they carried a net electrical charge and, if so, the polarity of that charge. Non-ionic surfactants have no net positive or negative charge, although they have more polar and less polar regions. Ionic surfactants bear an overall net charge, with cationic surfactants having a net positive charge and anionic surfactants having a net negative charge.

287 Examples of anionic surfactants which were used before the priority date included those containing carboxylate, sulfonate and sulfate ions as functional groups at their head. Examples of cationic surfactants which were used included amine salts, quaternary ammonium salts and, significantly for present purposes, SLS.

288 Examples of non-ionic surfactants which were used included fatty alcohols such as lauryl and cetyl alcohols, and fatty acid esters of alcohols such as propylene glycol, polyethylene glycol, sorbitan, sucrose and cholesterol.

289 Before and after the priority date, as Associate Professor Morton explained, the identification of surface stabilizers to be used in a pharmaceutical formulation was realised by trial and error; for present purposes we will put to one side for the moment whether this was routine. This was because absolute prediction of a surface stabilizer's performance in a given system was rarely achievable. Before the priority date, when selecting a surface stabilizer system for a pharmaceutical formulation, it was the practice to review the scientific literature to narrow the broad range of available surface stabilizers to those that had been successfully used in similar systems and with acceptable toxicological profiles. After identifying a range of potential candidates, one would then conduct a series of tests on those surface stabilizers involving different combinations and quantities for the purposes of identifying an effective combination

and quantity that would provide acceptable stability to small drug particles; again, we will put to one side for the moment whether this could be characterised as routine.

290 At p 26 lines 1 to 10, the specification states:

> The choice of a surface stabilizer for a fibrate is non-trivial and required extensive experimentation to realize a desirable formulation. Accordingly, the present invention is directed to the surprising discovery that nanoparticulate fibrate, preferably fenofibrate, compositions can be made.
>
> Combinations of more than one surface stabilizer can be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Surface stabilizers include nonionic, anionic, cationic, ionic, and zwitterionic surfactants.

291 This passage is followed by a lengthy list of surface stabilizers that can be used to perform the invention, as the primary judge explained (at [339]). The surface stabilizers referred to include HPMC, SLS, gelatin and others.

292 In this context, it is appropriate to set out some extracts from p 26 line 11 to p 27 line 24:

> Representative examples of surface stabilizers useful in the invention include, but are not limited to, hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctyl-sulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Speciality Chemicals))…PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.
>
> If desirable, the nanoparticulate fibrate, preferable fenofibrate, compositions of the invention can be formulated to be phospholipid-free.
>
> Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.
>
> Other useful cationic stabilizers include …

293 The specification later states at p 30 line 22 to p 31 line 13:

> In one embodiment of the invention, the preferred one or more surface stabilizers of the invention is any suitable surface stabilizer as described below, with the exclusion

> of PEG-derivatized vitamin E, which is a non-ionic compound. In another embodiment of the invention, the preferred one or more surface stabilizers of the invention is any suitable surface stabilizer as described below, with the exclusion of phospholipids. Finally, in another embodiment of the invention, the preferred one or more surface stabilizers of the invention is any substance which is categorized by the USFDA as GRAS ("Generally Recognized As Safe").
>
> Preferred surface stabilizers of the invention include, but are not limited to, hypromellose, docusate sodium (DOSS), Plasdone® S630 (random copolymer of vinyl pyrrolidone and vinyl acetate in a 60:40 ratio), hydroxypropyl cellulose SL (HPC-SL), sodium lauryl sulfate (SLS), and combinations thereof. Particularly preferred combinations of surface stabilizers include, but are not limited to, hypromellose and DOSS; Plasdone® S630 and DOSS; HPC-SL and DOSS; and hypromellose, DOSS, and SLS.
>
> The surface stabilizers are commercially available and/or can be prepared by techniques known in the art. Most of these surface stabilizers are known pharmaceutical excipients…

294 The specification also includes a description of other pharmaceutical excipients that may be used as binders, fillers, lubricants, sweeteners and flavourings. The description of excipients is followed by a description of the "nanoparticulate fibrate particle size". Page 32 line 24 to p 33 line 4 states:

> The compositions of the invention contain nanoparticulate fibrate particles, preferably nanoparticulate fenofibrate particles, which have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns), less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 run, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

295 It is not necessary to set out any further detail on this aspect at this point.

296 The specification then proceeds to describe what are said to be several "exemplary nanoparticulate fenofibrate tablet formulations" and "exemplary embodiments of the invention". As the primary judge explained (at [343]), the exemplary embodiments include descriptions of the invention in which it is said that the fenofibrate particles have an effective average particle size of less than about 2000 nm associated with a surface stabilizer that is not a phospholipid. Earlier as we have set out, at p 27 lines 15 and 16, it was stated that if desirable, fenofibrate compositions of the invention could be formulated to be phospholipid-free, although it was also stated (at p 27 lines 17 and 18) that phospholipids could be useful cationic surface stabilizers.

297 The description of the exemplary embodiments is followed by a section that describes methods for making the nanofibrate compositions. The specification states at p 36D lines 2 to 4 that "[t]he nanoparticulate fibrate, preferably fenofibrate, compositions can be made using, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in [US patent no. 5,145,684]". This statement is followed by numerous references to prior art describing methods of making nanoparticulate compositions.

298 The specification also includes a description of milling, microprecipitation and homogenization methods used to prepare the nanoparticulate fibrate compositions. These three methods are described at p 37 line 20 to p 39 line 5 although it is not necessary for us to set these out.

299 Further, the specification at p 42B to p 58 sets out and discusses eight examples which are said to illustrate the invention. The information presented includes a description of various formulations including details of particle sizes, redispersibility and a study of the food effect. The results presented are said at p 52 lines 11 to 14 to show that in one of the examples tested (example 5) the pharmacokinetic profile of the fibrate was not affected by the fed or fasted state of a subject ingesting the composition, that is, there was no food effect. At p 58 lines 8 to 18 it is also asserted that when compared to the conventional microcrystalline form of fenofibrate 160 mg dosage form, "the nanoparticulate fenofibrate dosage forms of the invention exhibit dramatically improved rates of dissolution".

300 For present purposes it is not necessary to further discuss these eight examples.

301 At p 6A lines 2 to 8, the specification sets out a boiler-plate provision:

> The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Relevant claims

302 Even though the asserted claims of the 807 patent are claims 1 to 7, 9, 11, 12, 18 to 21, 23, 24, 26, 27, 31, 32, 36 to 38, 40 to 45, 47, 49, 50, 56 to 59, 61, 62, 64, 65, 69, 70, 74 to 76 and 78 to 80 (the asserted claims), it is only necessary to set out claims 1 to 3 and 40:

1. A stable fenofibrate composition for oral administration comprising:

(a) particles of fenofibrate having a D_{50} particle size of less than about 500 nm, and

(b) at least one surface stabilizer,

wherein:

(i) the composition exhibits bioequivalence upon administration to a human subject in a fed state as compared to administration to a human subject in a fasted state; where bioequivalency is established by:

(a) a 90% Confidence Interval for AUC which is between 80% and 125%, and

(b) a 90% Confidence Interval for C_{max}, which is between 80% and 125%;

(ii) the composition redisperses in a biorelevant media; and

(iii) the composition is phospholipid-free.

2. A stable fenofibrate composition for oral administration comprising:

(a) particles of fenofibrate having a mean particle size of less than about 500nm, and

(b) at least one surface stabilizer, wherein the surface stabilizer is not selected from the group consisting of sorbitan esters, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters and polyoxyethylene stearates,

wherein:

(i) the composition exhibits bioequivalence upon administration to a human subject in a fed state as compared to administration to a human subject in a fasted state; where bioequivalency is established by:

(a) a 90% Confidence Interval for AUC which is between 80% and 125%, and

(b) a 90% Confidence Interval for C_{max}, which is between 80% and 125%;

(ii) the composition redisperses in a biorelevant media;

(iii) the composition is phospholipid-free.

3. A stable fenofibrate composition for oral administration comprising:

(a) particles of fenofibrate having a D_{90} particle size of less than about 700 nm, and

(b) at least one surface stabilizer,

wherein:

(i) the composition exhibits bioequivalence upon administration to a human subject in a fed state as compared to administration to a human subject in a fasted state; where bioequivalency is

established by:

(a) a 90% Confidence Interval for AUC which is between 80% and 125%, and

(b) a 90% Confidence Interval for C_{max}, which is between 80% and 125%;

(ii) the composition redisperses in a biorelevant media; and

(iii) the composition is phospholipid-free.

…

40. A method of treating a condition selected from the group consisting of hypercholesterolemia, hypertriglyceridemia, coronary heart disease, cardiovascular disorders, peripheral vascular disease, symptomatic carotid artery disease, mixed dyslipidemia, and increased risk of pancreatitis comprising administering to a subject an effective amount of a composition, wherein:

(a) the composition comprises particles of fenofibrate having a D_{50} particle size of less than about 500 nm and at least one surface stabilizer;

(b) the fenofibrate particles present in the composition redisperse in a biorelevant media; and

(c) administration of the composition to a human subject in a fasted state is bioequivalent to administration of the composition to a human subject in a fed state, wherein bioequivalency of the composition is established by:

(i) a 90% Confidence Interval for AUC which is between 0.80 and 1.25; and

(ii) a 90% Confidence Interval for C_{max}, which is between 0.80 and 1.25.

…

303 It is necessary to say something further about the concepts referred to in these claims. For this purpose, we summarise some evidence of Professor Prestidge from his first affidavit that was tendered before the primary judge although not in the appeal book, concerning particle size and the measurement of absorption.

304 First, drug particles typically have a range of particle sizes. Particle sizing techniques will measure this distribution of sizes. The distribution of particle sizes is often defined with respect to particle number, particle surface area or particle volume. Number-based distributions show the number of particles in a sample that have a particular particle size. In a surface area-based distribution, particle surface area rather than particle number is used to represent the particle size distribution. Similarly, in a volume-based distribution, particle volume is used to represent

the particle size distribution. Particle size distributions are most typically described by volume distributions. As volume is directly related to weight (mass) for constant density materials, volume-based distributions are considered to be equivalent to weight-based distributions in pharmaceutical science. The D_{50} particle size corresponds to the midpoint of the volume (weight) based size distribution. That is where 50% of particles are above this size and 50% of particles are below this size.

305 Particle size is measured directly after particles are prepared and prior to the inclusion of excipients that would interfere with particle size determination. Some excipients may not be completely soluble in the solvent and thus the particle size determination would also measure the insoluble excipient particles which would interfere with the particle size measurements of the drug. In addition, in order to accurately measure drug particle size after excipients are included, these particles would need to be separated from any insoluble excipients, which would be difficult.

306 Secondly, Professor Prestidge explained that drug absorption is determined by measuring and plotting the drug concentration in the bloodstream as a function of time to generate a pharmacokinetic profile. From this profile, one can determine various parameters. Figure 1 below is a typical absorption profile of a drug in a human subject over time. The parameter C_{max} is shown, which is the maximum drug concentration in the bloodstream. C_{max} is the highest point of the curve, which occurs at a time equal to T_{max}. Further, the parameter AUC is shown, which is the area under the curve which is determined from the pharmacokinetic profile.

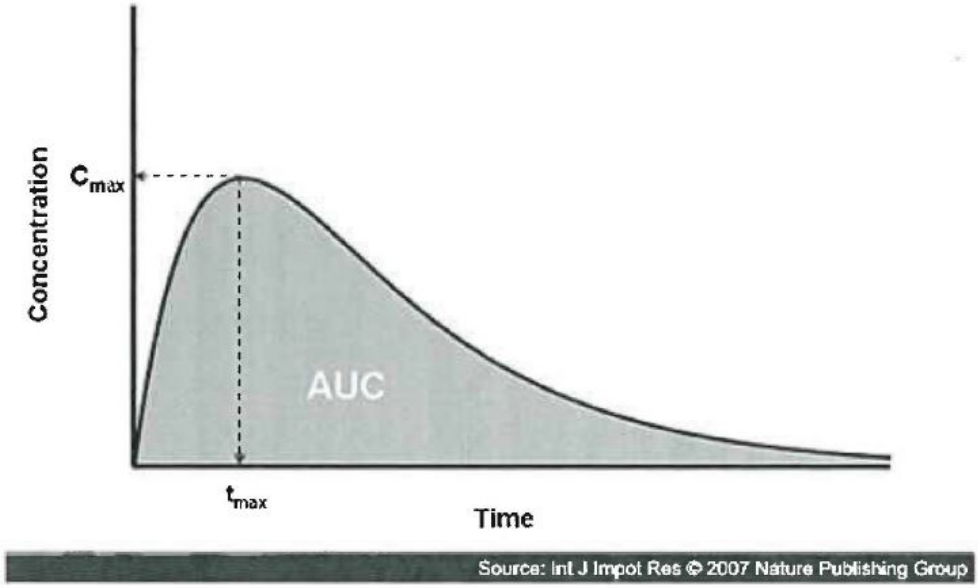

Figure 1: Typical plasma level curve after administration of an oral formation

307 When investigating whether there is a food effect in the sense that we have described earlier, a pharmacokinetic profile is generated where the pharmaceutical product is administered with and without food. In this context, administration in a fed state requires a human subject to have a meal before dosing. Regulatory bodies may define particular fed state conditions in their guidelines in relation to food effect studies.

308 We make two other points concerning the claims.

309 The claims refer to bioequivalency. Bioequivalence is established where two sets of pharmacokinetic data are compared and there is statistically no difference in their pharmacokinetic parameters, that is, AUC and C_{max}. The specific statistical similarity for bioequivalence is usually defined as a 90% confidence interval for AUC, which is between 0.80/80% and 1.25/125%, and a 90% confidence interval for C_{max}, which is between 0.80/80% and 1.25/125%.

310 Further, the claims make reference to "biorelevant medium". One is here dealing with a medium that is equivalent to the gastrointestinal tract. For example, gastric media contain a low pH environment. This could be simulated using, for example, a 0.01 M HCl aqueous solution. Contrastingly, intestinal media is near neutral pH and contains a number of physiological molecules, which may help increase the solubility of drugs. This could be simulated using, for example, a 0.1 M NaCl aqueous solution.

311 Before dealing with Mylan's appeal grounds, we should first say something about the 704 patent.

THE 807 PATENT: SECTION 7(3) INFORMATION

312 As we have said, the primary judge concluded that the claims of the 807 patent were obvious solely in light of common general knowledge as at the priority date. Accordingly, he considered that it was unnecessary to consider Sun Pharma's alternative case based upon common general knowledge and the 704 patent as s 7(3) information. Nevertheless his Honour made some brief observations concerning the 704 patent. Given the issues that have been raised before us on this appeal, it is convenient that we say something more elaborate about its disclosures.

313 The 704 patent (US 2002/0012704) entitled "Water-Insoluble Drug Particle Process" was published on 31 January 2002. The invention the subject of the 704 patent is, in essence, a five step process for the preparation of small particles containing a poorly water soluble drug. It was not disputed by Mylan that the 704 patent constituted s 7(3) information that a person skilled in the art could reasonably be expected to have ascertained, understood and regarded as relevant to the development task as at the priority date.

314 The specification states:

> [0001] The present invention relates to an improved process for the preparation of small particles containing a poorly water soluble drug, and in particular to an improved process for the preparation of small particles containing a poorly water soluble drug as a dispersion in an aqueous carrier and as dried small particles containing a poorly water soluble drug.
>
> [0002] There is a critical need in the pharmaceutical and other biological based industries to formulate industrially useful water-insoluble or poorly water soluble substances into formulations for oral, injectable, inhalation, ophthalmic, and other routes of delivery. Industrially useful water insoluble or poorly water soluble substances include water insoluble or poorly water soluble biologically useful compounds, imaging agents, pharmaceutically useful compounds and in particular water insoluble and poorly water soluble drugs for human and veterinary medicine.
>
> [0003] Microparticles of water insoluble or poorly soluble substances are small particles having diameters of from nanometers to micrometers and refer to solid particles of irregular, non-spherical or spherical shapes. When the insoluble and poorly soluble substances are therapeutically and diagnostically useful substances, formulations containing them as microparticles or small particles provide some specific advantages over unformulated non-micronized drug particles. These advantages include improved oral bioavailability of drugs that are poorly absorbed from the GI tract, development of injectable formulations that are currently available only in oral dosage form, less toxic injectable formulations that are currently prepared with organic solvents, sustained release of intramuscular injectable drugs that are

> currently administered through daily injection or constant infusion, preparation of inhaled, ophthalmic formulation of drugs that otherwise could not be formulated for nasal or ocular use, as well as other advantages.

315 The specification states that fenofibrate is a poorly water soluble compound used to reduce triglycerides levels in hypertriglyceridemic patients and plasma cholesterol and LDL-cholesterol in hypercholesterolemic and mixed dyslipidemic patients.

316 The process claimed in the 704 patent, as his Honour broadly described it (at [431]) and as summarised at [0026] of the specification, is a process of making small particles of, say, fenofibrate that involved five steps.

317 The first step involved mixing at high shear a mixture of fenofibrate and one or more surface active substances in an aqueous carrier above the melting point of the fenofibrate to form a heated suspension containing the fenofibrate.

318 The second step involved homogenizing the suspension to form a heated homogenate containing the fenofibrate.

319 The third step involved cooling the homogenate to form a transiently stable cooled homogenate containing the fenofibrate.

320 The fourth step involved applying a particle stabilizing energetic process to form a cooled dispersion of small particles containing the fenofibrate.

321 The fifth step involved optionally drying the cooled dispersion to form dried small particles containing the fenofibrate.

322 The specification contains a more detailed description of the process which includes a number of definitions of terms used throughout the specification, including definitions of "small particle" and "transiently stable" (see [0037] and [0040]). As his Honour said (at [432]), these definitions are important to an understanding of the five step process described in the specification and the particular formulations subsequently described.

323 In relation to fenofibrates specifically, the specification states:

> [0013] Fenofibrate or 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid 1-methylethyl ester is an example of a poorly water soluble compound. It is a benzophenone containing a para-chlorophenyl group and a para-isopropyloxycarbon-ylisopropoxyphenyl group, both of which are substantially hydrophobic groups. Fenofibrate exhibits a melting point reported to be in the range of 79 to 82° C. (Physician's Desk Reference, 1999 Edition, page 477), which is above that of the symmetrically unsubstituted benzophenone with a reported melting point range of 48

> to 51° C. but below that of the symmetrically substituted 4,4'-dichlorobenzophenone with a reported range of 144 to 146° C. (Aldrich Chemical Co. catalog, 1999).
>
> [0014] Fenofibrate acts as a potent lipid modulator agent offering unique and significant clinical advantages over existing products in the fibrate class of drugs. Fenofibrate produces substantial reductions in plasma triglyceride levels in hypertriglyceridemic patients and in plasma cholesterol and LDL-cholesterol in hypercholesterolemic and mixed dyslipidemic patients.
>
> [0015] Fenofibrate is a prodrug that is absorbed and then hydrolyzed by tissue and plasma esterases to fenofibric acid, its active metabolite. Fenofibric acid, responsible for the pharmacological activity, has a plasma half-life of about 20 hours. Fenofibrate is a poorly water soluble drug and is practically insoluble in water. It is normally poorly and variably absorbed, and has to be taken with food.
>
> [0016] Fenofibrate was first available in a pharmaceutical dosage form (Lipidil®) consisting of a hard gelatin capsule containing fenofibrate, lactose, pregelatinized starch and magnesium stearate. After oral administration, during a meal, about 60% of the dose of this conventional form is effectively absorbed and found in the blood as fenofibric acid (Weil et al., The metabolism and disposition of 14C-fenofibrate in human volunteers, Drug. Metabol. Dispos. Biol. Fate. Chem., 18 (1990) 115-120).

324 The specification also includes a discussion of surface active substances that might be used in performing the process, as his Honour pointed out (at [433]). Indeed, there is an extensive list of surface active stabilizers that are said to be useful to the invention. Further, phospholipid surface active substances including Phospholipon 100H and Phospholipon 90H are described as preferred, with the phospholipid known as Lipoid E80 (E80) being most preferred. It is convenient to set out the relevant passages:

> [0046] Examples of some suitable surface active substances that are useful in this invention include: (a) natural surfactants such as casein, gelatin, tragacanth, waxes, enteric resins, paraffin, acacia, gelatin, cholesterol esters and triglycerides, (b) nonionic surfactants such as polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxyl propylcellulose, hydroxyl propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, polyvinylpyrrolidone, and synthetic phospholipids, (c) anionic surfactants such as potassium laurate, triethanolamine stearate, sodium lauryl sulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, negatively charged phospholipids (phosphatidyl glycerol, phosphatidyl inosite, phosphatidylserine, phosphatidic acid and their salts), and negatively charged glyceryl esters, sodium carboxymethylcellulose, and calcium carboxymethylcellulose, (d) cationic surfactants such as quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride, (e) colloidal clays such as bentonite and veegum. A detailed description of these surfactants may be found in Remington's Pharmaceutical Sciences, and Theory and Practice of Industrial Pharmacy, Lachman et al, 1986.
>
> …
>
> [0048] Preferred surface active substances are phospholipid surface active substances and mixtures comprising phospholipid surface active substances. Suitable

phospholipids include animal and plant phospholipids; egg phospholipids; soya bean phospholipids; corn phospholipids; wheat germ, flax, cotton, and sunflower seed phospholipids; milk fat phospholipids; glycerophospholipids; sphingophospholipids; phosphatides; phospholipids containing fatty acid esters including palmitate, stearate, oleate, linoleate, and arachidonate which esters can be mixtures and mixtures of isomers in the phospholipids; phospholipids composed of fatty acids containing one or more than one double bonds such as dioleoyl phosphatidylcholine and egg phosphatidylcholine that are not stable as powders but are hygroscopic and can absorb moisture and become gummy; phospholipids composed of saturated fatty acids that are stable as powders and are less amenable to absorption of moisture; phosphatidylserines; phosphatidylcholines; phosphatidylethanolamines; phosphatidylinositols; phosphatidylglycerols such as dimyristoyl phosphatidylglycerol, L-alpha-dimyristoyl phosphatidylglycerol also known as 1,2-dimyristoyl-sn-glyccro-3-phospho(rac-1-glycerol) and also known as DMPG; phosphatidic acid; hydrogenated natural phospholipids; and commercially available phospholipids such as those available from Avanti Polar Lipids, Inc. of Alabaster, Ala., USA. In the absence of an internal counterion in the phospholipid, a preferred counterion is a monovalent cation such as sodium ion. The phospholipid may be salted or desalted, hydrogenated, partially hydrogenated, or unsaturated, natural, synthetic, or semisynthetic.

[0049] Preferred phospholipids include Lipoid E80, Lipoid EPC, Lipoid SPC, DMPG, Phospholipon 100H a hydrogenated soybean phosphatidylcholine, Phospholipon 90H, Lipoid SPC-3, and mixtures thereof. A currently most preferred phospholipid is Lipoid E80.

325 We also note that at an earlier point the specification states:

[0011] In one aspect while it is advantageous in very many cases to use particulate pharmaceutical formulations wherein particle sizes are stabilized by combinations of phospholipids and surface modifiers according to U.S. Pat. No. 5,922,355, it is sometimes desirable to produce pharmaceutical formulations or pre-formulations which are stabilized by biocompatible phospholipids without the use of additional surface active substances. This can be desirable, for example, when there is a subsequent need to modify the composition of a particle-containing formulation in a step following the formation of the particles such as by the addition of one or more additional ingredients that are not compatible with additional surface modifiers shown to be beneficial in U.S. Pat. No. 5,922,355, the disclosure of which is hereby incorporated by reference. In one aspect it is therefore desirable to produce drug particles stabilized by one or more phospholipids in the absence of additional surface modifiers but which exhibit enhanced stability toward particle growth and which maintain sub-micron and micron size particles on subsequent storage as suspension or solid dosage form.

326 Further, the specification states:

[0053] An admixture of a poorly water soluble drug and a surface active substance such as a phospholipid substance can be prepared by adding a surface active substance and the poorly water soluble drug to an aqueous carrier and then mixing at high shear, for example for up to 30 minutes at a shear rate of up to 10,000 rpm. As an example, an admixture of fenofibrate and a phospholipid substance can be prepared by adding a phospholipid substance and fenofibrate to an aqueous carrier and then mixing at high shear for up to 30 minutes at a shear rate of up to 10,000 rpm. Preferably the drug used to form the admixture is in the form of a powder or small crystals or small pieces that are less than about 5 mm in diameter to facilitate mixing. Larger sized crystals or masses of drug can be milled to about 5 mm or smaller before forming the admixture

of used in this invention to facilitate mixing.

…

[0057] After the poorly water soluble drug a surface active substance such as fenofibrate and a phospholipid substance are added to the aqueous carrier, the admixture can then be heated if not already so, preferably in the absence of oxygen such as under a nitrogen or argon atmosphere, until the temperature rises to a first temperature range that is at or above the melting point of the drug. In the case of fenofibrate the admixture in the aqueous carrier can be heated to between 79° C. (the reported lowest melting point of fenofibrate) and 99° C., preferably between 79° C. and 95° C., and most preferably between 80° C. and 90° C. In general it is preferred that the temperature is at or up to about 20° C. above the melting point of the drug. Thus, the preferred first temperature range is in general from the melting point of the drug to about 20° C. above the melting point of the drug. The aqueous carrier can be heated to the first temperature range before or after the addition of the drug and the surface active substance. The admixture is maintained at the first temperature range while high shear mixing is applied. The admixture when thus prepared comprises a crude emulsion of melted drug and surface active substance in the heated aqueous carrier.

327 Further, and as his Honour pointed out (at [434]), the specification describes how a suspension is prepared by mixing and heating milled particles of fenofibrate and one or more surface active substances in an aqueous carrier. The suspension is subjected to an "energetic process", for example, high shear mixing or microfluidization, to produce a heated homogenate. The heated homogenate is then cooled to form a cooled homogenate that is said to be transiently stable. The specification states that it was generally found that cooled homogenate with transiently stable particles of about .3 μm (ie. 300 nm) could be achieved.

328 The specification also includes a description of six different cooling methods that may be applied to the heated homogenate. One of these methods, which involved fast cooling in an isothermally cooled 4°C water bath, was said to produce cooled homogenates that maintained small particles containing fenofibrate to a greater degree than those produced by slower cooling methods. This was said to be especially true when E80 was used as the phospholipid substance. The specification states:

[0091] Cooled homogenate having particle size of less than 1 micrometer can usually be achieved by subjecting the heated homogenate containing melted drug to multiple homogenization passes prior to rapid cooling. The effect of multiple homogenization is to produce smaller particles, but the size reducing effect is non-linear and shows decreasing rates of return, i.e., the average particle size decreases non-linearly with an increasing number of passes.

[0092] In the case of fenofibrate, it was also found that increasing the number of heated homogenization passes from one to two followed by cooling produced a cooled homogenate with smaller particle size with Lipoid E80 but not with Phospholipon 100H or Phospholipon 90H. For example, at 3 hours after cooling, a cooled homogenate sample containing fenofibrate prepared according to method 1 had a

> particle size of 0.56 micrometers when the antecedent heated homogenate had been subjected to two passes of homogenization compared to a particle size of 2.42 micrometers when the antecedent heated homogenate had been subjected to one homogenization pass. When a heated homogenate had been subjected to 10 homogenization passes, the cooled homogenate had a particle size of 0.29 micrometers. It was generally found that cooled homogenate having particle size of about 0.3 micrometers could be achieved from heated homogenate that had been subjected to at least 5 homogenization passes. Additional homogenization produced smaller particles, but at decreasing rates per volume pass. For examples, particles as small as 0.05 micrometers can be achieved under homogenization conditions. Results for one and two homogenization volume passes as a function of phospholipid are displayed in Table 2.
>
> …
>
> [0095] Fast cooling of heated homogenates in a 4° C. bath under non-stirred conditions produces cooled homogenates with minimum change in morphology and particle size from observed in the heated homogenates prior to cooling. For example, we have discovered that fast cooling of heated homogenates containing a phospholipid as the surface active substance and fenofibrate as the drug in a 4° C. bath under non-stirred conditions produced non-crystalline cooled homogenates with minimum change in morphology and particle size from that observed in the heated homogenates prior to cooling. When samples of heated homogenate were held at 80° C. for up to one hour and then cooled to form cooled homogenates that were held for 30 minutes at 5° C., no differences in particle size could be detected as a function of the time the heated homogenate was held at 80° C. before cooling. For optimum processing speed, freshly prepared samples of heated homogenate can be cooled from the first temperature range to a second temperature range immediately after an adequate number of homogenization passes such as five passes of heated homogenization to provide cooled homogenates. However, cooled homogenates thus prepared appear to be transiently stable or metastable toward formation of crystals of drug that can grow larger and precipitate from the suspension of the cooled homogenate if allowed to stand. The formation of larger particles and crystals is enhanced if the cooled homogenate is disturbed such as by stirring or shaking. In another aspect of this invention, bulking agents can be added as solids or in solutions of aqueous carrier to the admixture of drug and a surface active substance in an aqueous carrier in the process of this invention.

329 Further, the smallest particles sizes recorded (.26 μm and .54 μm) relate to the cooled homogenate. These particles were described as only transiently stable. But the particle sizes ultimately achieved were closer to 1.0 μm (.87 μm or more).

330 Further, the specification at [0131] to [0202] sets out 23 examples which were said to be illustrative of the invention claimed. We will refer to three of these examples.

331 Example 15 is described in the following terms:

> [0145] A mixture of 225 parts of Lipoid E80 as the surface active substance, 750 parts of fenofibrate, 375 parts of sorbitol, and 750 parts of sucrose is homogeneously dispersed in 6000 parts of 10 mM pH 8.0+/-0.2 aqueous phosphate buffer using a ProScientific 400 high shear mixer at 2,000 to 3,600 rpm at ambient temperature for 30 minutes, and then heated to 95° C., 15° C. above the melting point of the drug, during continuous high shear mixing at 2,500 to 4,000 rpm. The heated suspension is

> then recirculatively homogenized for 10 batch volume cycles or passes using a Microfluidizer M110Y operated at 3,400 to 3,600 psig while maintained at 85° C. to 99° C. to form a heated homogenate containing the drug. After 10 passes, the heated homogenate is cooled by passage through a heat exchanger cooled by chilled water at 5° C. to 10° C. and the transiently stable cooled homogenate is further homogenized for 10 to 20 batch volume cycles or passes using a Microfluidics M110 EH homogenizer operated at 18,000 psig (peak) while maintained at 4° C. to 13° C. The resulting cooled dispersion comprising small particles containing fenofibrate of size less than 1.0 micron in diameter is then dried by freezing to about 40° C. and lyophilization under vacuum to produce dried small particles containing fenofibrate.

332 It would seem that the particles of fenofibrate that were ultimately produced in Example 15, which were said to be less than 1.0 μm in size, were above the particle sizes referred to in the claims of the 807 patent.

333 Example 20 relates to the food effect of a fenofibrate formulation prepared in accordance with Example 15, as his Honour pointed out (at [439]). The specification states that the formulation was administered to eight human subjects in a cross-over study that measured bioavailability of a single 160 mg oral dose in both fed and fasted conditions. The conclusion drawn from the data obtained, which was based on AUC ratios measuring patients' plasma levels of the drug over time, was that the bioavailability increased by less than 8% when the dose was taken in a fed condition compared with a fasted condition. Example 20 is described in the following terms:

> [0192] Demonstration of the absence of food effect with a microfluidized phospholipid-stabilized microparticle formulation of fenofibrate (IDD-PT™ fenofibrate) in human subjects.
>
> [0193] An IDD-P™ fenofibrate formulation prepared by a hot melt microfluidization process described herein under GMP conditions according to the method of Example 15 was dried by lyophilization and formulated into tablets containing 160 mg of fenofibrate. In the formulation, the IDD-P™ fenofibrate was in the form of microfluidized microparticles stabilized by phospholipid Lipoid E80 and was prepared by microfluidization in the presence of sucrose and sorbitol. The oral bioavailability of the tableted IDD-P™ fenofibrate formulation was tested in the fasting and fed states in a single dose pharmacokinetic study. The study consisted of the administration of a single IDD-P™ fenofibrate tablet containing 160 mg of fenofibrate in 8 human subjects using a crossover design with randomized sequences. The fed condition was obtained with a high fat meal containing 1000 Kcal and 50 g fat. The blood samples were collected before and after each administration at various time points over 96 hours. The drug concentration in blood samples was determined by high-pressure liquid chromatography by monitoring for the level of the metabolite, fenofibric acid. The bioavailability of the drug from a dosage form such as an orally administered composition of the drug is given by the accumulated amount of drug versus time detected in a patient, and is calculated as the area under the curve of a plot of fenofibric acid concentrations detected in blood versus time. The bioavailability ($AUC_{0-\infty}$) data obtained under the fed and fasted conditions are presented in Table 7. The food effect is represented by the ratio of the $AUC_{0-\infty}$ under fed and fasted conditions. The ratio of 95% (fasted/fed) demonstrates the essential absence of food effect on the

bioavailability of IDD-P™ fenofibrate. The ratio of the $AUC_{0-\infty}$ under fasted/fed conditions is 1.07. Thus the bioavailability of microfluidized phospholipid stabilized microparticles of fenofibrate increases by less than 8% between fasted and fed conditions in this example.

334 Example 23 is described in the following terms:

> [0202] A two-treatment, two-period, two-sequence crossover clinical study was performed to evaluate the relative bioavailability of fenofibric acid in blood in 24 healthy volunteers after single dose oral administration of a tablet formulation of this invention comprising phospholipid stabilized microparticles of fenofibrate. The fenofibrate tablet dosage form consisted of 160 mg of fenofibrate and was derived from a dried lyophilized powder of this invention that contained between 0.1% and 3% moisture, and that was obtained from a suspension of microparticles consisting of 10% fenofibrate, 3% Lipoid E80, 10% sucrose, and 5% sorbitol, and that was further blended with sucrose at 5% by weight of the powder plus magnesium stearate at 0.2% plus colloidal silica at 0.2%. The bioavailability of fenofibric acid from the formulation of this invention was compared relative to that of commercially available micronized fenofibrate (Tricor®) in a 200 mg capsule. Each dosage form was taken orally within 5 minutes after a low-fat test meal. The study was divided into 2 study periods, study period 1 and study period 2. At each period a single fenofibrate dose was administered to the subjects. There was a washout period of 10 days between the 2 administrations. Plasma samples were collected before each administration and during the 96 hours following each administration. Assay of fenofibric acid was performed with a validated analytical method (HPLC-UV) on the plasma samples. Relevant pharmacokinetic parameters were determined to evaluate the bioavailability of fenofibric acid after administration of each formulation, and the test formulation was compared to the reference formulation. The following results demonstrate bioequivalence between the formulation of this invention and the commercially available micronized fenofibrate (Tricor®) under low fat fed conditions.

335 It is not necessary to set out the Table although we were taken to this during the hearing.

336 There are 49 claims, but for present purposes it is convenient to set out claim 1 only:

> 1. A process for the preparation of small particles containing a poorly water soluble drug comprising the steps of
>
> (a) mixing at high shear an admixture of a poorly water soluble drug and one or more than one surface active substance in an aqueous carrier in the absence of an organic solvent within a first temperature range at or above the melting point of the poorly water soluble drug to form a heated suspension containing the drug wherein the drug is molten;
>
> (b) homogenizing said heated suspension in a first pressure range and within said first temperature range to form a heated homogenate containing the drug wherein the drug is molten;
>
> (c) cooling said heated homogenate to a second temperature range below the melting temperature of the poorly water soluble drug to form a transiently stable cooled homogenate containing the drug;
>
> (d) applying a particle stabilizing energetic process to said cooled homogenate within a second temperature range below the melting point of the drug and in a second pressure range to form a cooled dispersion of stabilized small particles containing the

drug; and

(e) drying said cooled dispersion to form dried small particles containing the poorly water soluble drug.

THE 807 PATENT: GROUNDS 33 – 35; 38

Introduction

337 Mylan says that the primary judge erred in finding that the asserted claims of the 807 patent were invalid for lack of an inventive step in light of common general knowledge.

338 In particular, it says that the primary judge erred in finding that the asserted claims lacked an inventive step in light of common general knowledge alone by reason of the following circumstances.

339 First, Mylan says that Sun Pharma did not adduce evidence from its experts that the asserted claims lacked an inventive step in light of common general knowledge alone. Rather, Sun Pharma's evidence was directed to the issue of whether the asserted claims lacked an inventive step when considered in the light of the 704 patent as s 7(3) information with common general knowledge. As a result, Mylan's evidence did not address whether the asserted claims lacked an inventive step in light of common general knowledge alone.

340 Secondly, Mylan says that the evidence of Sun Pharma's experts was that they would begin the hypothetical task by finding the 704 patent and trying to prepare compositions based upon it. And there was no evidence that the notional team would have sought to prepare fenofibrate compositions in light of common general knowledge alone.

341 Thirdly, Mylan says that the experts were not cross-examined at trial on the issue of whether the relevant claims lacked an inventive step in light of common general knowledge alone, and nor did they address such matters in the concurrent evidence sessions.

342 Fourthly, Mylan says that the case advanced by Sun Pharma at trial was that the asserted claims lacked an inventive step in light of the 704 patent together with common general knowledge.

343 Fifthly, Mylan says that the primary judge, having found that the asserted claims did not lack an inventive step in light of the 704 patent and common general knowledge (at [428] to [445]), erred in finding that those claims lacked an inventive step in light of common general knowledge alone (at [403] to [419]).

344 Finally, Mylan says that his Honour erred in relying upon Professor Roberts' evidence given in cross-examination (at [412] to [416]) in circumstances where Professor Roberts' evidence was given in the context of a development pathway that relied upon the process of preparing fenofibrate formulations described in the 704 patent, not common general knowledge alone.

345 Before turning to discuss Mylan's arguments in detail, it is appropriate to identify various findings made by his Honour concerning common general knowledge.

The primary judge's findings – common general knowledge

346 His Honour was satisfied that the following matters were common general knowledge as at the priority date (at [388]):

(a) For drugs administered orally in a solid dosage form to reach their site of action in the body, the drug must be released from the dosage form (disintegration), enter solution in the GI tract (dissolution) and be absorbed across the walls of the GI tract, where it enters into systemic circulation and is distributed to tissues and organs, including the site of action.

(b) As the drug is released from the dosage form and absorbed from the GI tract, the concentration of the drug in the blood begins to rise. Once the drug has entered circulation, it may be delivered to organs from which it may be metabolised and/or excreted. The amount of drug in the blood over time reflects the balance between the rate of absorption and the rate of elimination or excretion.

(c) When the rate of absorption and of elimination are equal, the concentration of drug in the blood reaches a peak. This peak is called C_{max}, and can be identified on a graph plotting a concentration-time profile as we have already explained.

(d) The AUC of a concentration-time profile reflects the total amount of the administered drug that reaches the systemic blood circulation, as we have already explained.

(e) AUC can be used to quantify a drug's "oral bioavailability", that is, the fraction of the drug that reaches the systemic blood circulation in its active form.

(f) Bioavailability may be measured as absolute bioavailability, being the amount of drug that reaches the systemic blood circulation when administered orally, compared with the amount of drug that reaches the systemic blood circulation

when administered intravenously. Alternatively, it may be measured as relative bioavailability, which compares the bioavailability of two different oral dosage forms.

(g) In developing solid oral dosage forms, it is frequently an objective to maximise oral bioavailability.

(h) To maximise oral bioavailability, it is necessary to consider a drug's physicochemical properties, as well as physiological factors which influence drug absorption from the GI tract.

(i) For poorly soluble drugs, the rate at which a drug enters solution, being its dissolution rate, is typically the rate-limiting step in the process of absorption and thus, bioavailability.

(j) The Biopharmaceutics Classification Scheme (**BCS**), which was introduced in 1995, provides a basis for making predictions concerning the likely rate and extent of drug absorption following oral administration. It provides, inter alia, that:

- Class I drugs (with high solubility and high permeability) exhibit rapid dissolution, and the rate of drug absorption may be primarily influenced by the rate of gastric emptying.
- Class II drugs have low solubility and high permeability. They are poorly soluble, but once in solution, are rapidly absorbed. For these drugs, dissolution is the rate limiting step.

(k) Particle size could be reduced using comminution or non-comminution methods.

(l) Comminution methods included: fluid energy (air jet) mills, which produce drug particles from 0.5 to 20 μm; ball milling, which can produce very small drug particles of 200 nm or less; media milling which produces particles from 50 nm to over 1 μm; and high pressure homogenisation which produces particle sizes from 50 nm to over 1 μm.

(m) In non-comminution methods, particle size is achieved by nucleation and growth of a precipitate until it reaches the desired size range. Non-comminution methods include precipitation and crystallisation, spray drying and freeze drying.

(n) Surface stabilizers are commonly used in methods of particle size reduction.

(o) When drug particles are reduced in size, the resulting small particles will generally demonstrate an increased tendency to clump or aggregate, to form larger units. This may be called agglomeration or flocculation. This occurs because reducing particle size increases the free energy of the system, and particles behave to reduce the energy.

(p) Particle aggregation is undesirable, since it will reduce the total surface area of the particles, and thereby reduce the dissolution rate.

(q) Particle aggregation can be prevented by adding materials which accumulate at the surface and impede particle aggregation (surface stabilizers). These surface stabilizers reduce the adhesion between small drug particles and provide an energy barrier to particle aggregation, either by providing a physical barrier to particle aggregation (steric hindrance), or by impeding particle aggregation by electrostatic or related forces.

(r) Relatively large polymeric molecules such as HPMC can be used for steric hindrance.

(s) Surfactants assist dissolution.

(t) For new formulations of drugs in clinical use, full clinical safety and efficacy trials will not be required if a new formulation is shown to be bioequivalent to an existing formulation with marketing approval.

(u) Fibrates are typically BCS Class II drugs. That is, they have low solubility in aqueous fluids and dissolution is the rate limiting step for absorption after oral administration.

347 His Honour also accepted that the following matters were also common general knowledge as at the priority date (at [389] and [390]):

(a) The more rapid and complete the drug's dissolution in the aqueous fluids of the GI tract and absorption from the GI tract, the less likely it is that food will impact drug absorption. Accordingly:

- For BCS Class I drugs, food typically has little effect on drug absorption.
- For BCS Class II drugs, the presence of food may result in an increase in drug absorption (a positive food effect). There are a number of

reasons for this. In particular, high fat meals may increase absorption, because fatty substances within the GI tract aid in the dissolution of poorly water soluble drugs.

(b) The dissolution rate can be quantified by the Noyes-Whitney equation, which indicates that the rate at which a drug administered in a solid form will dissolve in the fluids in the GI tract after oral administration depends on factors which include the drug's aqueous solubility and the total surface area.

(c) Drug particle size has important implications for bioavailability.

(d) Particle size reduction was widely used before May 2002 to increase dissolution rates.

(e) Surfactants and surface active agents such as the cationic surfactant sodium lauryl sulfate can be used to impede particle aggregation by electrostatic and related repulsion forces. In this context, surface active agents are examples of surface stabilizers.

348 There is a debate between the parties as to whether his Honour also found that it was a matter of common general knowledge that the identification of a suitable surface stabilizer, or suitable combination of surface stabilizers, requires routine trial and error testing, because absolute prediction of a surface stabilizer's performance in a given system is very rarely achievable; candidate surface stabilizers can be identified through a literature review then tested for suitability. His Honour recorded this item at [389(h)]. We will return to this matter later.

349 His Honour then addressed Sun Pharma's contention that the following matters also formed part of common general knowledge as at the priority date, which Mylan did not accept. First, all else being equal, a drug's dissolution rate increases as aqueous solubility and surface area increase. Smaller drug particles generally dissolve faster than larger particles. Secondly, there is a direct relationship between the surface area of a drug and its dissolution rate. Because the surface area increases with decreasing particle size, higher dissolution rates may be achieved through reduction of the particle size. But the mere increase in the surface area of the drug does not always guarantee an equivalent increase in dissolution rate. Rather, it is the increase in the effective surface area or the area exposed to the dissolution medium, and not the absolute surface area, that is directly proportional to the dissolution rate.

350 With regard to such matters, his Honour then addressed Mylan's reliance on the evidence of Professor Prestidge and Professor Roberts in support of the following propositions (at [391]):

(a) It is difficult to predict whether reducing the particle size of a drug will lead to an increased dissolution rate or removing the food effect due to the complex role of food in the dissolution of a drug.

(b) For example, food can affect the gastric emptying of the drug particles and the dissolved drug which are relevant to the drug reaching the intestines where most drugs are normally absorbed.

(c) Food can also affect the drug transit through the rest of the gastrointestinal tract and also affect the stability of the drug in the gastrointestinal tract and its metabolic transformation of drugs in the gastrointestinal wall and in the liver.

(d) In addition, different food components, for example, fat, protein and carbohydrates, and the effect of food on different drugs can vary between the drugs.

(e) Accordingly, without sufficient data, there is no proper basis for an expectation about the extent of the food effect for a fenofibrate formulation.

(f) Increasing the dissolution rate of a drug will not necessarily lead to a reduction in the food effect.

(g) Reducing the particle size of a drug to increase in surface area per unit weight of the drug, all else being equal, will not necessarily lead to the drug dissolving faster than larger particles and an improved bioavailability.

351 His Honour referred to Professor Prestidge's evidence to the following effect.

352 The Noyes-Whitney equation is used to describe the rate of dissolution for a drug. The implication arising from the Noyes-Whitney equation is that the rate of dissolution for a drug can be modified by altering the surface area of the drug, that is, changing the particle size of the drug. In particular, decreasing the particle size of a drug to maximise its surface area will generally increase the dissolution rate of the drug.

353 Generally, if the dissolution rate of a drug increases, the bioavailability of the drug will increase. However, this will depend on the particular drug and the reason for the low bioavailability.

354 Furthermore, in practice, the dissolution rate and food effect of a drug particle, regardless of its size, may be affected by the type of surface active substance that is used, as different surface active substances can have a different role at the drug particle interface. For example, the

surface active substance could reduce surface wettability and dissolution, that is, interaction of the drug particle with the water. There is also a range of other excipients used in pharmaceutical formulations which have an effect on drug dissolution and bioavailability. Therefore, while the Noyes-Whitney equation represents the general principle that reducing the particle size of a drug increases the dissolution rate, which may lead to a reduced food effect, in practice, it is not this straightforward because bioavailability may be affected by the stabilizer and other excipients used to formulate the drug.

355 In addition, food can impact the way a drug interacts with the body through several mechanisms, such as causing a delay in gastric emptying, stimulating bile flow, changing gastrointestinal pH, alternating luminal metabolism, and interactions of the drug with the food itself. Food can also increase blood flow to the liver and cause changes in first pass extraction, which leads to differences in bioavailability between the fed and fasted state. It is thus difficult to predict whether reducing the particle size of a drug will lead to an increased dissolution rate or removal of the food effect due to the complex role of food in the dissolution of a drug.

356 His Honour accepted this evidence in so far as it suggested that there were a number of factors that came into play when assessing whether reductions in drug particle sizes would increase dissolution rates and the food effect (at [393]). But his Honour said that it was important to note that this evidence was expressed at a high level of generality and was not directed specifically to drugs with low solubility and high permeability, that is, BCS Class II drugs.

357 His Honour then went on to say that he did not think Professor Prestidge's evidence, and the evidence of Professor Roberts to like effect, was inconsistent with the general proposition that, at least in the case of low solubility and high permeability drugs, reducing the particle size was likely to increase bioavailability and reduce the food effect. As Professor Roberts himself said, "… it is generally understood in the pharmaceutical community that as the dissolution rate of a drug increases, the food effect of the drug decreases". But we note that Professor Roberts did make some qualifications. It is convenient to set out the following extracts from his second affidavit:

> Furthermore, it is generally understood in the pharmaceutical community that as the dissolution rate of a drug increases, the food effect of the drug reduces. However, based on my experience and knowledge, I understand that food not only has a complex and multifaceted role in the dissolution of a drug, food can also affect the gastric emptying of the drug particles and the dissolved drug which are relevant to the drug reaching the intestines where most drugs are normally absorbed. There are other means in which food intake can influence the bioavailability of drugs. In addition to interfering with tablet disintegration, drug dissolution and gastric emptying, it may also affect the drug

> transit through the rest of the gastrointestinal tract and also affect the stability of the drug in the gastrointestinal tract and its metabolic transformation of drugs in the gastrointestinal wall and in the liver. In addition, different food components (for example fat, protein and carbohydrates) and the effect of food on different drugs can vary between the drugs. The complex impact of food on dissolution and gastric emptying makes it difficult to determine or predict the extent of the food effect on drug bioavailability of certain drugs, such as fenofibrate. Accordingly, without sufficient data, there is no proper basis for an expectation about the extent of the food effect for this fenofibrate formulation and thus I could not reasonably predict whether a food effect would be removed.
>
> Therefore, reducing the particle size of a drug to increase in surface area per unit weight of the drug, all else being equal, will not necessarily lead to the drug dissolving faster than larger particles and an improved bioavailability. Despite the general principles described by the Noyes-Whitney equation, in practice, there are other factors that may affect the dissolution rate of a drug. Furthermore, increasing the dissolution rate of a drug will not necessarily lead to a reduction in the food effect.

358 His Honour was satisfied that a person skilled in the art as at the priority date would understand that as a general proposition, higher dissolution rates may be achieved through the reduction of particle size (at [394]). He found that the skilled addressee would understand that whether a reduction in particle size of a drug would lead to an increased dissolution rate or removal of the food effect would depend upon the role played by food in the dissolution of a drug. But he found, generally speaking and all else being equal, that smaller drug particles were likely to dissolve faster than larger drug particles. Further, the more rapid and complete the drug dissolution, the less likely that there would be a food effect.

359 His Honour was of the opinion that Professor Prestidge confirmed as much in his oral evidence when he said:

> … if you're exploring a nanoparticle option as a – as a formulation strategy for something like fenofibrate, you would be trying to produce a stable formulation with the smallest possible size, because we know size correlates with surface area, correlates with dissolution and hence absorption in the body, so that's the whole reasoning for doing this.

The appeal

360 Mylan says that his Honour's conclusion of a lack of inventive step based upon common general knowledge alone was inconsistent with the evidence of Sun Pharma's experts, Associate Professor Morton and Dr Williams, that they would begin the hypothetical task by finding the 704 patent and then try to prepare compositions based upon it.

361 Further, Mylan says that there was no evidence that the notional team would have sought to prepare fenofibrate compositions based on common general knowledge alone. According to Mylan, no expert gave evidence that he would have approached the hypothetical task of

developing a pharmaceutical formulation of fenofibrate based on common general knowledge alone.

362 We should say now that we accept that Dr Williams and Associate Professor Morton addressed in their written evidence the hypothetical task of developing a pharmaceutical formulation of fenofibrate for use in the management of dyslipidaemia including in patients affected by diabetes mellitus (the relevant task). They approached the relevant task by first conducting a literature review which found the 704 patent. Then, armed with the information in the 704 patent, those experts suggested that they would proceed to prepare formulations of fenofibrate disclosed in that patent. But in their written evidence they did not expressly explain the steps that they would have taken in response to the relevant task, armed only with common general knowledge.

363 Mylan says that Dr Williams gave evidence that compared to prior art formulations of fenofibrate, the formulations of the 704 patent provided increased bioavailability and elimination of the food effect and that he would have worked to prepare a solid oral dosage form of fenofibrate, such as a tablet or a capsule, using the process described in the 704 patent to achieve increased oral bioavailability and elimination of the food effect that had been observed with previous, micronised fenofibrate formulations.

364 To similar effect, Mylan says that Associate Professor Morton stated that he would have had regard to, and been substantially guided and assisted by, the 704 patent in carrying out the relevant task and that he would have worked to prepare a solid oral dosage form of fenofibrate, such as a tablet or capsule, using the general nature of the processes described in the 704 patent.

365 Mylan says that its experts Professor Roberts and Professor Prestidge in their written evidence responded to the hypothetical development pathway suggested by Dr Williams and Associate Professor Morton which relied upon the information in the 704 patent. It says that neither Professor Roberts nor Professor Prestidge gave evidence that they would have approached the relevant task based on common general knowledge alone.

366 Further, Mylan says that the joint expert questions which were addressed in the expert concurrent evidence at trial concerning the 807 patent were not directed to common general knowledge concerning the 807 patent but rather the 704 patent (see question 30). Mylan says that on the issue of inventive step, the experts during the concurrent evidence sessions were only asked questions and proffered answers in the context of the 704 patent. Mylan says that

none of the experts gave evidence at trial that they would have approached the relevant task based on common general knowledge alone.

367 More generally, Mylan says that Sun Pharma did not advance a case at trial that the asserted claims lacked an inventive step in light of common general knowledge alone. Rather, Sun Pharma ran a s 7(3) case relying upon the 704 patent. As we have noted, it was not in dispute that the 704 patent constituted s 7(3) information that, as at the priority date, a person skilled in the art could reasonably be expected to have ascertained, understood and regarded as relevant to the development task.

368 Indeed, Mylan says that given the nature of the written and oral evidence it is unsurprising that at no time did Sun Pharma submit that the claimed invention was obvious in light of common general knowledge alone. It says that Sun Pharma's case before the primary judge was that the information in the 704 patent formed a fundamental part of the development pathway that would be pursued in seeking to develop a pharmaceutical formulation of the drug fenofibrate.

369 Further, Mylan says that the primary judge fell into error (at [402] to [410]) in summarising Sun Pharma's inventive step analysis without regard to the information contained in the 704 patent.

370 Further, Mylan says that his Honour took Professor Roberts' evidence out of context. Mylan points out that the primary judge found Professor Roberts' evidence to be "of considerable assistance in understanding how the notional team would have proceeded if seeking to address the problem to which the 807 Patent [was] directed as at 24 May 2002" (at [411]). The primary judge also relied upon Professor Roberts' evidence given in cross-examination (at [412] to [416]). But in so doing, Mylan says that the primary judge failed to acknowledge that Professor Roberts' evidence was given in the context of a development pathway which relied upon the process of preparing fenofibrate formulations described in the 704 patent, not common general knowledge alone.

371 Further, Mylan says that the primary judge omitted the contribution made by the 704 patent when he made the following findings in respect of the development pathway that the notional team would undertake:

> [417] Professor Roberts' evidence satisfies me that as at 24 May 2002, if the notional team had been presented with the problem addressed in the 807 patent, it is likely that it would have sought to produce a new fenofibrate formulation using very small fenofibrate particles (which Professor Prestidge described as the "nanoparticle option") and a combination of SLS and HPMC to stabilize the fenofibrate particles and

to assist their dissolution in the GI tract.

[418] From that point the work of the notional team in optimizing the fenofibrate formulation to maximise bioavailability by reducing the fenofibrate particle size, and increasing the stability of the formulation, would be completely routine. This work would involve straightforward experimentation aimed at optimizing the formulation by varying the ratio of fenofibrate, HPMC and SLS in order to minimise particle size and maximise the stability of the formulation. None of this work would require the exercise of any inventive ingenuity on the part of the notional team or necessitate the use of any information that was not common general knowledge as at 24 May 2002.

[419] The development pathway I have just outlined was acknowledged by Professor Roberts to be logical. It is a development pathway that I am satisfied the notional team would have been likely to follow as at 24 May 2002 in the expectation that it may well produce a fenofibrate formulation that substantially eliminated, or at least substantially reduced, the food effect.

372 Mylan says that the primary judge's failure to take into account the fundamental contribution made by the information contained in the 704 patent to the development pathway is significant. There was no evidence that the process and examples described in the 704 patent formed part of the common general knowledge.

Discussion

373 In our view, the primary judge's conclusion of obviousness based on common general knowledge alone was not inconsistent with the expert evidence as such.

374 Further, his Honour was not precluded from finding obviousness in the light of common general knowledge considered separately merely because Sun Pharma also invoked information of the kind mentioned in s 7(3). Reliance on a document meeting the requirements of s 7(3) does not diminish the content of common general knowledge.

375 Sun Pharma accepted before us that it did not substantively present two obviousness cases, namely, one based on common general knowledge considered separately, and one based on common general knowledge considered with s 7(3) information (cf the primary judge's characterisation of Sun Pharma's case at [396]). It only substantively presented the latter. But in our view this did not preclude his Honour from determining that the foundation of common general knowledge alone was sufficient to render the invention obvious; indeed we note that Sun Pharma's amended particulars of invalidity (at [8(a)]) clearly pleaded such a case as one of the alternatives.

376 However the case was run, the primary judge was always required to first determine the content of common general knowledge. This was also a necessary foundation for the s 7(3) case. It is

trite to observe that the s 7(3) information is not considered in isolation. Rather, it is considered together with common general knowledge.

377 The Act expressly recognises that information that forms part of common general knowledge is separate from s 7(3) prior art information. It is well established that common general knowledge constitutes part of the mental equipment of those concerned in the art. It is "the background knowledge and experience which is available to all in the trade in considering the making of new products, or the making of improvements in old" (*Lockwood No 2* at [55] citing Aickin J in *Minnesota Mining and Manufacturing Co v Beiersdorf (Australia) Ltd* (1980) 144 CLR 253 at 292). Of course, the party alleging obviousness must usually establish the state of common general knowledge by evidence. Information cannot be treated as part of common general knowledge unless there is some evidence, directly or by inference, of its general acceptance and assimilation by persons skilled in the art.

378 However the case was run, the primary judge necessarily had to determine the foundation of common general knowledge. It was always open to him to consider the question of inventive step based upon that foundation alone.

379 The primary judge observed that Sun Pharma's case "was largely based upon common general knowledge and also the oral evidence of Professor Roberts" ([403]). Professor Roberts' evidence in the concurrent evidence sessions was not confined to an attempt to prepare formulations in the 704 patent. Other aspects of his evidence went to matters of pharmaceutical science at the priority date.

380 Mylan says that the difficulty for Sun Pharma with the finding (at [403]) is that the evidence of Professor Roberts that the primary judge relied on to find lack of inventive step did not form part of common general knowledge. Rather, Mylan says that this evidence formed part of the evidence which was prior art information only available under s 7(3). It makes this point because it says that Professor Roberts' evidence that the judge relied on was responding to questions in respect of the 704 patent.

381 Mylan says that the evidence of Professor Roberts relied upon by the primary judge (at [412] to [417]) was only given in the limited context of the information contained in the 704 patent. It is said that this is evident from the questions that he was asked in cross-examination where Sun Pharma's counsel took Professor Roberts to Examples 15 and 20 in the 704 patent and

then asked him whether he would reduce the particle size. Similarly, Sun Pharma's counsel took Professor Roberts to the 704 patent and asked him whether he would change the stabilizer.

382 Further, Mylan says that the subject of HPMC being used as a possible stabilizer first arose by Sun Pharma's counsel referring Professor Prestidge and then Professor Roberts to HPMC as being one of the stabilizers referred to in the 704 patent.

383 Mylan also says that Professor Roberts' evidence that he "would give them [SLS and HPMC] a go" was also in the context of Sun Pharma's counsel asking Professor Roberts about the process described in the 704 patent.

384 Similarly, Professor Roberts' evidence that "it's a gamble" was in response to a question by Sun Pharma's counsel as to whether Professor Roberts would be "optimistic" of achieving a particle size of around 300 nm by taking Example 20 in the 704 patent and varying the use of stabilizers by using SLS and HPMC.

385 Further, Mylan also points out that the fact that the cross-examiners asked the experts questions about the disclosures in the 704 patent and not common general knowledge alone is unsurprising given that the parties had agreed joint expert subjects based on the 704 patent and not common general knowledge alone.

386 In our opinion, even if the questioning of particular witnesses assumed an awareness of or arose from the context of the 704 patent, that does not entail that his Honour could not use such evidence as a basis for finding common general knowledge.

387 First, it is not a question of what particular witnesses said or would have done. One is looking at the legal construct of the person skilled in the art and common general knowledge in that context. Regardless of s 7(3) and the 704 patent, that question had to be assessed on the totality of the evidence before his Honour, including the evidence of experts such as Professor Roberts.

388 Secondly, this was not a case where his Honour was taking the *content* of the 704 patent and contaminating the base of common general knowledge by reference to that content. He assessed and ascertained such a base without such contamination.

389 Thirdly, it is to be recalled that the relevant task was not predicated on locating or using the 704 patent. It was "the task of developing a pharmaceutical formulation of the drug fenofibrate for use in the management of …".

390 Further, Mylan says that the evidence of Professor Roberts relied upon by the primary judge was different to the evidence given by the other experts in the proceeding. Therefore it could not be considered to form part of the background knowledge and experience that was available to all in the relevant field.

391 But this point is misconceived. Professor Roberts' evidence in relevant respects was not contradicted by the other experts. Further, given the construct within which his Honour was considering common general knowledge, there was no bar to his Honour taking the evidence of one expert to inform himself on that question.

392 Further, even if it be the case that Dr Williams and Associate Professor Morton knew little if anything about fenofibrates before seeing the 704 patent, one is here dealing with the question of common general knowledge and the notional team, which is a broader lens.

393 Further, Mylan says that the matters that the primary judge found formed part of the common general knowledge at [388] to [394] were insufficient to support a finding of lack of inventive step. But as to his Honour's common general knowledge findings ([388(g), (i), (j), (l), (n), (q), (r), (t) and (u)] and [389] to [394]), which were either not sought to be challenged or have not successfully been challenged before us on this appeal, such matters demonstrated that it was well understood by the priority date that by reducing the particle size of poorly soluble permeable drugs, that is, BCS Class II drugs, and by formulating those particles with suitable surface stabilizers, which were usually selected by a routine process of trial and error, their dissolution profile and therefore their oral bioavailability could generally be improved, thereby reducing the food effect.

394 Although the 704 patent confirmed that such general principles applied to fenofibrate, it was in any event common general knowledge that fibrates including fenofibrate were typically BCS Class II drugs. So, one would have expected such general principles to apply.

395 In our view, the primary judge's conclusion is therefore unsurprising:

> 445 The 704 Patent is significant in that it confirms that by reducing the size of fenofibrate particles in a fenofibrate composition suitable for oral administration, it may be possible to eliminate or substantially eliminate the food effect. However, in this respect, I do not think it would tell the notional team anything more than it would already deduce from the common general knowledge.

396 Mylan says that the common general knowledge identified by the primary judge at [388] to [394] did not support such general principles.

397 Mylan accepts that the primary judge did find that "a person skilled in the art as at 24 May 2002 would understand that, as a general proposition, higher dissolution rates may be achieved through the reduction of particle size" (at [394]). But his Honour qualified this proposition at [394] by saying that the skilled addressee would understand that whether a reduction in particle size of a drug would lead to an increased dissolution rate or removal of the food effect can depend upon the role played by food in the dissolution of a drug and generally speaking, all else being equal, smaller drug particles would be more likely to dissolve faster than larger drug particles.

398 Further, Mylan says that although Sun Pharma submitted that the 704 patent confirmed that such general principles applied to fenofibrate, this cannot assist Sun Pharma as it did not contend or establish that the 704 patent formed part of common general knowledge. In any event, Mylan says that the 704 patent does not provide any support. The 704 patent does not provide any information on the dissolution rate of the resultant fenofibrate formulation. Further, the fenofibrate formulations of the 704 patent were prepared using the specific five step methodology disclosed in the 704 patent, and not by a routine process of trial and error. Further, Professor Roberts did not consider the process for preparing a fenofibrate composition using the 704 method to be "straightforward". The 704 method involved a number of steps, and some of those steps had the potential to fail if care was not taken. Mylan says that the complexity of the method disclosed in the 704 patent is inconsistent with the proposition that it is a simple matter to produce smaller particles of a drug with a surface stabilizer to reduce the food effect.

399 Further, Mylan says that the primary judge's finding at [445] does not confirm such general principles. The primary judge's finding does not refer to the solubility, dissolution profile or bioavailability of fenofibrate or the use of surface stabilizers in formulating fenofibrate. In any event, the primary judge's comment concerning common general knowledge is at odds with the list of common general knowledge identified by him at [388] to [394], which does not include any matters going to the nature of fenofibrate, its existing formulations or problems with those formulations.

400 We reject Mylan's contentions. Professor Roberts said (at [5.11] and [5.12]):

> Furthermore, it is generally understood in the pharmaceutical community that as the dissolution rate of a drug increases, the food effect of the drug reduces. However, based on my experience and knowledge, I understand that food not only has a complex and multifaceted role in the dissolution of a drug, food can also affect the gastric emptying

of the drug particles and the dissolved drug which are relevant to the drug reaching the intestines where most drugs are normally absorbed. There are other means in which food intake can influence the bioavailability of drugs. In addition to interfering with tablet disintegration, drug dissolution and gastric emptying, it may also affect the drug transit through the rest of the gastrointestinal tract and also affect the stability of the drug in the gastrointestinal tract and its metabolic transformation of drugs in the gastrointestinal wall and in the liver. In addition, different food components (for example fat, protein and carbohydrates) and the effect of food on different drugs can vary between the drugs. The complex impact of food on dissolution and gastric emptying makes it difficult to determine or predict the extent of the food effect on drug bioavailability of certain drugs, such as fenofibrate. Accordingly, without sufficient data, there is no proper basis for an expectation about the extent of the food effect for this fenofibrate formulation and thus I could not reasonably predict whether a food effect would be removed.

Therefore, reducing the particle size of a drug to increase in surface area per unit weight of the drug, all else being equal, will not necessarily lead to the drug dissolving faster than larger particles and an improved bioavailability. Despite the general principles described by the Noyes-Whitney equation, in practice, there are other factors that may affect the dissolution rate of a drug. Furthermore, increasing the dissolution rate of a drug will not necessarily lead to a reduction in the food effect.

401 This and other evidence including that referred to by the primary judge at [391] and [392] adequately supported the following findings made by his Honour:

> 393 I accept this evidence in so far as it suggests that there are a number of factors that come into play when assessing whether reductions in drug particle sizes will increase dissolution rates and the food effect. However, it is important to note that it is expressed at a high level of generality and is not directed specifically to drugs with low solubility and high permeability (ie. BCS Class II drugs). I do not think Professor Prestidge's evidence, and evidence of Dr Roberts to like effect, is inconsistent with the general proposition that, at least in the case of low solubility and high permeability drugs, reducing the particle size is likely to increase bioavailability and reduce the food effect. As Dr Roberts himself said "… it is generally understood in the pharmaceutical community that as the dissolution rate of a drug increases, the food effect of the drug decreases."
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> 394 I am satisfied that a person skilled in the art as at 24 May 2002 would understand that, as a general proposition, higher dissolution rates may be achieved through the reduction of particle size. The skilled addressee would understand that whether a reduction in particle size of a drug would lead to an increased dissolution rate or removal of the food effect can depend upon the role played by food in the dissolution of a drug. However, generally speaking, all else being equal, smaller drug particles would be more likely to dissolve faster than larger drug particles. Further, the more rapid and complete the drug dissolution, the less likely that there will be a food effect. I think Professor Prestidge confirmed as much in his oral evidence when he said:
>
> > … if you're exploring a nanoparticle option as a – as a formulation strategy for something like fenofibrate, you would be trying to produce a stable formulation with the smallest possible size, because we know size correlates with surface area, correlates with dissolution and hence absorption in the body, so that's the whole reasoning for doing this.

402 In our view, the generality of the evidence supported the *general* principles and the widespread acceptance thereof, even if there were exceptions. The fact that there were possibilities for departure did not deny that one would undertake the hypothetical development task assuming the general principles applied. We reject Mylan's contention that the primary judge at [393] and [394] went well beyond the evidence.

403 In summary, we reject these grounds of appeal.

THE 807 PATENT: GROUND 36

404 Mylan asserts that the primary judge erred in finding that the notional team would know of the need for a new fenofibrate formulation suitable for oral administration that eliminated the food effect and that this problem was common general knowledge (at [399] to [401], [404] and [445]).

The primary judge's reasons

405 His Honour said that the invention described in the 807 patent is not one in which any inventive step resides in the inventors' perception of the problem to which their experimental work was then directed (at [399]). His Honour referred to the fact that p 6 lines 15 to 24 of the specification contains an acknowledgement that the bioavailability of fenofibrate, a drug that is insoluble in water, had different effects when administered orally depending on whether it was administered in a fed or fasted condition. His Honour said that, although the specification refers also to "other problems", for example, the size and number of the conventional oral dosages, these are directly related to low bioavailability of the drug when orally administered in its conventional, that is, micronized form.

406 His Honour said that he was satisfied that the various problems to which the 807 patent was directed were well known and common general knowledge as at the priority date. In particular, it was common general knowledge that fenofibrate was a poorly soluble drug the therapeutic effect of which depended, when taken in oral dosage form, on whether the patient was fed or fasted at the time of administration; he referred to this as the food effect.

407 Further, his Honour said that the invention described in the 807 patent was not one in which any inventive step resided in the use of the formulations of the invention in a method of treatment (at [400]).

408 His Honour said that if any of the relevant claims involved an inventive step, it would reside not in the inventors' perception of the problems associated with the oral administration of fenofibrate, but in the inventors' solution to those problems represented by the particular formulations claimed (at [401]).

409 Further, his Honour said:

> 445 The 704 Patent is significant in that it confirms that by reducing the size of fenofibrate particles in a fenofibrate composition suitable for oral administration, it may be possible to eliminate or substantially eliminate the food effect. However, in this respect, I do not think it would tell the notional team anything more than it would already deduce from the common general knowledge.

The appeal

410 Mylan says that it was not open to the primary judge, in the absence of any evidence to this effect, to find that the notional team would know of the need for a new fenofibrate formulation suitable for oral administration that eliminated the food effect, and that this was a problem which formed part of common general knowledge (at [399], [404] and [445]).

411 According to Mylan, the evidence did not support a finding that common general knowledge included knowledge that there was a need to address the food effect for existing fenofibrate formulations. Further, it says that this was not an issue identified by the parties for determination.

412 Further, Mylan says that the list of common general knowledge matters identified by the primary judge did not include any matters going to the nature of fenofibrate, its existing formulations or problems with those formulations (at [386] to [394]).

413 The primary judge found that it was common general knowledge as at 24 May 2002 that "[f]or BCS Class II drugs, the presence of food may result in an increase in drug absorption (a positive food effect)" and that fibrates of which fenofibrate was a member were "typically" BCS Class II drugs (at [389(a)] and [390]). But Mylan says that this does not equate to knowledge that existing formulations of fenofibrate had a food effect. Further, it does not equate to knowledge that there was a need for a new fenofibrate formulation suitable for oral administration that eliminated the food effect.

414 Mylan says that there was no evidence that the skilled addressee knew that fenofibrate was a BCS Class II drug or, if it was, that it had a food effect. Further, it says that although some

tendered documents such as the 704 patent disclosed that existing formations of fenofibrate had a food effect, none of those documents were part of common general knowledge.

415 Further, Mylan says that the experts' approach to the relevant task did not proceed on the basis that, without regard to the 704 patent, there was a need for a new fenofibrate formulation suitable for oral administration that eliminated the food effect.

416 It points out that Sun Pharma's experts found the 704 patent when responding to the relevant task, but the relevant task did not refer to the need to eliminate or even address the food effect when formulating fenofibrate.

417 Mylan had to accept that the 704 patent disclosed a formulation of fenofibrate that may eliminate or substantially eliminate the food effect, but it said that the 704 patent did not form part of common general knowledge. It submitted that without regard to the 704 patent, the need for a new fenofibrate formulation suitable for oral administration that eliminated the food effect was not a problem that could be attributed to the notional team. Therefore, seeking to eliminate the food effect was not a legitimate starting point (*AstraZeneca v Apotex* at [203] per the plurality).

418 More generally, it said that there was no evidence that the relevant problem formed part of common general knowledge.

Discussion

419 We reject Mylan's submission that there was no evidence before the primary judge that the problem was common general knowledge.

420 Dr Williams' evidence was that he understood before the priority date that fibrates belonged to Class II in the BCS classification scheme. So, they were poorly water-soluble but had high permeability. Indeed, when he was given the task of formulating fenofibrate, but before he had seen the 704 patent, Dr Williams identified that fibrates were typically BCS Class II, so that low solubility in aqueous fluids was likely to be an important consideration. Further, he understood that the presence of food in the GI tract commonly led to an increase in the rate of absorption following administration. As he said in his third affidavit:

> Before May 2002, I understood that fibrates belong to Class II in the BCS classification to which I referred in paragraphs 83 to 85 of my First Affidavit. As I explained there, drugs belonging to BCS Class II are poorly water-soluble (that is, they have low solubility) but, once in solution, are quite rapidly absorbed across the GI tract wall (that is, they have high permeability), with the result that dissolution is commonly the rate-

limiting step for absorption following oral administration of BCS Class II drugs.

Furthermore, as I explained in paragraph 98 of my First Affidavit, before May 2002 I understood that the presence of food in the GI tract commonly leads to an increase in the rate at which BCS Class II drugs are absorbed following oral administration, including for the reason that the presence of fats in foodstuffs, and bile salts released following ingestion of a meal, typically act to increase the dissolution rate (and hence absorption) of BCS Class II drugs.

421 Further, Dr Williams said in his first affidavit:

> Before May 2002, I was familiar with fibrates as a class of drugs used in the management of dyslipidaemia. Before May 2002, I was also aware of some general properties of fibrates, including that drugs in this class typically have the properties of BCS Class II drugs, and understood that low solubility in aqueous fluids was likely to be an important consideration when formulating such drugs for oral administration. I was also aware that fibrates are esters that are converted to an active metabolite by esterases (that is, enzymes that cleave ester bonds) during or shortly after their absorption into the body. Furthermore, I was aware that fibrates are generally used in the treatment of raised blood lipids and related conditions.
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> …
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> Paragraph 14 of the "Background" section records that fenofibrate is a potent lipid modulator. Before May 2002, I was aware that fibrates were used in the treatment of lipid disorders, as I explained in paragraph 130, above.
>
> …
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> Paragraphs 13 and 15 of the 704 Patent record that fenofibrate is a poorly water soluble drug, is poorly absorbed after oral administration, and normally needs to be taken with food. This is consistent with the understanding of fibrates generally that I had before May 2002. As I explained in paragraph 85(b), above, in the case of drugs with very low water solubility, dissolution of the drug in the GI tract fluids is commonly the rate-limiting step for drug absorption after oral administration. As I explained in paragraph 98, above, absorption of such drugs may be increased by the presence of food in the GI tract, by mechanisms including slowed gastric emptying, increased gastric volume, increased GI tract blood flow, and the solubilizing effects of fats present in food and of bile acids secreted into the GI tract after a meal. Before May 2002, I understood that many poorly water soluble drugs were recommended to be taken with food, to enhance drug absorption from the GI tract.

422 Although it may be accepted that Dr Williams referred to the 704 patent in parts, he was in essence confirming his prior knowledge.

423 This evidence is consistent with the primary judge's findings at [388(j) and (u)] and [389(a)]. It was common general knowledge that BCS Class II drugs had low solubility and high permeability, so that once in solution they were rapidly absorbed. Further, Mylan did not contest that, for BCS Class II drugs, the presence of food may result in a positive food effect. The primary judge's findings as to the evidence in relation to food effect (at [388] to [394]) accurately record the evidence of Professor Roberts and Professor Prestidge.

424 Mylan says that although as at the priority date Dr Williams had some high-level knowledge about fibrates, he did not have any specific knowledge about the fenofibrate formulations that were on the market at that date, nor whether those formulations had a food effect and thus were open to improvement in that context.

425 Mylan accepts that the primary judge found at [389] and [390] that it was common general knowledge as at the priority date that "[f]or BCS Class II drugs, the presence of food may result in an increase in drug absorption (a positive food effect)" and at [388(u)] that fibrates, of which fenofibrate was a member, were typically BCS Class II drugs. But it says that this does not equate to knowledge that existing formulations of fenofibrate had a food effect; nor does it equate to knowledge that there was a need for a new fenofibrate formulation suitable for oral administration that eliminated the food effect.

426 Mylan says that there was no evidence that the skilled addressee knew that fenofibrate was a BCS Class II drug or, if it was, that it had a food effect. Further, whilst some tendered documents such as the 704 patent disclosed that existing formulations of fenofibrate had a food effect, none of those documents were established to be part of common general knowledge of the notional team.

427 In our view, the invention in the 807 patent concerned fenofibrates, a member of the class of fibrates. There was evidence before the primary judge that established that it was common general knowledge that fibrates were of BCS Class II and therefore may have a food effect. Moreover, there was no reason to conclude, as a matter of common general knowledge, that fenofibrates were not typical of that class.

428 We accept though that his Honour may have overstated the evidence when he said:

> 399 … In particular, it was common general knowledge, as at that date, that fenofibrate was a poorly soluble drug the therapeutic effect of which depended, when taken in oral dosage form, on whether the patient was fed or fasted at the time of administration ("the food effect").

429 Sun Pharma's point, with which we agree, was more that it was common general knowledge that fibrates generally were BCS Class II drugs and may well have a food effect. So it was submitted in oral submissions:

> And in the absence of any evidence causing a person of skill in the art to think that fenofibrate might be an exception to the class, there is no reason to think that it didn't form a conventional member of the class. And so whilst there is, we accept, a more narrow proposition expressed at the conclusion of 399 than is seen in the evidence, it doesn't affect his Honour's reasoning, because it was sufficient for the purposes of

> obviousness based on common general knowledge alone of the common general knowledge as to fibrates as a class to gather that.
>
> …
>
> [T]here was evidence from both Professor Williams and Professor Roberts that it was desirable to avoid the food effect if possible. And so once you know there's a real likelihood of BCS Class II, and therefore food effect, then you are motivated to proceed so as to avoid the impact of any food effect without necessarily having to know the extent of it.

430 Further, we agree with Sun Pharma that it would be passing strange if armed with the common general knowledge about BCS Class II drugs and a likely food effect, in the absence of any reason to think that fenofibrate was not typical of its class, the notional team would proceed as if there were no food effect. Mylan accepted that it was common general knowledge that fibrates were typically BCS Class II drugs. So, they had low solubility in aqueous fluids, and dissolution was the rate limiting step for absorption after oral administration.

431 Mylan says that its senior counsel asked Dr Williams to assume that the notional drug team was told certain matters as part of the development brief which included that existing fenofibrate formulations had a food effect, so as to inquire whether the 704 patent would have met that development brief. Dr Williams confirmed that it did. Mylan's senior counsel did not ask Dr Williams whether he was aware of this problem without regard to the 704 patent or whether it formed part of the common general knowledge. But whether that be so cannot avail Mylan. Independently of that questioning, there was evidence to support his Honour's findings.

432 Further, Mylan says that before seeing the 704 patent, Sun Pharma's experts were given the relevant task. But the relevant task did not refer to the need to eliminate or even address the food effect when formulating fenofibrate. Sun Pharma's experts found the 704 patent when responding to the relevant task and the 704 patent disclosed a formulation of fenofibrate that may eliminate or substantially eliminate the food effect. But accepting all this to be so, where does it go? None of this is to deny that there was a sufficient evidentiary foundation before his Honour. The fact that the relevant task did not refer to eliminating the food effect does not entail that the food effect problem was not part of common general knowledge.

433 For these reasons we reject this ground of appeal.

THE 807 PATENT: GROUND 37

434 Mylan asserts that the primary judge erred in finding that "the notional team would try HPMC and SLS, both of which were commonly used in the formulation of pharmaceuticals to prevent or reduce particle agglomeration and to assist in dissolution" (at [408]).

The primary judge's reasons

435 Before his Honour, Sun Pharma submitted that the claimed invention was obvious because, as at the priority date, the notional team, seeking to solve the problem to which the 807 patent was directed, would have been directly led as a matter of course to develop a pharmaceutical formulation consisting of very small particles of fenofibrate stabilized by HPMC and SLS in an aqueous dispersion suitable for use in the preparation of a stable composition suitable for oral administration, the bioavailability of which did not depend on the food effect. It was contended that the notional team would have followed this development pathway in the expectation that the resulting composition might well have eliminated the food effect.

436 His Honour recorded Sun Pharma's contention that the claimed invention was obvious largely based upon common general knowledge and the oral evidence of Professor Roberts (at [403]).

437 His Honour summarised Sun Pharma's inventive step analysis in the following terms (at [404] to [410]). First, the problem to be addressed was common general knowledge. The notional team would know of the need for a new fenofibrate formulation suitable for oral administration that eliminated the food effect. Secondly, the notional team would understand that the best way to go about improving bioavailability and eliminating the food effect, would be to produce very small particles of fenofibrate for use in the new formulation. This was because, generally speaking, the smaller the particle size the more rapid and complete the dissolution of the drug. Thirdly, the notional team would also understand that it could produce very small fenofibrate particles of 200 nm or less using a variety of well known techniques including ball milling, media milling, high pressure homogenization or a combination of these techniques. Fourthly, the notional team would understand that because very small fenofibrate particles would have a tendency to agglomerate, it would be necessary to use surface stabilizers in order to prevent or reduce any such agglomeration. Fifthly, the notional team would try HPMC and SLS, both of which were commonly used in the formulation of pharmaceuticals to prevent or reduce particle agglomeration and to assist in dissolution. Sixthly, determining the concentration(s) of surface stabilizer to fenofibrate in the new formulation would be straightforward. The notional team would use the critical micelle concentration (**CMC**) as a guide for determining how much

HPMC and SLS was required in the new formulation to achieve and maintain the desired particle size. So, by following this development pathway, the notional team would more than likely produce stable fenofibrate particles of about 200 nm or less in size that were suitable for use in the preparation of a new fenofibrate formulation with high bioavailability and no food effect.

438 His Honour then went on to say (at [411]) that he found Professor Roberts' evidence to be of considerable assistance in understanding how the notional team would have proceeded if seeking to address the problem to which the 807 patent was directed as at the priority date.

439 He recorded that Professor Roberts accepted that if he was seeking to reduce or eliminate the food effect, he would seek to reduce the size of the fenofibrate particles and that this would lead him to identify a preferable surfactant or surface stabilizer (at [412]). His Honour recorded that Professor Roberts also accepted that SLS and HPMC, either alone or in combination, would be leading candidates that he would try if he were seeking to reduce the particle size of fenofibrate. Professor Roberts said that based on his knowledge as at the priority date, he would give them a go. His Honour took this to mean that Professor Roberts considered that such a combination would be worth trying.

440 His Honour found that Professor Roberts knew that HPMC could be used as a surface stabilizer, that it was very effective at coating particles so that they did not agglomerate, and that it had a steric effect (at [413]). He found that Professor Roberts also knew that SLS, a negatively charged surface active agent, would assist with the dissolution of the fenofibrate in the GI tract. Professor Roberts also knew that the mechanism of action of the HPMC and SLS would have a complementary effect.

441 His Honour recognised that Professor Roberts dealt in his oral evidence with the issue of stabilizer concentration (at [414]). According to his Honour, Professor Roberts' evidence showed that it would be a straight-forward process to establish a suitable ratio of stabilizer to fenofibrate by using the CMC to establish the maximum concentration of stabilizer that should be used. But once the CMC was exceeded, there would be little if any additional effect. Professor Roberts also made it clear, according to his Honour, that the relevant CMC could be established by methods that were common general knowledge as at the priority date.

442 His Honour went on to say that Professor Roberts made clear that he could not be certain that a fenofibrate formulation that used HPMC and SLS would work (at [415]). After indicating

that the 807 patent showed that such a combination could be used to produce stabilized fenofibrate particles of about 300 nm in size, his Honour recorded that Professor Roberts gave the following evidence:

> MR MURRAY: Yes. Are you able to express an opinion as to your level of optimism putting the 807 aside?
>
> PROF ROBERTS: It's a gamble. I mean, a whole – all sorts of developments are gambles. Sometimes they work; sometimes they don't. I think I would be very – what's the word? – foolhardy to suggest to you that I would be sure it would work.
>
> MR MURRAY: Thanks. Do you think the logic – the rationale for that approach of changing the surface agent using, for example, SLS and HPMC, has a found [sic] rationale as a matter of chemistry value?
>
> PROF ROBERTS: I might have used that, but others may not agree with me.
>
> MR MURRAY: I'm only asking about you .....
>
> HIS HONOUR: Yes, but it's – I think he's asking whether you would accept that it's a logical way to proceed.
>
> PROF ROBERTS: I think it is.
>
> HIS HONOUR: Back in 2002.
>
> MR MURRAY: Yes.
>
> PROF ROBERTS: I think it is.

443 Notwithstanding Professor Roberts' use of the word "gamble", his Honour's impression of this evidence as a whole was that Professor Roberts would have had a reasonable expectation, but could not be certain, that a formulation that used HPMC and SLS to stabilize nanoparticles of fenofibrate would work; so, they could be combined to produce a stable formulation of fenofibrate particles that were less than 300 nm in size and small enough to eliminate the food effect (at [416]).

444 Professor Roberts' evidence satisfied his Honour that if the notional team had been presented with the problem addressed in the 807 patent as at the priority date, it is likely that it would have sought to produce a new fenofibrate formulation using very small (nano-sized) fenofibrate particles and a combination of SLS and HPMC to stabilize the fenofibrate particles to assist their dissolution in the GI tract (at [417]).

445 Further, his Honour found that the work of the notional team in optimizing the fenofibrate formulation to maximise bioavailability by reducing the fenofibrate particle size and to increase the stability of the formulation would be routine (at [418]). This work would involve straightforward experimentation aimed at optimizing the formulation by varying the ratio of

fenofibrate, HPMC and SLS in order to minimise particle size and to maximise the stability of the formulation. His Honour found that none of this work would require the exercise of any inventive ingenuity on the part of the notional team or necessitate the use of any information that was not common general knowledge as at the priority date.

446 Indeed, his Honour referred to the fact that such a development pathway was acknowledged by Professor Roberts to be logical (at [419]). It was a development pathway that his Honour was satisfied the notional team would have been likely to follow as at the priority date in the expectation that it may well produce a fenofibrate formulation that substantially eliminated, or at least substantially reduced, the food effect.

447 His Honour then addressed and disposed of Mylan's arguments.

448 First, Mylan emphasised that the formulations of the invention had to be stable. His Honour was satisfied that this requirement would be satisfied by the optimized formulation produced by the notional team (at [421]). According to his Honour, Professor Roberts' evidence explained how SLS and HPMC could be used to stabilize the fenofibrate particles.

449 Secondly, Mylan also emphasised that the formulations of the invention had to contain fenofibrate particles less than about 500 nm in size. His Honour was satisfied that particle sizes as small as 100 nm or less could be achieved using high pressure homogenization and that such sizes could be maintained using SLS and HPMC to impede particle aggregation (at [422]). His Honour found that such particle size reduction and stabilization techniques were well known to pharmaceutical formulators as at the priority date.

450 Thirdly, Mylan emphasised that the formulations of the invention had to meet the specified bioequivalence requirements. His Honour said that it was implicit in the teaching of the 807 patent that the bioequivalence requirement would most likely be satisfied using a formulation comprising stable fenofibrate particles of 500 nm or less in size (at [423]). His Honour recited that the smaller the particle size, the larger the surface area of the particles, which would lead to a more rapid and complete dissolution in the GI tract. Further, his Honour said that the dissolution process would also be assisted by the presence of SLS. In his view, rapid and complete dissolution of the fenofibrate particles in the GI tract was likely to eliminate the food effect.

451 Fourthly, Mylan also emphasised the requirement that the formulations of the invention must meet the specified redispersion criteria. His Honour said that it was difficult to see what, if

anything, this requirement added to the bioequivalence requirement (at [424]). His Honour went on to say that if the fenofibrate particles did not disperse in the GI tract, which the biorelevant media referred to in the claims was intended to replicate, then the formulation could not reasonably be expected to exhibit the bioequivalence required by the claims. In his Honour's view, the redispersion requirement added nothing of substance to the other requirements of the relevant claims.

452 Fifthly, Mylan also relied on the requirement in some of the claims that the formulation be phospholipid free. His Honour did not think that the notional team would be drawn to phospholipids as offering a suitable stabilizer alone or in combination with other compounds (at [425]). His Honour said that HPMC and SLS would have been perceived to be much more suitable stabilizers and were obvious candidates, whereas phospholipids were not. In any event, so his Honour said, if the formulations of the invention otherwise lacked an inventive step, they were not rendered inventive by the addition of the requirement that they be phospholipid free.

453 Before turning to our analysis, it is convenient at this point to say something about the dependent claims. His Honour addressed the dependent claims (at [426] and [427]). The requirements in the dependent claims beyond those found in the independent claims related to the form of the oral dosage, its composition, its pharmacokinetics and its therapeutic effect or the use to which it was put. Mylan did not suggest before his Honour that any of the dependent claims could be valid if it was accepted that the relevant independent claims were invalid for lack of inventive step. In any event, his Honour was satisfied that none of the dependent claims involved any additional inventive step. His Honour said that the reduction in tablet size, the reduction in the amount of fenofibrate present, and differences in the dissolution profiles were all a function of the size of the fenofibrate particles of 500 nm or less in the relevant pharmaceutical compositions (at [427]). These findings have not been challenged and we need say nothing further specifically concerning the dependent claims.

The appeal

454 Mylan says that the primary judge erred in finding that "the notional team would try HPMC and SLS, both of which were commonly used in the formulation of pharmaceuticals to prevent or reduce particle agglomeration and to assist in dissolution" (at [408]).

455 Mylan says that the evidence was that Professor Roberts might do this as a replacement for the phospholipids used in the 704 patent, but only after modifying the 704 patent method to omit

the melting and cooling steps. But it says that he was not asked whether he would try those two agents as an option when designing a formulation in the absence of the 704 patent.

456 In any event, Mylan says that even armed with the 704 patent, Professor Roberts' evidence was that trying HPMC and SLS was not necessarily obvious and that "others may not agree" with his approach.

457 Further, Mylan says that the evidence from the other experts was that they would have tried the method of formulating fenofibrate described in the 704 patent using phospholipids, which were the preferred surface stabilizers according to the 704 patent.

458 Mylan says that Dr Williams' evidence was that armed with the 704 patent his preference would have been to use a particular type of phospholipid, namely Lipoid E80, because it was referred to in the 704 patent as the most preferred stabilizer.

459 Further, Mylan says that Associate Professor Morton's evidence was that armed with the 704 patent he would also have tried Lipoid E80 first and then tried something that were not phospholipids further down the line.

460 Further, Mylan says that Professor Prestidge's evidence was that he considered the inventors of the 704 patent to have engaged in considerable optimisation to arrive at the method disclosed in the 704 patent to formulate fenofibrate. Such optimisation included exploring different phospholipids and different phospholipid drug ratios. But he would not have known how to further optimise the method disclosed in the 704 patent beyond the steps the inventors had taken.

Discussion

461 In our opinion, there was no error in the finding made by the primary judge that the notional team would likely try HPMC and SLS. In any event, we note that the asserted claims did not require the use of any specific stabilizer. Claims 40 to 45, 47, 49, 50, 56 to 59, 61, 62, 64, 65, 69 to 70 and 78 to 80 just required "at least one surface stabilizer". Claims 1, 2, 3, 4, 5, 6, 7, 11, 12, 20, 21, 23, 24, 26, 27, 31 and 32 required at least one surface stabilizer but precluded the use of a phospholipid.

462 In our view, there was adequate evidence before his Honour to conclude that the identification of a suitable surface stabilizer, or a suitable combination of surface stabilizers, required only routine trial and error testing. Of course, exact predictive accuracy of a surface stabilizer's

performance in a given system is rarely achievable. But candidate surface stabilizers would usually be identified through a literature review and then tested for suitability as part of routine trial and error testing.

463 Mylan says that the primary judge did not accept Sun Pharma's submission at trial that "[t]he identification of a suitable surface stabilizer, or suitable combination of surface stabilizers, requires routine trial and error testing, because absolute prediction of a surface stabilizer's performance in a given system is rarely achievable. Candidate surface stabilizers can be identified through a literature review then tested for suitability". Mylan says that the primary judge recorded Sun Pharma's submission that this formed part of common general knowledge at [389(h)] but did not accept this submission at [390] or elsewhere. Mylan says further that Sun Pharma has not contended in its notice of contention that the primary judge ought to have made this finding.

464 We accept that there is some drafting infelicity in his Honour's reasons. But even if it is unclear whether his Honour was making a finding of common general knowledge concerning the matter in [389(h)], the following should be noted.

465 First, such a finding is implicit in what the primary judge said (at [412]):

> Professor Roberts accepted that if he was seeking to reduce or eliminate the food effect, he would seek to reduce the size of the fenofibrate particles and that this would lead him to identify a preferable surfactant or surface stabilizer. He also accepted that SLS and HPMC, either alone or in combination, would be leading candidates that he would try if he were seeking to reduce the particle size of fenofibrate. He said that, based on his 2002 knowledge, he "would give them a go" meaning, as I understood his evidence, that he considered such a combination would be worth trying.

466 Secondly, Associate Professor Morton gave the following evidence in his first affidavit (at [84] to [92]):

> After I had provided the information recorded in paragraphs 71 to 83, above, I was asked by Ashurst to provide a more detailed explanation of surface stabilizers. I comment on those matters in paragraphs 85 to 92, below. The account of surface stabilizers which I provide in those paragraphs is, necessarily, a significantly simplified account of the relevant scientific principles.
>
> In simplified terms, the surface stabilizers which I utilised in the course of my work before (and after) May 2002 to reduce or prevent aggregation of small drug particles operated on two broad principles. First, I used substances which accumulate at the surface of drug particles and impede particle aggregation as a physical barrier, referred to as steric hindrance. Secondly, I utilized surfactants and surface active agents which impede particle aggregation by electrostatic or related repulsion forces. Some surface stabilizers exert their effects by a combination of these mechanisms.
>
> When I refer to surface stabilizers that prevent or reduce particle aggregation by "steric

hindrance", I am referring (in simplified terms) to compounds that coat the surface of drug particles, for example, relatively large polymeric molecules that occupy considerable space at the molecular level, prevent those drug particles from coming into close contact with one another. Well before May 2002, I was familiar with a variety of polymeric compounds capable of being used as surface stabilizers for small drug particles, including various derivatives of cellulose, for example, polyvinylpyrrolidone and hydroxypropyl methylcellulose.

When I refer to "surfactants", I am referring to "amphiphilic" molecules which have both a hydrophobic (or "water hating") part and a hydrophilic (or "water-loving") part. Before May 2002, I understood that many surfactants were useful for preventing or reducing aggregation of small particles of a hydrophobic drug. I understood that, when adequately mixed with small particles of a hydrophobic drug, the hydrophobic part of surfactant molecules would orientate towards the surface of the drug particles, while the hydrophilic part of surfactant molecules would orientate towards surrounding water molecules and, in this way, reduce the tendency of the hydrophobic drug particles to aggregate together.

Before and since May 2002, I (and, to my observation, other pharmaceutical scientists with whom I have interacted in the course of my work) have generally categorised surfactants as "non-ionic", "cationic" or "anionic", depending upon whether they carry a net electrical charge and, if so, the polarity of that charge. "Non-ionic" surfactants have no net positive or negative charge (although they have more "polar" and less "polar" regions). Ionic surfactants bear an overall net charge, with "cationic" surfactants having a net positive charge and "anionic" surfactants having a net negative charge.

Examples of anionic surfactants with which I was familiar well before May 2002 included those containing carboxylate, sulfonate and sulfate ions as functional groups at their head. Examples of cationic surfactants with which I was familiar well before May 2002 included amine salts and quaternary ammonium salts and sodium lauryl sulfate.

Examples of nonionic surfactants with which I was familiar before May 2002 include fatty alcohols such as lauryl and cetyl alcohols, and fatty acid esters of alcohols such as propylene glycol, polyethylene glycol, sorbitan, sucrose and cholesterol.

Before May 2002 I and, to my observation, my colleagues referred to amphoteric surfactants as zwitterionic. Zwitterionic refers to a neutral molecule with both positive and negative charges.

Before and after May 2002, in the course of my employment at the CDFS and Vectura, the identification of surface stabilizers to be used in a pharmaceutical formulation was realised by routine trial and error. This was because absolute prediction of a surface stabilizer's performance in a given system was very rarely achievable. Before May 2002, when selecting a surface stabilizer system for a pharmaceutical formulation, it was my routine practice to review the scientific literature to narrow the extremely broad range of available surface stabilizers to those that have been successfully used in similar systems and with acceptable toxicological profiles. After identifying a range of potential candidates, I would then conduct a series of routine tests on those surface stabilizers involving different combinations and quantities, for the purpose of identifying an effective combination and quantity that would provide acceptable stability to small drug particles.

467 Thirdly, Dr Williams said (at [154]):

> In my experience of working on the development of new pharmaceutical formulations before (and after) May 2002, the selection of pharmaceutical excipients, such as surface stabilisers and bulking agents, typically involved an iterative process of screening a number of candidate excipients until one (or more than one) was identified as meeting the target specification. When developing new formulations, my colleagues and I generally selected a candidate excipient (often one that we had a preference for based on past experience), assessed its performance and, if necessary, moved to an alternative excipient until we identified one that met our specification requirements. The type of testing used to assess an excipient's performance depended upon the function which the excipient was intended to perform in the dosage form under development. In the case of surface stabilisers of the kinds referred to in paragraphs 46 to 50 of the 704 Patent, performance may be assessed by measuring the size of small drug particles combined with different surface stabilisers. This type of trial and error screening of excipients formed a routine part of the work of the teams of which I was a member at Faulding and Sigma when developing new formulations before (and after) May 2002.

468 Professors Prestidge and Roberts responded to this evidence. But the controversy between the experts was not over whether it was common general knowledge that you could and would screen for potential stabilizers, but whether you would need to if you were following the 704 patent. On the totality of the evidence, in our view it was common general knowledge that you would so screen and that the notional team would endeavour to do so.

469 In our view, the primary judge's conclusions at [417] and [418] were supported by the evidence.

470 Professor Roberts confirmed that he would have looked at AUC and C_{max} in assessing food effect. He also confirmed that if the C_{max} showed that there was a food effect, an obvious choice would be to reduce particle size. Indeed, one would seek to obtain the smallest possible particle size. He gave the following evidence:

> MR MURRAY: Now, if you were to test this formulation for its C_{max} values, fed versus fasted for the purpose of assessing a food effect and you saw that the drug was not being absorbed quickly enough to eliminate a food effect, an obvious choice in optimising the formulation would be to try and decrease the particle size, wouldn't it?
>
> PROF ROBERTS: Yes, it would be.

471 Further, Professor Prestidge explained that:

> So my points are, yes, in – in this sort of formulation, if you're exploring a nanoparticle option as a – as a formulation strategy for something like fenofibrate, you would be trying to produce a stable formulation with the smallest possible size, because we know size correlates with surface area, correlates with dissolution and hence absorption in the body, so that's the whole reasoning for doing this. And then I would add that there has been a large amount of optimisation here and it would be very difficult to – based around phospholipids and based around this 704 patent, I wouldn't know where to go, for instance, in the next step to actually – to further optimise what's presented here. Does that help?

472 It may be accepted that such evidence was being given in the context of being questioned concerning the 704 patent. But the point is that it was well open to his Honour to use it to inform himself on the question of common general knowledge.

473 In our view, his Honour was entitled to find that the use of surface stabilizers to prevent particle aggregation in particles of reduced size was common general knowledge, with examples including HPMC and SLS. Further reference to some of the evidence is not out of place at this point.

474 Professor Roberts identified SLS as a promising candidate as a surface stabilizer. More generally, Professor Prestidge explained that to counter particle aggregation, charge repulsion and steric repulsion are two of the major mechanisms. He explained that SLS is negatively charged and provides electrostatic repulsion. And he explained that HPMC is polymeric and provides steric repulsion. Professor Roberts' evidence was that HPMC and SLS in combination would be a good complement, because of their different mechanisms, and that SLS and HPMC in combination would be leading candidates. He would use them in a concentration that reflected the CMC, using techniques that he had learned as an undergraduate in the early 1990s. Professor Roberts agreed that his approach of combining HPMC and SLS had a sound rationale, and was a logical way to proceed in 2002. It is worth setting out some of his evidence:

> MR MURRAY: Thanks. Now, if you were – sorry. Excuse me a minute, your Honour. The – would you regard HPMC as a surface stabiliser in the way that we were discussing that concept earlier?
>
> PROF ROBERTS: More so than a phospholipid. Yes.
>
> MR MURRAY: Thanks. And – sorry. Just to be clear, where do you put sodium lauryl sulfate on that spectrum of nomenclature?
>
> PROF ROBERTS: That's probably even better.
>
> MR MURRAY: Thank you.
>
> PROF ROBERTS: But I have to say – make it clear that the actual hypromellose and the sodium lauryl sulfate have different mechanisms.
>
> MR MURRAY: Yes. One is ionic and one is not?
>
> PROF ROBERTS: No, there's also a steric effect from hypromellose.
>
> MR MURRAY: Yes.
>
> PROF ROBERTS: So it actually sort of not just only coats it but sort of creates a bit of an environment of a – sort of that stops material getting close to it
>
> MR MURRAY: Thanks. So if you were to identify – just relying on your May 2002

knowledge of a combination, for example, of sodium lauryl sulfate and HPMC, do you see them as a good complement for one another because they have those different mechanisms?

PROF ROBERTS: I do.

MR MURRAY: Thanks. And so if with the 704 patent you had – seeing its claim to a virtual elimination of the food effect but being concerned by the absence of C_{max} data and, upon investigating it, seeing that C_{max} demonstrated a – something of a food effect, I think you agreed one obvious thing to do would be to try and reduce the particle size further so as to reduce or eliminate that food effect. In that context, identifying a preferable surfactant or surface stabiliser than that disclosed in the 704 patent would be an obvious thing to do, wouldn't it?

PROF ROBERTS: I wouldn't say it's necessarily obvious, but that's what I would do

MR MURRAY: Thank you. And of the list of possible what the patent describes as surface active substances, several candidates are mentioned, including sodium lauryl sulfate and HPMC. And you regard each of those and in combination as leading candidates for alternative excipients you would try in that context?

PROF ROBERTS: Yes, recognising that's intuition. I've got no experimental data to prove it.

MR MURRAY: I understand.

PROF ROBERTS: So I could be wrong.

MR MURRAY: Sure. But, based on your 2002 knowledge, that's the thought process that would have occurred to you.

PROF ROBERTS: I would give them a go.

MR MURRAY: Thanks. And you would use them across a range of concentrations, looking – sorry. Let me take it back a step. You don't know in advance what concentration will achieve, if any concentration will, what concentration will achieve the desired stability of a smaller particle size, do you?

PROF ROBERTS: Once you go above the critical micelle concentration, then higher concentrations don't tend to be that much more effective.

MR MURRAY: I see.

PROF ROBERTS: So therefore I would use the critical micelle concentration as a bit of a guide as to my maximum concentration.

MR MURRAY: And how do you identify that?

PROF ROBERTS: There's a turbidimetric – there's a range of physical methods you can use which – and, in fact, you will probably find this in the literature – which tells you when the material is purely going to the surface and when it starts to form these micelles in solution.

MR MURRAY: And that was an approach to this kind of formulation that you engaged in in May 2002?

PROF ROBERTS: In fact, I learned it as an undergraduate, which is probably a decade or so earlier than that.

475 It is appropriate to elaborate on some of the other evidence, albeit that it was adduced in the context of questioning concerning the 704 patent.

476 Professor Roberts thought that there probably was a better surface active agent than phospholipids that could be used, that it was desirable to use multiple surface modifiers to achieve a better result, and that he would have been "very surprised if you did not find another surfactant would actually improve the outcome enormously". Accordingly, he would have sought to identify a preferable surfactant or surface stabilizer other than phospholipids.

477 Further, Associate Professor Morton was using at the priority date the phospholipid Lipoid E80. But he explained that "one of the issues that we were very familiar with Lipoid E80 is that it's not chemically very stable, so it oxidizes if it's not treated well". For that reason, he explained that he would have been interested in exploring stabilizers other than phospholipids.

478 Further, Professor Prestidge said that phospholipids were extremely poorly water soluble and they were not usually used as surface stabilisers. He stated:

> I think I've made – obviously there is this interesting combination of how they act – actually, one thing I would like – if I can add some more information here to help the court. I've got a thought about phospholipids. Phospholipids are extremely poorly water soluble and it's much more – because they're not the normal amphiphilic – they haven't got a highly water soluble end. They have got this hydrophilic – hydrophobic bit – lipophilic bit, the tail, and the head is not so strong. So one thing that might be useful for our discussion here is to realise that phospholipids, as Professor Roberts pointed out briefly there, I believe, they form a large number of self-assembling structures in solution.
>
> So it's interesting that you don't normally use a phospholipid to stabilise a surface in a normal aqueous environment at low temperature. So I think what has happened here in this case where we use this high temperature, then we've got a different ..... different degree of ..... activity. So, to me, I would say the evidence for strong surface stabilisation is probably more likely in that first 5 step where the phospholipid and the fenofibrate are taken to that high temperature and homogenised, and then you've got a – you've probably then got some association of the phospholipid with those fenofibrate generic droplets. So that's more in that case like an emulsifier. It's a little bit – it's more difficult to actually consider it in a situation as a stabiliser in aqueous solution at low – normal room temperature ..... but yes, in that point there, I did actually consider it being a surface – active surface substance.

479 Further, although Dr Williams would have started with a phospholipid based on the 704 patent, he expected that a formulation group would think of non-phospholipid candidates as well.

480 Mylan says that Sun Pharma mischaracterised the experts' evidence in a number of respects.

481 It says that Professor Roberts thought, faced with the 704 patent, that a better surface active agent than phospholipids could be used. But he said that "what that agent is and how it should

be used, I don't know". For that reason, he explained that he would be interested in exploring stabilizers other than phospholipids including the alternative stabilizers described in the first part of the 704 patent. He eventually agreed that HPMC and SLS were worth trying after being referred to the 704 patent, but that did not equate to him being directly led to try these stabilizers.

482 Further, it says that Professor Roberts' evidence was that his choice of stabilizers was not "necessarily obvious" but rather what he would try and he indicated that "others may not agree with him".

483 Further, Mylan says that none of the other three experts gave evidence that they would use HPMC and SLS in light of common general knowledge alone or that they would expect those stabilizers to work to stabilize fenofibrate particles having a particle size less than 500 nm.

484 Further, it says that notwithstanding Professor Roberts' evidence that his choice of stabilizers was not necessarily obvious and that others may disagree, the other experts were not asked by Sun Pharma whether they would use HPMC or SLS.

485 In all the circumstances, Mylan says that Sun Pharma did not discharge its evidentiary burden of establishing that HPMC and SLS were suitable stabilizers when formulating fenofibrate in light of common general knowledge alone. But we disagree.

486 The primary judge's decision that the notional team would use SLS and HPMC was based on Professor Roberts's evidence (at [411] to [417]). And that evidence was given as part of questioning concerning the 704 patent. But there was sufficient evidence for his Honour to conclude that the notional team would be directly led to try these stabilizers based on common general knowledge alone.

487 Further, Mylan's complaint that Professor Roberts was not asked about the steps he would take in the absence of the 704 patent does not assist Mylan. The important matters about testing for the food effect and the properties of BCS Class II drugs were raised independently of the 704 patent. Further, techniques for particle size reduction and the need for surface stabilizers were matters of common general knowledge.

488 Further, Professor Roberts' evidence that using HPMC and SLS as alternative stabilizers was not "necessarily obvious" needs to be seen in the context of the totality of his evidence. He had earlier agreed that it was obvious to try to decrease particle size if he saw a food effect. But he had concerns about using phospholipids. Accordingly, he agreed that he would have

used alternatives, of which HPMC and SLS were the leading candidates. We agree with Sun Pharma that his observations that "others may not agree" with his approach reflects nothing more than appropriate circumspection about speaking for others.

489 Further, as Sun Pharma points out, Mylan put Professor Roberts forward as an expert witness qualified to express relevant opinions on the issues as a reasonable proxy for the hypothetical person skilled in the art. In those circumstances, the primary judge was quite entitled to rely on his evidence, particularly after assessing the witnesses during the concurrent evidence sessions.

490 We accept that, concerning the use of HPMC and SLS, Professor Roberts stated that "[he had] no experimental data to prove [that they would work]" and "[s]o [he] could be wrong", however, he "would give them a go". And we accept that Sun Pharma did not establish that the other experts shared Professor Roberts' views in respect of using HPMC and SLS in formulating fenofibrate. Nevertheless, his Honour was entitled to rely upon Professor Roberts' evidence and to make the findings that he did. We see no error.

491 In summary, we reject this ground of appeal.

THE 807 PATENT: GROUNDS 39 – 42

The appeal

492 These grounds of appeal raise various points.

493 First, Mylan asserts that the primary judge erred in finding that, based on Professor Roberts' evidence, the notional team would have had an expectation of success in the sense required by the reformulated Cripps question (at [415] and [416]).

494 Secondly, it asserts that the primary judge erred in finding, based on Professor Roberts' evidence, that the notional team would have had a reasonable expectation that a formulation that used HPMC and SLS to stabilize nanoparticles of fenofibrate would work; that is, they could be combined to produce a stable formulation of fenofibrate particles that were less than 300 nm in size and small enough to eliminate the food effect (at [416]).

495 Thirdly, it asserts that the primary judge erred in finding that the requisite expectation of success required by the reformulated Cripps question was satisfied by the evidence of Professor Roberts given that he considered it to be a "gamble" whether a fenofibrate formulation that used a combination of HPMC and SLS would work (at [415] and [416]).

496 Mylan says that Professor Roberts' evidence was that he considered it to be a "gamble" as to whether a fenofibrate formulation that used a combination of HPMC and SLS, but did not include the heating and cooling steps of the 704 patent, would work. He said that it would be "foolhardy to suggest to you that I would be sure it would work".

497 Mylan says that Professor Roberts' comments do not provide a basis for a finding of a reasonable expectation that a formulation that used HPMC and SLS, but did not use the heating and cooling steps of the 704 patent, to stabilize nanoparticles of fenofibrate, would work.

498 Mylan says that the 704 patent expressly disclosed a preference for phospholipids and the stipulated heating and cooling steps in order to address the food effect, but failed to obtain a stable nanoparticulate. It says that Professor Roberts' evidence that using HPMC and SLS was a "logical way to proceed" is to the same effect as his evidence that he "would give them a go". So, this was evidence which the primary judge earlier found to mean no more than they "would be worth trying" ([412]).

499 Moreover and fourthly, Mylan says that the primary judge, having found (based upon the evidence of Professors Prestidge and Roberts (at [391] and [392])) that "there are a number of factors that come into play when assessing whether reductions in drug particle sizes will increase dissolution rates and the food effect" (at [393]), erred in failing to give any or any sufficient weight to such evidence in answering the reformulated Cripps question, including the requirement as to the expectation of success.

500 Mylan says that *Hässle v Alphapharm* made clear that "worthwhile to try" falls short of "worth a try with a reasonable expectation of success". In the course of rejecting the test of "worthwhile to try" or "worth a try", the plurality (at [67]) referred with approval to the well known passage from the reasons of Buckley LJ in *Re Beecham Group Ltd's (Amoxycillin) Application* (1980) 97 RPC 261 at 296.

501 In the circumstances, Mylan says that the primary judge erred in finding that the requisite expectation of success required by the reformulated Cripps question was established on the evidence.

Discussion

502 The reformulated Cripps question does not require certainty of outcome. It requires that the skilled addressee be directly led as a matter of course to try the claimed invention in the expectation that a particular research path "might well produce" a useful result (*Hässle v*

Alphapharm at [53]). It does not require the skilled addressee to know that the steps will produce a useful result.

503 In context, Professor Roberts' reference to a gamble should be understood as meaning only that he could not be certain. That is how the primary judge understood his evidence.

504 Professor Roberts characterised HPMC as very effective in coating particles so that they did not agglomerate and SLS as promising and probably even better than HPMC as a surface stabilizer. Given those characteristics, he identified them as leading candidates to combine.

505 Professor Roberts also gave evidence, albeit in the context of being asked about the 704 patent:

> PROF ROBERTS: My experience has been when you use combinations of surface active agent that you oftentimes end up with a better product than just one alone. Phospholipid we need to recognise as very poorly insoluble in water.
>
> MR MURRAY: Yes.
>
> PROF ROBERTS: And therefore I would be very surprised if you did not find another surfactant would actually improve the outcome enormously.

506 It is therefore apparent that he considered the leading candidates HPMC and SLS were likely to improve the outcome significantly.

507 Professor Roberts' view that it was logical to proceed by using that combination of surfactants reflected his opinion, based on his experience, that the combination was likely to work, not merely that the combination was worth a try.

508 Further, it should not be overlooked that the optimisation of stabilizers relying on routine trial and error was an aspect of common general knowledge either found by his Honour or supported by the evidence.

509 Further, the primary judge explained that it was his impression, notwithstanding the language of "gamble", that the evidence of Professor Roberts as a whole (including the passage reproduced at [415]) supported the proposition that the skilled addressee would have had a reasonable expectation but not a certainty that a combination of HPMC and SLS would work ([416]). We are not in a position to gainsay that impression. Indeed, when one reads the relevant transcript, we do not perceive any error in his Honour's assessment or understanding of that evidence.

510 Further, in his Honour's view, Professor Roberts' reluctance to state his expectation as a certainty (see [415]) reflected appropriate scientific caution, not a lack of expectation. We agree.

511 Mylan says that the primary judge erred in finding that "… my impression of this evidence as a whole was that he would have had a reasonable expectation (but could not be certain) that a formulation that used HPMC and SLS to stabilize nanoparticles of fenofibrate would work …" ([416]). It says that considering the question asked of him, Professor Roberts' evidence was that he was not even optimistic that it would work. Further, Professor Roberts' response was in respect of varying Example 20 of the 704 patent, not common general knowledge alone as the primary judge incorrectly found at [416].

512 Further, Mylan says that Professor Roberts' evidence that using HPMC and SLS was a "logical way to proceed" to varying the 704 patent method is to the same effect as his evidence that he "would give them a go". But that evidence falls short of "worth a try with a reasonable expectation of success".

513 Given the advantages the primary judge had in assessing Professor Roberts' oral evidence, and given that the primary judge took the statement at [415] into account, we are not persuaded that the primary judge erred in the ways contended for by Mylan. To answer the reformulated Cripps question in a particular case can sometimes be tricky and is an evaluative question upon which, in a border-line case, reasonable minds might differ. The present case is one which is close to the line. Accepting that we have assessed the evidence and made our own evaluation, we are not persuaded that his Honour made any error in the conclusion that he reached.

514 In summary, we reject these grounds of appeal. More generally, as none of Mylan's grounds of appeal have been made out, its appeal concerning the 807 patent fails.

THE 807 PATENT: NOTICE OF CONTENTION

515 Sun Pharma raised two points in its notice of contention concerning the 807 patent, but it is only necessary to now consider its first point on the obviousness question dealing with both common general knowledge and the 704 patent as s 7(3) information; it was not disputed that the 704 patent was s 7(3) information for present purposes.

516 Sun Pharma contends that *if* the primary judge did not find that each of the asserted claims of the 807 patent was obvious in light of common general knowledge as it existed before the priority date of the asserted claim, considered together with the 704 patent, then his Honour

should so have found. We will come back to the conditional *if* later, although we are not in doubt that it is misplaced in the sense that we are satisfied that his Honour did not so find.

517 Sun Pharma's notice of contention states that the 704 patent disclosed a fenofibrate composition for oral administration comprising particles of fenofibrate and at least one surface active agent, which would act as a surface stabilizer. Further, a skilled addressee reading the 704 patent at the priority date would have realised that it disclosed a process for formulating fenofibrate that allowed smaller doses to be used than conventional formulations and that it asserted that it had virtually eliminated the food effect. Further, a skilled addressee would have appreciated that it was the reduced particle size of fenofibrate that achieved these benefits, given the matters disclosed in [0013] to [0015] of the 704 patent. By reducing the particle size of poorly soluble permeable drugs and by formulating those particles with suitable surface stabilizers, their dissolution profile and therefore their oral bioavailability could generally be improved, reducing the food effect. And the 704 patent demonstrated that this general principle applied to fenofibrate particles.

The primary judge's reasons

518 His Honour commenced by setting out a description of aspects of the 704 patent (at [429] to [439]). We have set out the content of the 704 patent more fully earlier in our reasons.

519 His Honour then noted (at [440]) that Mylan relied on evidence given by Professor Prestidge that the contents of the 704 patent would not lead him to expect that he could produce fenofibrate particles having a particle size of less than 500 nm that were stable.

520 His Honour recited that his evidence was that the skilled addressee would understand from reading the 704 patent that the authors of that document had already attempted to optimise the fenofibrate composition disclosed in that document and that they had "done quite a wide range of … detailed formulation". Professor Prestidge also observed that:

> They've explored different phospholipids; they've explored different phospholipid to drug ratios; they've explored a number of other variables in terms of the cooling method, so there's – there's quite a large amount of optimisation gone on in this process … then come out with this – what presumably is their – is their lead formulations.

521 His Honour also set out the following parts of Professor Prestidge's affidavit responding to evidence given by Associate Professor Morton:

> … Associate Professor Morton states that, from using the 704 Method, "I would expect to achieve a fenofibrate particle size in the order of 300 nm with a limited number of

> homogenization passes (in the manner described in paragraph 92 of the 704 Patent)" and that "a fenofibrate average particle size as small as 50 nm could be achieved by increasing the number of homogenization passes used in the manufacturing process (in the manner also explained in paragraph 92 of the 704 Patent)". I agree that the 704 Patent provides a basis for an expectation that particle sizes of 0.30 μm (300 nm) and 0.05 μm (50 nm) are achievable with repeated homogenisation passes. However, the content of the 704 Patent does not lead me to expect that I could produce fenofibrate particles having a particle size of less than 0.50 μm (500 nm) that are stable. Indeed, I refer to my statements in … above regarding the fact that the particles in a cooled homogenate in step (c) of the 704 Method are transiently stable. Specifically, I refer to … above, where I discuss the cooled homogenates referred to in paragraph [0092] of the 704 Patent with particle sizes of 0.3 μm (300 nm) and 0.05 μm (50 nm), which I understand are transiently stable, and thus not physically stable. With repeated emphasis in the 704 Patent that the particles in the cooled homogenates are only transiently stable, I do not consider there to be any basis, having read the 704 Patent, for an expectation to be able to prepare stable particles having a particle size less than 0.50 μm (500 nm).

522 His Honour also recited (at [442]) that Professor Roberts gave evidence to the same general effect. His Honour recorded that Professor Roberts said that he did not see any proper basis to expect that particles of less than 500 nm produced using the method described in the 704 patent would be stable. Professor Roberts said that he would not expect that he would be able to achieve stable fenofibrate particles with a D_{50} particle size of less than 500 nm following that method.

523 Further, the evidence was also that the 704 patent employed melting and cooling steps to form a cooled homogenate that gave rise to stability concerns, regardless of what surface stabilizers were used (at [434], [441] and [442]).

524 Further, in the 704 patent phospholipids were the only surface stabilizers discussed in detail and used in the method disclosed to produce fenofibrate formulations. Indeed, the 704 patent described phospholipids as preferred (at [0048]) in comparison to other known surface stabilizers.

525 Accordingly, by following the 704 patent the notional team would not have been directly led to the claimed invention with a reasonable expectation of success. Rather, the notional team would have failed at an early stage. This is because it would not have been able to produce a stable formulation of particles of about 500 nm or less employing the method described in the 704 patent using a phospholipid as the surface stabilizer. Moreover, even if it had not used a phospholipid as the surface stabilizer, there would still have been stability concerns regardless of the surface stabilizer used.

526 In his Honour's opinion, the evidence did not establish that a skilled team endeavouring to apply the teachings of the 704 patent with a view to producing a fenofibrate composition containing small particles of fenofibrate, could produce a stable formulation of particles of about 500 nm or less using a phospholipid as the surface stabilizer (at [443]).

527 His Honour said that the expert witnesses who gave evidence in relation to the suitability of various surface active agents agreed that phospholipids, including E80, were not particularly good surface stabilizing agents (at [444]). In the circumstances, his Honour said that it was necessary to be very cautious before concluding that the notional team would be able to obtain fenofibrate particle sizes of 500 nm or less by using a phospholipid as a surface stabilizer even if it was minded to use such a compound for that purpose.

528 Finally, his Honour observed that the 704 patent was significant in that it confirmed that by reducing the size of fenofibrate particles in a fenofibrate composition suitable for oral administration, it may be possible to eliminate or substantially eliminate the food effect (at [445]). But in this respect, his Honour did not consider that it would tell the notional team anything more than it would already deduce from the common general knowledge.

Discussion

529 Sun Pharma says that the asserted claims were obvious in light of common general knowledge considered together with the information in the 704 patent, there being no dispute that the 704 patent would have been ascertained, understood and regarded as relevant.

530 Sun Pharma says that the primary judge held that the 704 patent was significant in that it confirmed that by reducing the particle size of fenofibrate, it may be possible to eliminate or substantially eliminate the food effect. But he considered that it would not tell the notional team anything more than it would already deduce from the common general knowledge ([445]). For this reason, so Sun Pharma says, the primary judge concluded that the patent was not of any assistance to Sun Pharma's obviousness case ([428]).

531 Sun Pharma says that on one reading, the primary judge found that the asserted claims were obvious in light of common general knowledge considered together with the 704 patent. It says that the finding that the 704 patent would not tell the notional team anything more than the common general knowledge logically leads to the same answer when the 704 patent is considered with common general knowledge as when common general knowledge is

considered separately. We think that this is a mischaracterisation of what his Honour was saying and will return to this in a moment.

532 Sun Pharma says that although the 704 patent disclosed phospholipids as the preferred stabilizers, the expert witnesses agreed that phospholipids were not good stabilizing agents ([444]). Further, a wide range of alternative stabilizers were disclosed as suitable in the 704 patent (at [0046] and [0047]), including HPMC and SLS.

533 Further, Sun Pharma says that whilst the 704 patent demonstrated the general principles about reducing the food effect in BCS Class II drugs applied to fenofibrate by reference to the AUC data, the 704 patent did not report on C_{max} of fenofibrate achieved when the formulation of the 704 patent was administered under fasted and fed conditions.

534 Further, it would seem that regulatory documents tendered as part of the written evidence of Professor Roberts concerning an embodiment of the 704 patent indicated that the 704 formulation did not meet the bioequivalence requirements in the asserted claims of the 807 patent for C_{max} in the fed vs fasted conditions.

535 Professor Roberts confirmed that he would have looked at both AUC and C_{max} in assessing food effect, and that he knew that for fenofibrate, the C_{max} would reflect any food effect; we have set out the relevant passages of his evidence earlier. Professor Roberts confirmed that if the C_{max} showed that there was a food effect, an obvious choice would have been to reduce particle size, indeed seeking to obtain the smallest possible particle size that one could.

536 Sun Pharma says that given the formulator's desire to obtain the smallest possible particle size, it would have been obvious to try and maintain the particle size of 50 to 300 nm described in the 704 patent as transiently stable by treating the surface of the drug particles to facilitate dissolution in water. This would be done by choosing a surface active agent that was not hydrophobic.

537 Further, Sun Pharma says that because the 704 patent revealed that the phospholipid formulations were only transiently stable at 50 to 300 nm (see at [0026], [0040], [0069]), this provided motivation to the skilled team not merely to accept the formulations of the 704 patent, but to try to improve them through the processes of routine trial and error which was accepted to be part of common general knowledge.

538 Sun Pharma says that on the basis of the evidence and the primary judge's findings of fact, it would have been obvious to a skilled addressee in light of common general knowledge and

armed with the 704 patent to formulate a stable fenofibrate composition for oral administration comprising particles of fenofibrate having a D_{50} particle size of less than about 500 nm to improve dissolution and therefore bioavailability, and at least one surface stabilizer which was not a phospholipid and was most likely a combination such as HPMC and SLS that would complement each other.

539 Sun Pharma says that the skilled addressee would understand that by reducing particle size and using a surface active agent, the food effect could be substantially eliminated, and the composition would redisperse in biorelevant media.

540 On that basis, Sun Pharma says that each of the asserted claims of the 807 patent was also obvious in light of common general knowledge considered together with the 704 patent.

541 We reject Sun Pharma's notice of contention point.

542 In our view, the primary judge correctly rejected Sun Pharma's lack of inventive step case based on the 704 patent ([428]). This was on the basis, inter alia, of the expert evidence referred to by the primary judge at [440] to [442], which his Honour correctly summarised and recorded in part.

543 Further, after referring to this evidence, the primary judge found (at [443]) that:

> In my opinion the evidence does not establish that a skilled team endeavouring to apply the teachings of the 704 Patent with a view to producing a fenofibrate composition containing small particles of fenofibrate, could produce a stable formulation of particles of about .5 μm (500 nm) or less in size using a phospholipid as the surface stabilizer.

544 Not only has that conclusion not been shown to be in error, but in our view, based upon our own review of the 704 patent and the evidence, it is quite correct.

545 Further, we reject the conditionality of Sun Pharma's notice of contention by reference to "if". Sun Pharma has mischaracterised the primary judge's finding at [445]. The primary judge's finding that the 704 patent would not tell the notional team anything more than what it would already know from common general knowledge was only in one respect, namely, "by reducing the size of fenofibrate particles in a fenofibrate composition suitable for oral administration, it may be possible to eliminate or substantially eliminate the food effect". That finding did not refer to the solubility, dissolution profile or bioavailability of fenofibrate or the use of surface stabilizers in formulating fenofibrate.

546 Further, the primary judge did not find that, in light of the 704 patent, the notional team would be directly led to trying to produce a fenofibrate composition containing a stable formulation of particles of 500 nm or less using any stabilizer other than a phospholipid. Indeed, the evidence adduced before the primary judge included evidence of the skilled addressee's understanding that the inventors had already attempted to optimise the fenofibrate compositions disclosed. Moreover, the lead formulations all included phospholipids.

547 Further, it is important not to overlook Professor Roberts' evidence concerning the melting and cooling steps in the 704 patent. One of his uncertainties concerned obtaining a stable formulation of particles having a size of 500 nm or less in addition to the selection of a stabilizer(s). Professor Roberts' evidence was that the selection of a different stabilizer(s) alone may not yield stable particles having a particle size of 500 nm or less. Moreover, there was no detailed evidence of what steps Professor Roberts would have taken instead of the melting and cooling steps.

548 The notional team would not likely have employed the melting and cooling steps in the 704 patent. Indeed, Professor Roberts explained that he would have avoided the heating step described in the 704 patent so as to avoid forming an undesirable crystalline form. He would have made this change because he would have wanted fewer steps or steps that were less likely to go wrong. It is worth setting out his evidence:

> MR MURRAY: Thanks very much. Just a minute, please, your Honour. Based on your May 2002 knowledge, Professor Roberts, you would regard it as – sorry. You would be optimistic certainly – let me make it clear what I mean by optimistic. Not certain but optimistic that you could, by taking what you're told in the 704 patent and optimising the formulation that was used to obtain the tablets in example 20, that by varying the use of surfactant or surface stabiliser such as by using SLS and HPMC, you would have been optimistic that you could have stabilised that particle size at around the 300 nanometre range that had been obtained at step B.
>
> PROF ROBERTS: Can [I] express a real concern I have with all of this?
>
> MR MURRAY: Yes.
>
> PROF ROBERTS: I don't know what physical form will end up with a fenofibrate, so if we end up with a crystalline form which is actually terribly insoluble - - -
>
> MR MURRAY: Yes.
>
> PROF ROBERTS: - - - we could be in a worse situation than we had before we started.
>
> MR MURRAY: Yes.
>
> PROF ROBERTS: So the process of melting – I just don't know – because there's a number of cooling steps.

MR MURRAY: Yes.

PROF ROBERTS: If you slow down the cooling, you can end up with, in fact, a more robust crystal which will dissolve even as an intrinsic dissolution rate - - -

MR MURRAY: Yes.

PROF ROBERTS: - - - which is actually much slower than another crystalline form - - -

MR MURRAY: Yes.

PROF ROBERTS: - - - and I'm just not certain what I would end up with - - -

MR MURRAY: Thank you.

PROF ROBERTS: - - - so I would prefer to be cautious and actually avoid that step.

MR MURRAY: Avoid which step?

PROF ROBERTS: The molten step. The actual, sort of, molten and then, sort of, trying to bring it back into some crystalline form.

MR MURRAY: Thanks.

PROF ROBERTS: I just don't know what the outcome would be.

MR MURRAY: Thank you. And so that was a view you reached on the 704 patent without the benefit of the 807 patent?

PROF ROBERTS: Correct.

MR MURRAY: Thanks. And so as a matter of your chemical chemistry instincts, you thought that it would be sensible, in taking the learning of 704, not to use the heating step.

PROF ROBERTS: I would feel much more comfortable with less steps and with ones that are less likely to go wrong.

MR MURRAY: And if you had taken that approach, can I put my earlier question to you about being optimistic that you would have stabilised at around that 300 nanometre range?

PROF ROBERTS: Well, I think the hindsight were the 807 – it was 807, I think it is - - -

MR MURRAY: Yes.

PROF ROBERTS: - - - actually shows that is the case.

MR MURRAY: Yes. Are you able to express an opinion as to your level of optimism putting the 807 aside?

PROF ROBERTS: It's a gamble. I mean, a whole – all sorts of developments are gambles. Sometimes they work; sometimes they don't. I think I would be very – what's the word? – foolhardy to suggest to you that I would be sure it would work.

549 Further, the 704 patent did not report on the C_{max} for fenofibrate when the formulations of the 704 patent were administered under fed and fasted conditions. Contrastingly, asserted claims 1, 2, 3 (and dependent claims 4 to 39), and 40, 41, 42 (and dependent claims 43 to 80) of the

807 patent claim C_{max} values at a 90% confidence interval for C_{max} which is between 0.80/80% and 1.25/125%.

550 In summary, for all these reasons his Honour correctly rejected Sun Pharma's case based upon both common general knowledge and the 704 patent as s 7(3) information. Sun Pharma's point of contention must be rejected.

THE 964 PATENT: BACKGROUND

The issue

551 The primary judge held that claims 12 and 13 of the 964 patent were not fairly based on the matter described in the specification for that patent and, accordingly, that the claims were invalid. Mylan contends that the primary judge erred in so finding: grounds 22 to 25 of the amended notice of appeal. Mylan seeks a declaration that Sun Pharma threatens to infringe claims 12 and 13 of the 964 patent and a certificate of validity which includes those claims.

Claims 12 and 13

552 Claims 12 and 13 need to be considered in the context of, amongst other claims, claim 1. The claims are as follows:

> 1. An immediate-release fenofibrate composition comprising:
>
> (a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 μm, a hydrophilic polymer and, optionally, a surfactant; said hydrophilic polymer making up at least 20% by weight of (a); and
>
> (b) optionally one or several outer phase(s) or layer(s).
>
> …
>
> 12. A composition comprising fenofibrate having a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or with 0.025M sodium lauryl sulfate.
>
> 13. The composition according to any one of the preceding claims, in the form of a tablet.

553 In short, the primary judge found that the specification only disclosed a composition comprising fenofibrate in a micronized form having a size less than 20 μm and did not disclose any composition comprising fenofibrate having the dissolution profile in claim 12: [287]. To understand the primary judge's reasoning it is necessary to consider the terms of the specification.

The specification

554 The specification identifies at p 1 lines 5-37 that:

> The present invention relates to a novel pharmaceutical composition having high bioavailability through improved dissolution, and a method for preparing it. The invention more particularly relates to a pharmaceutical composition for administration by oral route, containing an active ingredient of poor aqueous solubility.
>
> Numerous active ingredients suffer from the disadvantage of being poorly soluble in an aqueous medium, thus having an insufficient dissolution profile and, consequently, poor bioavailability within the organism, following oral administration. The therapeutic dose required to be administered must thus be increased in order to obviate this disadvantage. This particularly applies to numerous hypolipemiant active ingredients, such as those belonging to the fibrate family.
>
> Fenofibrate is a well-known hypolipemiant from the family of fibrates, which is commercially available in various doses (100 and 300 mg for example Secalip®) but in a form leading to poor bioavailability of the active ingredient. Indeed, due to it [sic] poor hydrosolubility, fenofibrate is poorly absorbed in the digestive tract and consequently its bioavailability is incomplete, irregular and often varies from one person to another.
>
> To improve the dissolution profile of fenofibrate and its bioavailability, thereby reducing the dose requiring to be administered, it would be useful to increase its dissolution so that it could attain a level close to 100%.
>
> Moreover, for patient comfort, it is advantageous to seek a dosage form that only requires the medicament to be taken once daily while giving the same effect as one administered several times daily.

555 Page 2 lines 1-33 describe the prior art in these terms:

> EP-A-0330532 discloses a method for improving bioavailability of fenofibrate. This patent describes the effect of co-micronizing fenofibrate with a surfactant, for example sodium laurylsulfate in order to improve fenofibrate solubility and thereby increase its bioavailability. This patent teaches that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than the improvement that would be obtained either by adding a surfactant, or through solely micronizing the fenofibrate, or, yet again, through intimately mixing the fenofibrate and surfactant, micronized separately. The dissolution method employed is the conventional rotating blade technique (European Pharmacopoeia) : product dissolution kinetics are measured in a fixed volume of the dissolution medium, agitated by means of a standardized device; a test was also carried out with an alternative technique to the European Pharmacopoeia, using the continuous-flow cell method.
>
> The process of EP-A-0330532 leads to a new dosage form in which the active ingredient, co-micronized with a solid surfactant, has improved fenofibrate dissolution, and thus increased bioavailability, which makes it possible, for a given level of effectiveness, to decrease the daily dose of the medicament: respective 67 mg and 200 mg instead of 100 mg and 300 mg.
>
> However, the preparation method in that patent is not completely satisfactory inasmuch as it does not lead to complete bioavailability of the active ingredient, and suffers from several disadvantages. The technique of co-micronizing fenofibrate with a solid surfactant does, it is true, improve dissolution of the active ingredient, but this

dissolution remains, however, incomplete.

556 The specification continues in these terms at p 2 line 34 to p 3 line 12:

> There is thus a need to improve fenofibrate bioavailability in order to attain, over very short periods of time, a level close to 100% (or, in any case, better than the following limits: 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes in a medium consisting of 1200 ml water to which 2% Polysorbate 80 is added, or of 1000 ml of water to which 0.025M sodium lauryl sulfate sodium [sic] is added, with a blade rotation speed of 75 rpm), and this even when dissolution media having a low surfactant content are used.
>
> Applicant has found that, surprisingly, it is possible to resolve this problem by a new method for preparing a pharmaceutical composition by spraying a suspension of the active ingredient onto an inert hydrosoluble carrier. The present invention also relates to pharmaceutical compositions thus prepared.

557 After a further discussion of the prior art the specification includes consistory statements as follows at p 5 line 1 to p 6 line 4:

> Thus, the present invention provides an immediate-release fenofibrate composition comprising:
>
> (a) an inert hydrosoluble carrier covered with at least one layer containing a fenofibrate active ingredient in a micronized form having a size less than 20 μm, a hydrophilic polymer and, optionally, a surfactant; said hydrophilic polymer making up at least 20% by weight of (a); and
>
> (b) optionally one or several outer phase(s) or layer(s).
>
> In one embodiment, a surfactant is present with the active ingredient and the hydrophilic polymer
>
> The invention also provides a composition comprising fenofibrate having a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or in a dissolution medium constituted by water with 0.025M sodium lauryl sulfate.
>
> A method for preparing a pharmaceutical composition is also provided, comprising the steps of:
>
> (a) preparing a fenofibrate suspension in micronized form with a particle size below 20 μm, in a solution of hydrophilic polymer and, optionally surfactant;
>
> (b) applying the suspension from step (a) to an inert hydrosoluble carrier;
>
> (c) optionally, coating granules thus obtained with one or several phase(s) or layer(s).
>
> Step (b) is preferably carried out in a fluidized-bed granulator.
>
> The method can comprise a step in which products obtained from step (b) or (c) are compressed, with or without additional excipients.
>
> The invention also provides a suspension of fenofibrate in micronized form having a size less than 10 μm, in a solution of hydrophilic polymer and, optionally, surfactant.

558 At p 8 lines 16-25 the specification provides that:

> The compositions according to the invention comprise, in general, based on the total composition weight excluding the outer phase or layer, an inert hydrosoluble carrier making up from 10 to 80% by weight, preferably 20 to 50% by weight, the fenofibrate representing from 5 to 50% by weight, preferably from 20 to 45% by weight, the hydrophilic polymer representing from 20 to 60% by weight, preferably 25 to 45% by weight, the surfactant making up from 0 to 10% by weight, preferably 0.1 to 3% by weight.

559 At p 9 lines 12-27 the specification states:

> The composition according to the invention is prepared by a novel process comprising spraying a suspension of the active ingredient in a micronized form in a solution of a hydrophilic polymer and, optionally, a surfactant, onto the inert cores.
>
> When a surfactant is present, the active ingredient can be co-micronized with the surfactant. One will then use with advantage the teachings of EP-A-0330532.
>
> The method according to the invention consists in using the fluidized bed granulation principle, but with specific starting materials, in order to arrive at an improved dissolution profile and thus, at elevated bioavailability. In particular, the invention employs a suspension of the micronized active ingredient in a solution of a hydrophylic polymer and, optionally, a surfactant.

560 At p 10 lines 13-15 the specification notes that:

> The compositions according to the invention can also be prepared by other methods, for example by spraying a solution of the micronized active ingredient onto the hydrosoluble inert carrier.

561 The specification then provides at p 11 lines 15-21 that:

> The invention also covers this novel suspension.
>
> Without wishing to be tied down to a specific theory, applicant believes that this novel method, through the use of a micronized active ingredient suspension in a hydrophilic polymer solution, enabled a novel composition to be obtained in which the active ingredient is in a non-re-agglomerated form.

562 The specification continues by providing four examples which are said at p 11 lines 22-23 to "illustrate the invention without limiting it".

THE 964 PATENT: GROUNDS 22 - 25

The primary judge's reasons

563 The primary judge identified that:

> 277 Section 40(3) of the Act, as it stood prior to its amendment by the *Intellectual Property Laws Amendment (Raising the Bar) Act 2012* (Cth), states that a claim must be (inter alia) "fairly based on the matter described in the specification".

564 The primary judge then explained the relevant principles stating:

> 278 In *Lockwood Security Products Pty Limited v Doric Products Pty Ltd (No 1)* (2004) 217 CLR 274 ("*Lockwood No 1*") the High Court (Gleeson CJ, McHugh, Gummow, Hayne and Heydon JJ) referred with approval to a passage in the judgment of Barwick CJ in *Olin Corporation v Super Cartridge Co Pty Ltd* (1977) 180 CLR 236 (and also approved *Kimberly-Clark Australia Pty Ltd v Arico Trading International Pty Ltd* (2001) 207 CLR 1 at [15]) in which the Chief Justice said at 240:
>
> > The question whether the claim is fairly based is not to be resolved … by considering whether a monopoly in the product would be an undue reward for the disclosure. Rather, the question is a narrow one, namely whether the claim to the product being new, useful, and inventive, that is to say, the claim as expressed, travels beyond the matter disclosed in the specification.

565 The primary judge continued at [279] to the effect that s 40(3) requires a "real and reasonably clear disclosure" of what is claimed, but that this question is not answered solely by reference to the preferred embodiments. The primary judge noted that the High Court said:

> [68] Erroneous principles. The comparison which s 40(3) calls for is not analogous to that between a claim and an alleged anticipation or infringement. It is wrong to employ "an over meticulous verbal analysis". It is wrong to seek to isolate in the body of the specification "essential integers" or "essential features" of an alleged invention and to ask whether they correspond with the essential integers of the claim in question [*CCOM Pty Ltd v Jiejing Pty Ltd* (1994) 51 FCR 260 at 281, per Spender, Gummow and Heerey JJ].
>
> [69] "Real and reasonably clear disclosure". Section 40(3) requires, in Fullagar J's words, "a real and reasonably clear disclosure" [*Société des Usines Chimiques Rhône-Poulenc v Commissioner of Patents* (1958) 100 CLR 5 at 11]. But those words, when used in connection with s 40(3), do not limit disclosures to preferred embodiments.
>
> > "The circumstance that something is a requirement for the best method of performing an invention does not make it necessarily a requirement for all claims; likewise, the circumstance that material is part of the description of the invention does not mean that it must be included as an integer of each claim. Rather, the question is whether there is a real and reasonably clear disclosure in the body of the specification of what is then claimed, so that the alleged invention as claimed is broadly, that is to say in a general sense, described in the body of the specification." [*Rehm Pty Ltd v Websters Security Systems (International) Pty Ltd* (1988) 81 ALR 79 at 95, per Gummow J]
>
> Fullagar J's phrase serves the function of compelling attention to the construction of the specification as a whole, putting aside particular parts which, although in isolation they might appear to point against the "real" disclosure, are in truth only loose or stray remarks.

566 At [280] the primary judge said that *Lockwood No 1* is "authority for the proposition that a consistory clause may provide a fair basis for a claim which mirrors its language but not if there are other matters disclosed in the specification which show that the invention is narrower than the consistory clause suggests". The primary judge referred in particular to *Lockwood No 1* at [99] that:

> … the correct position is that a claim based on what has been cast in the form of a consistory clause is not fairly based if other parts of the matter in the specification show that the invention is narrower than that consistory clause. The inquiry is into what the body of the specification read as a whole discloses as the invention [*Welch Perrin & Co Pty Ltd v Worrel* (1961) 106 CLR 588 at 612-613]. An assertion by the inventor in a consistory clause of that of which the invention consists does not compel the conclusion by the court that the claims are fairly based nor is the assertion determinative of the identity of the invention. The consistory clause is to be considered by the court with the rest of the specification.

567 The primary judge observed at [281] that the invention described in the specification for the 964 patent has a number of aspects. His Honour said:

> 282 One aspect of the invention described is an immediate release fenofibrate composition containing (inter alia) fenofibrate in a micronized form having a size less than 20 μm. I will refer to this as the immediate release formulation. The immediate release formulation is the subject of independent claim 1.
>
> 283 Another aspect of the invention described is a method of preparing the formulation of the invention. This method comprises a number of steps the first of which is the preparation of fenofibrate in micronized form with a particle size below 20 μm suspended in a solution of hydrophilic polymer and, optionally, a surfactant. This is the method claimed in independent claim 14. The form and size of the fenofibrate as used in the method corresponds with the form and size of the fenofibrate referred to in the immediate release formulation.
>
> 284 A further aspect of the invention described is the suspension that is prepared as the first step of the method. This is the suspension claimed in independent claim 17.

568 The primary judge posed the question for resolution in these terms:

> 286 The question is whether the specification also contains a real and reasonably clear disclosure of an invention consisting of "[a] composition comprising fenofibrate" with a particular dissolution profile as claimed in independent claim 12 that need not contain fenofibrate in micronized form.

569 The primary judge answered the question as follows:

> 287 In my view, when read as a whole, the specification discloses an invention comprising a fenofibrate composition that includes fenofibrate in micronized form having a size less than 20 μm, an inert hydrosoluble carrier and a hydrophilic polymer. It does not disclose an invention (or an aspect of an invention) comprising any composition of fenofibrate that has the improved dissolution profile.

570 The primary judge said at [288] and [289]:

> (a) The passage at p 2 line 34 to p 3 line 6 of the specification (commencing with the words "There is thus a need to improve fenofibrate bioavailability…") does not describe the invention, but the problem which is said to have been solved.

(b) The problem is said to have been solved by making the product most broadly described at p 5 lines 1-10 (the consistory clause which refers to an immediate release fenofibrate composition including fenofibrate in a micronized form having a size less than 20 μm) using the method described at p 5 lines 21-34 (the consistory clause for a method for preparing a pharmaceutical composition comprising the steps of, inter alia, preparing a fenofibrate suspension in micronized form with a particle size below 20 μm).

(c) The dissolution profile at p 5 lines 13-20 (the consistory clause for claim 12 commencing "The invention also provides a composition comprising fenofibrate having a dissolution of at least…"), in the primary judge's words, "is not a statement of the invention but a statement of an advantage of the invention". The primary judge then said:

> To the extent that the consistory statement at page 5 lines 13-20 of the specification may suggest otherwise, I regard it as inconsistent with what is disclosed elsewhere in the document including at page 8 lines 16-25, page 9 lines 12-27 (when read with page 10 lines 13-15), page 11 lines 15-21, and, I would add, other parts of the consistory clause.

Those parts of the specification are set out above.

(d) The formulations used in the Examples include particles of micronized fenofibrate that are less than 20 μm in size, and an inert hydrosoluble carrier and a hydrophilic polymer. While the specification makes clear that the invention described is not limited by the Examples, the "description of the composition of the formulations used in the Examples form part of the matter disclosed and must be taken into account when seeking to characterise the invention described in the specification when read as a whole".

The appeal

571 Mylan submitted that the primary judge fell into error by construing the invention described in the specification too narrowly. In particular, his Honour construed the specification as requiring the invention to involve a composition or a method of preparing a formulation containing fenofibrate in a micronized form having a size less than 20 μm. While these are embodiments of the invention, the invention is more broadly described in the specification so as to provide a fair basis for claims 12 and 13.

572 According to Mylan, the invention is a novel pharmaceutical composition comprising fenofibrate having high bioavailability through improved dissolution, and a method of

preparing the same. After describing the need to improve fenofibrate bioavailability at p 2 line 34 to p 3 line 6, the specification describes various embodiments of the invention which are subsequently claimed including the embodiment for claim 12. In a non-limiting way, the specification then exemplifies embodiments of the invention by reference to Figures 1 and 2 and the Examples. Although the primary judge recognised the Examples to be non-limiting at [289], he appears to have read down the invention by reference to the Examples.

573 Mylan submitted that:

> Contrary to the primary judge's finding (J [286], [287], Pt A Tab 15, 78-79), the specification does not require the composition of the invention to contain fenofibrate in a micronised form of less than 20 μm. Rather, the specification requires a pharmaceutical composition comprising fenofibrate having high bioavailability through improved dissolution, which had not been achieved by the prior art. The improved dissolution is reflected in the dissolution profile claimed in claim 12. As the specification makes clear, this may be achieved by a pharmaceutical composition of claim 1, made in accordance with the method of claim 14.

574 According to Mylan, it is not possible to read the references in the consistory clause for the invention claimed in claim 12, that the invention "also" provides "a" composition with the relevant dissolution profile, as mere stray words. As Mylan put it, nothing in the text of that consistory clause limits the composition to the composition which is contained in the immediately preceding consistory clause for the invention claimed in claim 1. Contrary to the primary judge's approach, this is not a mere statement of the advantage of the invention described in the immediately preceding consistory clause, but is a statement of another embodiment of the invention separate and distinct from the invention earlier described.

575 Sun Pharma submitted that Mylan had suggested no error in the primary judge's exposition of the relevant principles, including to the effect that a consistory clause could not provide a fair basis for a claim where other matters disclosed in the specification showed that the invention is narrower than the consistory clause suggests: see, in addition to *Lockwood No 1*, *Sigma Pharmaceuticals (Australia) Pty Ltd v Wyeth* [2011] FCAFC 132; (2011) 119 IPR 194 at [90], [91], [94], [95], [98], [99], [169], [170], [240]-[250] and *AstraZeneca v Apotex* at [413]-[421].

576 According to Sun Pharma, the primary judge's construction of the 964 specification was correct. The specification discloses a particular immediate release fenofibrate composition, and a method for preparing it. It employs a suspension of fenofibrate in micronized form in a solution of a hydrophilic polymer sprayed onto an inert hydrosoluble carrier. The

concentration of polymer used in the composition disclosed is essential to secure the increased dissolution rate and bioavailability.

577 Sun Pharma stressed that after identifying the need to improve fenofibrate bioavailability on p 3 line 34 to p 4 line 6, the specification stated as follows (Sun Pharma's emphasis):

> Applicant has found that, surprisingly, it is possible to resolve this problem by **a new method for preparing a pharmaceutical composition by spraying a suspension of the active ingredient onto an inert hydrosoluble carrier. The present invention also relates to a pharmaceutical composition thus prepared**.

578 Sun Pharma noted that the specification discloses:

> (a) p 5 lines 3 -10: that the invention relates to an immediate release fenofibrate composition comprising: (a) an inert hydrosoluble carrier coated with at least one layer containing a fenofibrate active ingredient in a "micronized form" having a size less than 20 μm, a hydrophilic polymer, and optionally, a surfactant, with the hydrophilic polymer making up 20% of the weight of (a) and (b) optionally one or more outer phases or layers; and
>
> (b) p 5 lines 21-35, p 9 lines 12-16, p 10 lines 3-16: a method for preparing a pharmaceutical composition, comprising the steps of preparing a fenofibrate suspension in micronized form with a particle size below 20 μm, in a solution of hydrophilic polymer and optionally a surfactant, applying the suspension to an inert hydrosoluble carrier (preferably in a fluidised bed granulator), and optionally coating granules thus obtained with one or several phases or layers.

579 Sun Pharma continued, submitting:

> The specification states that "the applicant believes that this novel method, through the use of a micronized active ingredient suspension in a hydrophilic polymer solution, enabled a novel composition to be obtained in which the active ingredient is in a non-re-agglomerated form" (page 11lines 16 to 21 (Pt A Tab 2, 11)). It is clear that use of the particular approach to formulating fenofibrate described is essential to avoiding re-agglomeration of the micronized drug particles, and thereby achieving increased dissolution rate and bioavailability.

580 With respect to the consistory clause for the invention claimed in claim 12, Sun Pharma submitted:

> The specification explains that the invention also provides a composition comprising fenofibrate having a specified dissolution profile (page 5 lines 13 to 20 (Pt A Tab 2, 5)). However, this dissolution profile is characteristic of and achieved by the composition which is described. The specification does not identify any other means of obtaining this dissolution rate profile.

581 According to Sun Pharma:

> This is a paradigm example of the principle to which the High Court referred in *Lockwood (No. 1)* at [99]. Consideration of the 964 specification as a whole makes clear that the invention disclosed is narrower than that identified at page 5 lines 13-20 (Pt A Tab 2, 5). The primary judge was correct in finding at PJR [288] (Pt A Tab 15,

71) that the dissolution profile specified at page 5 lines 13-20 (Pt A Tab 2, 5) is not a statement of the invention but a statement of an advantage of the invention, and that neither claims 12 nor claim 13 is fairly based.

Discussion

582 Sun Pharma's submissions to the effect that the reasoning of the primary judge about claims 12 and 13 of the 964 patent involve no error should be accepted.

583 First, the consistory clause on which Mylan relies (p 5 lines 13 to 20) must be read in the context of the specification as a whole, including what immediately precedes and follows it on p 5 lines 1 to 12 and p 5 lines 21 to 34. When read in context, it is apparent that it is not necessary to treat the words "also" ("The invention also provides…") and "a" ("…a composition comprising fenofibrate") as stray words. The better reading of p 5 lines 13 to 20 of the specification is that the invention to which reference is made is "the present invention [which] provides an immediate release fenofibrate composition" described at p 5 lines 1 to 12 and made in accordance with the method described at p 5 lines 21 to 34. It is this invention which also provides a composition comprising fenofibrate with the relevant dissolution profile. The words "a composition", on their natural and ordinary meaning, do not suggest any composition at large. Rather, they are linked to the invention which has already been described, being the immediate release fenofibrate composition. It is this composition which provides the relevant dissolution profile.

584 Mylan's submission that the words "also" and "a" indicate a separate and distinct embodiment of the invention does not readily conform to the natural and ordinary reading of the relevant part of the specification in context. The statement is that the invention "also provides something". In other words, the statement assumes that the invention has already been described. And the invention which has already been described is the immediate release fenofibrate composition. Nor is it necessary for the definite article "the" to be used, so as to refer to "the composition", to confine the description to the immediate release fenofibrate composition. What is being conveyed is that the invention, being the immediate release fenofibrate composition, also provides a composition which has the relevant dissolution profile. As the primary judge put it at [288], the passage on which Mylan relies is not a statement of the invention but a statement of an advantage of the invention.

585 The other parts of the specification on which the primary judge relied are consistent with this construction of the specification. They all involve the fenofibrate in a micronized form. In particular, the passage on which Mylan relies at p 5 lines 13 to 20 sits between two statements

of the invention both of which involve fenofibrate in micronized form having a size less than 20 μm. As Sun Pharma put it, there is no disclosure of any other method of obtaining the relevant dissolution profile. The dissolution profile is achieved by the composition which is described.

586 The primary judge did not read down the invention by reference to the Examples. The Examples are all consistent with the specification construed as a whole in which the dissolution profile is an advantage achieved by the composition which is disclosed, being the immediate release fenofibrate composition. The inconsistency which the primary judge had in mind at [288] is inconsistency between the fact that the disclosure elsewhere in the specification makes clear that the invention is to the immediate release fenofibrate composition and a method for preparing it, and Mylan's construction of the passage on p 5 lines 13 to 20 to the effect the invention extends to any composition of fenofibrate which satisfies the dissolution profile. As Sun Pharma submitted, this is a paradigm example of claims which travel beyond the matter disclosed in the specification.

587 For these reasons, the primary judge was correct to conclude that claims 12 and 13 of the 964 patent are not fairly based on matter described in the specification. Grounds 22 to 25 of the amended notice of appeal must be dismissed.

CONCLUSION AND DISPOSITION

588 For these reasons, Mylan's appeal and Sun Pharma's notice of contention should be dismissed. Mylan should pay Sun Pharma's costs.