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Case No: HC07 C0222
HC08 C00423

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 12 February 2009

Before :

THE HONOURABLE MR JUSTICE KITCHIN

- -

Between :

ratiopharm (UK) Limited	**Claimant**
and	
Alza Corporation	**Defendant**
and	
Janssen-Cilag Limited	**Part 20 Claimant**
- and between -	
(1) Alza Corporation **(2) Janssen-Cilag Limited**	**Claimants**
and	
Sandoz Limited	**Defendant**

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- -

Mr Antony Watson QC and **Mr Mark Chacksfield** (instructed by **S.J. Berwin LLP**) appeared for **ratiopharm**
Mr Antony Watson QC and **Mr Tom Mitcheson** (instructed by **Taylor Wessing LLP**) appeared for **Sandoz Limited**
Mr Michael Tappin and **Mr Joe Delaney** (instructed by **Linklaters LLP**) appeared for **Alza Corporation** and **Janssen-Cilag Limited**

Hearing dates: 25 – 28 November and 1 December 2008

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Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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THE HONOURABLE MR JUSTICE KITCHIN

MR. JUSTICE KITCHIN :

Introduction

1. These are two actions for infringement and revocation of European Patent (UK) No 1 381 352 ("the Patent"). Alza Corporation is proprietor of the Patent and Janssen-Cilag Limited is its exclusive licensee. In this judgment I refer to them collectively as "Alza". The Patent has a priority date of 16 March 2001 and is directed to transdermal patches for administering fentanyl, a potent opioid analgesic, through the skin. Alza sells patches made in accordance with the invention under the name Durogesic DTrans.

2. Alza complains that ratiopharm and Sandoz (collectively "the defendants") have infringed the Patent by selling fentanyl transdermal patches under the names Osmach and Mezolar Matrix respectively. They dispute infringement and contend the Patent is invalid on the following grounds:

    i) Anticipation by:

        a) International Patent Application WO 01/26705 A2 ("Samyang");

        b) a 1996 article by Roy et al. ("Roy").

    ii) Obviousness in the light of common general knowledge, Roy and the following further publications:

        a) a 2000 conference poster by Yu et al. ("the Yu Poster").

        b) a 2000 conference abstract by Yu et al. ("the Yu Abstract");

        c) European Patent Application 0 913 158 A1 ("Permatec");

        d) United States Patent 5 006 342 ("Cygnus");

        e) European Patent Application 0 622 075 A1 ("Hercon").

    iii) Insufficiency. The defendants contend the claims of the Patent are so uncertain it is not possible to determine their scope and they are therefore uninfringeable or insufficient. They also contend it requires undue experimentation to determine whether a product infringes. Both allegations depend upon the proper interpretation of the claims.

3. Finally, I should mention that Alza has made a conditional application to amend the Patent in the event I find it anticipated by Samyang. This application is not resisted.

The skilled person

4. The Patent is addressed to, and must be read through, the eyes of the person skilled in the art. In the end there was no dispute between the parties that the skilled person in this case is a team of people with experience in the formulation of transdermal patches. The team would have expertise in physical chemistry and chemical

engineering and would include persons familiar with conducting and analysing *in vitro* and *in vivo* studies.

The witnesses

5. Each side relied on the evidence of a single expert. Alza called Dr David Enscore. He graduated from North Carolina State University with a BSc in Chemical Engineering in 1973 and was awarded a PhD in Chemical Engineering in 1977. He was then awarded a post-doctoral fellowship at the Centre National de la Recherche Scientifique, the largest governmental research organization in France. Between 1979 and 1995, Dr Enscore worked at Alza. He began as a senior chemical engineer researching bio-erodible polymers and formulation development for transdermal dosage forms. During the course of his employment, he held directorship posts in a number of different areas of the business including Physical Sciences and New Product Discovery. In 1994, he became the Executive Director of Transdermal Product Development where he was responsible for development of specific drug delivery technologies. In his time at Alza, Dr Enscore was involved in 15 to 20 product development activities and led the development of three commercially successful transdermal patches for controlled release pharmaceuticals, namely nicotine, clonidine and testosterone. He also led the initial development of the liquid reservoir Durogesic patches, but, due to commitments on other projects, transferred responsibility for the later stages of this project to one of his colleagues. In 1995, Dr Enscore left Alza and spent the next eight years working on the application of polymer technology to other modes of drug delivery. He returned to transdermal drug delivery in 2003 before becoming an independent consultant in 2007.

6. The defendants make no criticism of the way Dr Enscore gave his evidence under cross examination but suggest that aspects of his written reports were overstated or wrong and that overall they were argumentative documents which presented a view which Dr Enscore did not support in person. In my judgment these criticisms are overstated. I accept that he qualified some of his written evidence in the course of his cross examination, but not in such a way as to cast doubt on his objectivity. The defendants also submit that Dr Enscore was hampered because he left the transdermal delivery field in 1995 and was not particularly aware of events which happened thereafter until the priority date including, most importantly, the introduction of six drug in adhesive products. There is, I think, more force in this criticism. Dr Enscore accepted that he did not work actively in the transdermal field over this period but suggested he did, to some extent, look at new products and market trends out of personal interest. Nevertheless, overall, I have no doubt Dr Enscore was trying to assist me throughout and I have found his evidence of great assistance.

7. Dr Walters gained a Membership of the Institute of Biology in 1974 and was awarded his PhD in 1979 based upon his work on the effects of nonionic surface-active agents on epithelial membranes. From 1978 until 1980 he was a postdoctoral fellow in the laboratories of Dr Gordon Flynn at the University of Michigan, College of Pharmacy where he gained experience of drug delivery through the skin. Following a further post-doctoral period at the University of Bath, School of Pharmacy, Dr Walters was employed first, by Fisons Pharmaceuticals to establish a section concerned with skin drug delivery and then, from 1986, by Eastman Kodak in Rochester, New York to work in their emerging Pharmaceutical Division as a

transdermal delivery scientist. In about 1992, Dr Walters joined An-eX Analytical Services Ltd ("An-ex"), an independent contract research and development laboratory that offers a range of specialist services to the pharmaceutical, cosmetic, chemical and agrochemical industries. The research and development activities of An-eX are focused primarily in the dermal and transdermal field and include prediction of dermal permeation, formulation development, formulation evaluation, assessment of bioequivalence, skin penetration enhancement or retardation, demonstration of efficacy and risk assessment. During his time at An-eX, Dr Walters has managed over 100 projects in the dermal and transdermal drug delivery fields. Between 1992 and 2001, he contributed to the development of dermatological and transdermal systems containing a wide range of pharmaceuticals, including hydrocortisone, hydromorphone, hydroxytamoxifen, ketoprofen, ibuprofen, methotrexate, niacinamide, nicotine, norethisterone, oestradiol, oxybutynin, piroxicam and testosterone. The transdermal systems he investigated included sprays, powders, semi-solids, membrane-controlled and drug-in-adhesive systems. By 2001, he had considerable experience working with academics and industry formulating and evaluating transdermal drug delivery systems and had hands on experience of patch formulation.

8. Alza suggest that Dr Walters was at times somewhat argumentative and unwilling to answer the questions he was asked. I reject this submission. I found Dr Waters to be well informed, clear and objective and I believe he too was doing his best to assist me throughout his cross examination. A more substantive criticism was that his reports were inevitably tainted by hindsight because it was apparent to him from the way he was presented with the prior art that the focus of the case was subsaturated drug in adhesive fentanyl patches. I believe Dr Walters accepted this was so, and it is a matter which I have had well in mind in assessing the weight to be attached to his evidence.

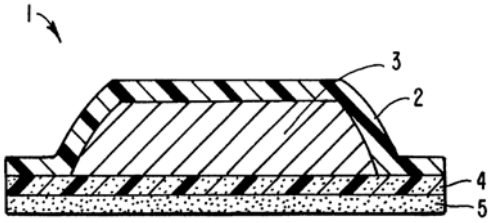
Common general knowledge

9. The common general knowledge is the common stock of knowledge of the persons skilled in the relevant art. It includes all the information which those persons would generally regard as a good basis for further action, and it forms part of their mental equipment when they come to consider specific items of prior art: *General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd* [1972] RPC 457 at 482; *Beloit Technologies Inc v Valmet Paper Machinery Inc* [1997] RPC 489 at 494. In the present case it became apparent after the cross examination there was a good deal of common ground.

The main classes of transdermal devices

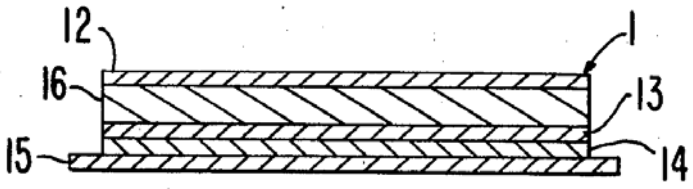
10. For many years before the priority date, Alza had sold a transdermal fentanyl patch under the name Durogesic for the treatment of chronic pain. This patch was sold in a range of sizes and was designed to be used in a three day treatment regimen, in that each patch provided an amount of fentanyl sufficient to induce and maintain analgesia over three days, after which the patient would remove the patch and apply a new one.

11. Durogesic was a liquid reservoir system and had the structure depicted below:



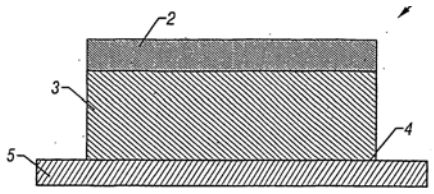
12. It had two important features: first, a liquid reservoir (3) containing fentanyl above the saturation concentration, with the result that the reservoir contained undissolved crystals of fentanyl; and second, a rate controlling membrane (4). This latter feature is essential when the drug is present as a liquid and it has a number of important properties. It decreases the *in vitro* release rate of the drug from the patch and increases the system rate control, and so reduces the variability in transdermal drug flux due to the inherent variability in the permeability of the skin. The reduced system release rate also means that the flux profile will decay more slowly than a corresponding system without a rate controlling membrane. Importantly, the membrane acts as an "artificial skin barrier" to ensure that the drug flux onto the skin will not exceed a certain level determined by the membrane. This is a useful safety feature in any case where there is a concern as to the effect that a large uncontrolled dose of the drug might have. In addition, the Durogesic patch had a backing layer (2) and the external surface of the rate controlling membrane was coated with an adhesive (5). The adhesive was covered by a protective release liner (not depicted). In use, the release liner was removed and the adhesive layer pressed against the skin of the patient. It was, however, recognised that liquid reservoir systems did suffer from certain disadvantages. In particular, it was perceived the presence of undissolved drug could cause stability problems during storage, although these were not known with Durogesic. Moreover, the patches were relatively complicated to fabricate.

13. There were two other well known patches in 2001, namely multi-laminate and monolithic patches. A typical multi-laminate patch is depicted below:



14. In this patch, a solid state (polymer) reservoir (16) is sandwiched between a backing layer (12) and a rate controlling membrane (13). The external surface of the rate controlling membrane is coated with an adhesive layer (14). A peelable release liner (15) is then applied to the adhesive layer. Sometimes the rate controlling membrane is omitted.

15. Finally, there is the monolithic, otherwise known as the drug in adhesive or matrix patch:



16. This, the most simple design, comprises a self-adhesive reservoir (3), commonly made of polyacrylate, sandwiched between a peelable release liner (5) and a backing layer (2). It may, in addition, comprise a further thin adhesive layer (4) where the adhesive reservoir does not itself provide sufficient adhesion over the working life of the patch.

17. An important difference between the depicted monolithic systems on the one hand and liquid reservoir and typical multi-laminate systems on the other is the absence of the rate controlling membrane. They therefore lack this element of system rate control, as I shall explain. However, they were recognised to have other advantages, notably they might be thinner and hence more cosmetically appealing and with better adherence characteristics than the other systems. It was also well known they could be used to deliver extended release of certain drugs, such as estradiol, over a three day period. They were also more simple to make, more robust and less open to abuse than liquid reservoir patches.

The mechanism of transdermal drug delivery and patch design

18. It was well known that in a transdermal drug delivery system, both the skin and the patch provide resistance (respectively, R_{skin} and R_{sys}) to drug permeation. The total or net resistance is a function of both and may be represented by the fomula: $R_{net} = R_{skin} + R_{sys}$

19. The rate at which the drug is delivered (the flux) is determined by the resistance it experiences. The reciprocal of the flux equals the resistance. Hence: $1/J_{net} = 1/J_{skin} + 1/J_{sys}$

20. In this formula J_{sys} is the flux from the patch. It represents the drug release rate from the patch into an infinite sink, that is to say the rate of drug release from the patch without considering the effect of the skin.

21. J_{skin} represents the flux across the skin. For a drug to enter the systemic circulation it has to partition into the upper layers of the skin and then diffuse through the lower layers until it reaches the capillaries. These layers present a tortuous path for drug migration and limit the rate of transdermal drug permeation.

22. Importantly, the flux across the skin (J_{skin}) is not affected by the concentration of the drug in the reservoir of the patch, but instead by the degree of saturation of the drug in the reservoir. This is what provides the chemical potential. It follows that J_{skin} is not a fixed parameter. If the drug in the reservoir is at a high concentration relative to its saturation concentration, the flux across the skin will be higher.

23. The system release rate (J_{sys}) is affected by a number of factors, most importantly the physical properties of the system and the chemical potential of the drug in the reservoir. If a rate control membrane is included between the drug reservoir and the

skin, this will act so as to provide an additional resistance to drug release from the system. It can thus be used to provide an upper limit to J_{sys} or to increase R_{sys} relative to R_{skin}.

24. As Dr Enscore says in his first report, these formulae are not immediately intuitive. But they show that even if the skin provides more resistance to drug transport than the transdermal patch, the patch will nevertheless still have an effect on the total resistance and will reduce the total net flux of the drug.

25. It was also known that the permeability of skin varies greatly both between and within individuals. If the resistance of the skin (R_{skin}) is low, the flux may be correspondingly high. But what effect this will have on the net flux (J_{net}) will depend on the resistance of the patch (R_{sys}). Even if R_{skin} becomes very small, R_{net} can never be less than R_{sys}, and so the rate of drug release from the patch into the bloodstream (J_{net}) can never be higher than the intrinsic rate of release of drug from the patch itself (J_{sys}). Hence the patch can be used to produce a rate controlling effect because it provides an effective upper limit on the rate of systemic drug absorption.

26. This is, in practice, one of the uses of a rate control membrane. It ensures an upper limit for J_{sys} which cannot be exceeded. It also increases the proportion of the overall rate control provided by the patch. Hence a patch with a rate control membrane will release drug at a lower and less variable rate than an otherwise equivalent patch with no rate control membrane.

27. There is one other important aspect of patch design which follows from the foregoing. In the case of subsaturated patch reservoirs, the chemical potential begins to decrease as soon as the drug is released from the patch. By contrast, in the case of saturation plus excess patch reservoirs, the chemical potential remains constant until all the undissolved drug is exhausted, at which point it begins to decline. This property of saturation plus excess patches will tend to ensure that the delivery rate of the drug remains relatively constant – a characteristic referred to as 'zero order kinetics'. It also follows that a subsaturated monolith patch will release drug at a lower rate than an equivalent saturation plus excess monolith patch due to the lower chemical potential of the drug. But that is not to say the skilled person had no means of controlling delivery from a subsaturated monolith patch. To the contrary, he knew sustained delivery could be improved by, for example, using a thicker slab or selecting an adhesive with a higher solubility for the drug to be delivered.

Properties of fentanyl

28. It is common ground the skilled person would have known that fentanyl is a potent opioid and that the major side effect associated with an overdose is respiratory depression. Alza also suggests fentanyl was known to have a narrow therapeutic window in that the gap between the minimum efficacious dose and the maximum tolerated dose is narrow. I am satisfied this was so. As a general rule, its therapeutic window for an average sized opioid naïve patient is approximately 0.5-2.0 ng/ml, although this varies from individual to individual and for opioid tolerant patients the figures may be substantially higher. I am also satisfied it was known there is up to a five fold difference between individuals in terms of skin permeability, even without taking into account damaged skin. For all these reasons patients were generally

started on a low dose of fentanyl that was unlikely to cause harm, and the dose was then gradually increased until analgesia was established.

In vitro and in vivo testing

29. There is no dispute that the development of a patch usually began with *in vitro* testing. This involved determining the rate of drug release from the patch and of drug permeation across small samples of human skin. The skilled team knew that measuring the flux of a drug from a patch through human skin *in vitro* could provide a basis for making reasonable predictions about *in vivo* performance, and hence plasma levels.

The Patent

30. The Patent is entitled "Transdermal Patch for Administering Fentanyl". Paragraph [0001] of the specification explains that the invention relates to a method and patch for the transdermal administration of fentanyl and its analogues for analgetic purposes. In particular, it is said the invention relates to a subsaturated patch for administering fentanyl to a subject through skin over an extended period of time.

31. The background of the invention is elaborated in paragraphs [0002] through [0013]. At the outset the specification explains that fentanyl and its analogues are powerful synthetic opioids used in both human and veterinary medicine.

32. Paragraph [0003] states that the transdermal administration of fentanyl has been suggested in numerous patents including US Patent 4, 558, 580, which discloses the reservoir system of the Durogesic patch.

33. Paragraph [0004] explains that a transdermal patch is typically a small adhesive bandage that contains the drug to be delivered and which can take several forms. The simplest type is identified as an adhesive monolith comprising a drug-containing reservoir disposed on a backing. The reservoir is typically formed from a pharmaceutically acceptable pressure sensitive adhesive but, in some cases, can be formed from a non-adhesive material, in which case the skin-contacting surface is provided with a thin layer of a suitable adhesive. The rate at which the drug is administered to a patient from these patches can vary due to normal person-to-person and skin site-to-skin site variations in the permeability of skin to the drug.

34. The specification continues in paragraph [0005] by describing the more complex multilaminate or liquid reservoir types of patch in which a drug release-rate controlling membrane is disposed between the drug reservoir and the skin-contacting adhesive. It says that this membrane reduces the effects of variations in skin permeability by decreasing the *in vitro* release rate of drug from the patch. The specification suggests this type of patch is generally preferred when a highly potent drug is being administered but recognises that it has the disadvantage of usually having to cover a larger area of skin than a monolithic patch to achieve the same drug administration rate.

35. Paragraphs [0006] and [0007] elaborate the difference between subsaturated and depot (saturation plus excess) patches. In subsaturated patches the drug is completely dissolved in the reservoir. By contrast, depot patches contain an excess

of undissolved drug over the saturation concentration. Because transdermal patches deliver drug by diffusion through the skin, the delivery rate of the drug from the patch is proportional to the level of saturation of the drug in the reservoir. In a depot patch, the excess drug allows the reservoir to remain saturated with the drug after the patch is applied so it can deliver the drug at the greatest rate for as long as the excess is present. A subsaturated patch, however, will typically exhibit a continuous decrease in the degree of saturation of the drug in the reservoir and the administration rate of the drug will tend to decrease continuously during use. The specification then suggests that depot patches are therefore preferred where a relatively constant drug administration rate is desired but it recognises that the presence of undissolved drug or other constituents in a patch can cause stability and other problems during storage and use.

36. The specification then turns to a consideration of fentanyl and its characteristics. Paragraph [0008] suggests that fentanyl has a narrow therapeutic index, with the therapeutic effect obtained only over a narrow range of concentrations; concentrations below the range being ineffective and concentrations above the range being associated with serious and potentially lethal side effects. Paragraph [0009] continues that because of the wide variations in individual drug clearance rates and the subjective nature of pain and the dangers associated with overdose, patients typically need to be titrated upwards to determine the appropriate dose. Treatment begins with a dose that is expected to be safe and it is then gradually increased until adequate analgesia is obtained. Over time, both tolerance to opioids and an increase in the severity of pain may occur and so doses may subsequently be increased or supplemented with other analgesics. In addition, some patients require the rescue use of other opioids for the treatment of breakthrough pain alongside their baseline treatment.

37. Paragraph [0010] explains that Durogesic is a patch that administers fentanyl for three days and is indicated for the treatment of chronic pain. At the end of each three day period the patch is removed and replaced with a fresh patch. It is contemplated that doses may be increased over time and that other analgesics may be needed to deal with breakthrough pain. Paragraph [0011] relates that because of fentanyl's high potency and narrow therapeutic index, Durogesic was designed as a rate controlled liquid reservoir depot patch.

38. Paragraphs [0012] and [0013] then explain that the inventors claim to have discovered that fentanyl can be safely and analgetically effectively delivered over periods of at least three days from non-rate controlled, monolithic, subsaturated patches with the advantage of simple fabrication and improved stability and comfort. Paragraph [0013] says that the patch of the invention is bioequivalent or pharmacologically equivalent to Durogesic.

39. The Patent then provides some definitions. Paragraph [0026] explains that the term bioavailabilty refers to the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action. The rate and extent are established by pharmacokinetic-parameters, such as the area under the blood or plasma drug concentration-time curve (AUC) and the peak blood or plasma concentration (C_{max}) of the drug. Paragraph [0027] continues that two different products are considered to be bioequivalent if they produce substantially the same pharmacokinetic effects when studied under similar experimental conditions.

Bioequivalence may therefore be demonstrated using pharmacokinetic measures such as AUC and C_{max} of the drug.

40. Paragraph [0028] explains that two different products are considered to be pharmacologically equivalent if they produce substantially the same therapeutic effects when studied under similar experimental conditions.

41. The detailed description of the invention begins in paragraph [0043], where it is stated:

> "The practice of the present invention will employ, unless otherwise indicated, conventional methods used by those in pharmaceutical product development within those of skill of the art. Such techniques are explained fully in the literature. See, e.g., Patini, G.A. and Chein, Y.W., Swarbrick, J. and Boylan, J.C., eds, Encyclopedia of Pharmaceutical Technology, New York: Marcel Dekker, Inc., 1999 and Gale, R., Hunt, J. and Prevo, M., Mathiowitz, E., ed, Encyclopedia of Controlled Drug Delivery Patches, Passive, New York: J Wiley & Sons, Inc, 1999."

42. This paragraph is of some importance. It reveals the patentee thought the process of formulation of the patch to be conventional. Rather, the invention lies in the idea of providing a non-rate controlled, monolithic, subsaturated patch for the transdermal delivery of fentanyl and analogues at a rate and in an amount sufficient to induce and maintain analgesia over a period of at least three days. Paragraph [0046] explains that if the reservoir is made from a material that does not have adequate adhesive properties then the skin contacting surface may be formulated with a thin adhesive coating.

43. Various ingredients are listed in the following paragraphs. At paragraph [0050] is a list of pharmaceutically acceptable polyacrylate adhesives, all of which were well known at the priority date. At paragraph [0052] various preferred concentrations of fentanyl are given. Paragraphs [0053] to [0060] then describe the materials which can be used for fabricating the various layers of the patches of the invention, none of which are said to be other than standard.

44. There then follows a section on the drug administration. Paragraph [0061] explains that upon application to the skin, the drug in the reservoir of the patch diffuses into the skin where it is absorbed into the blood stream to produce a systemic analgesic effect. The onset of analgesia depends upon various factors, such as potency of the drug, the solubility and diffusivity of the drug in the skin, the thickness of the skin, the concentration of the drug within the skin application site and the concentration of the drug in the drug reservoir, amongst other factors.

45. In a similar vein, paragraph [0063] elaborates that when continuous analgesia is required a depleted patch should be removed and a fresh patch applied. Since absorption of the drug from the fresh patch into the new application area usually occurs at substantially the same rate as absorption by the body of the residual drug within the application site of the depleted patch, blood levels will remain substantially constant. But it is clear that analgesia may not be complete. The

specification teaches that doses may be increased over time and that other analgesics may be used to deal with breakthrough pain.

46. Paragraphs [0064] and [0065] then explain that preferred embodiments of the invention exhibit a normalised C_{max} (peak plasma concentration normalised for the rate of drug delivered) and a standardised C_{max} (peak plasma concentration standardised per unit area of the drug delivery system) within wide ranges. More helpfully, paragraph [0065] also explains that steady-state administration rates obtainable for a fentanyl patch according to the invention range from 1 to 300 μg/h; preferably 2 to 250 μg/h; and more preferably 5 to 200 μg/h.

47. The Patent then describes various illustrative examples. Examples 1 to 7 describe the preparation of monolithic transdermal patches using polyacrylate adhesive. Example 8 describes *in vitro* tests carried out on the patches of the invention and Durogesic patches using a diffusion-cell apparatus to obtain *in vitro* drug flux. The results are displayed in Figure 3 of the Patent. Examples 10 and 11 then describe *in vivo* tests, and the results appear in Tables 1 to 4 and are illustrated in Figures 7 and 8. The results of these various tests are summarised at paragraph [0096]:

> "Thus, as evidenced from the results tabulated above and illustrated in Figures 3-8, the monolithic, subsaturated, transdermal patch of the present invention comprising a drug reservoir comprising a single phase polymeric composition comprising a subsaturation concentration of the drug, are bioequivalent products to the rate-controlled, saturated DURAGESIC fentanyl system. In particular, the monolithic subsaturated patches according to the invention display pharmacokinetic parameters comparable to the transdermal DURAGESIC fentanyl system."

The claims

48. Two claims are alleged to have independent validity, claims 1 and 21.

49. Claim 1 reads:

> A monolithic transdermal patch for administering fentanyl, alfentanil, carfentanil, lofentanil, remifentanil, sufentanil or trefentanil through the skin comprising:
>
> (a) a backing layer;
>
> (b) a reservoir disposed on the backing layer, at least the skin contacting surface of said reservoir being adhesive; said reservoir comprising a single phase polymeric composition free of undissolved components containing an amount of a drug selected from the group consisting of fentanyl, alfentanil, carfentanil, lofentanil, remifentanil, sufentanil and trefentanil sufficient to induce and maintain analgesia in a human for at least three days;

> characterised in that the reservoir is formed from a polyacrylate adhesive and has a thickness of 0.0125 mm (0.5 mil) to 0.1 mm (4 mil).

50. Claim 21 reads:

> The patch of any one of claims 1 to 20 which is completely free from a rate controlling membrane.

51. In the end the parties agreed there is no difference between them and that I should decide the case on the basis that claim 1 already includes the limitation of claim 21, namely the patch does not have a rate controlling membrane. It follows that if claim 1 is invalid then claim 21 must also fall.

Construction

52. The correct approach to the interpretation of a patent was explained by the House of Lords in *Kirin Amgen v Hoechst Marion Roussel* [2004] UKHL 46; [2005] RPC 169. The question is what the skilled person would have understood the patentee to be using the language of the claim to mean. For this purpose the language chosen is usually of critical importance. On the other hand, it has to be recognised the patentee is trying to describe something he regards as new.

53. Moreover, as Aldous J explained in *Rediffusion Simulation v Link-Miles* [1993] FSR 369, there is seldom a case where a person asked to look at every word of a specification to try to destroy it, cannot make out a case of potential ambiguity. The specification is to be read through the eyes of the skilled person attempting to give it a practical meaning and ascertain the intention of the draftsman rather than take it apart word by word.

54. In the end only two issues of construction fall to be determined. I address them in turn.

monolithic

55. This is relevant to the allegation of lack of novelty. The defendants say that although the term "monolithic" might normally be understood to refer to just a single slab of material, in the context of the Patent it clearly goes wider. In particular, the Patent expressly covers patches including a backing layer and patches where an additional layer of adhesive is added on the skin side to provide extra adhesion, and explains such patches should be understood to be monolithic. Accordingly, contend the defendants, the claim covers patches containing two adhesive slabs which each contain an analgesic drug and which lie on top of one another to form a multilaminate (as in Cygnus) or side by side to form a binary patch (as in some of the examples of Samyang).

56. I am unable to accept that the claim is this broad. The Patent uses the term monolithic to describe a patch containing a drug containing adhesive reservoir in the form of a single slab disposed on a backing. It explains that if the reservoir material is insufficiently adhesive then a thin adhesive coating may be added, but such that the reservoir may still be considered to be in contact with the skin. This is entirely

consistent with the evidence of Dr Enscore that the key feature of a monolithic patch is that a single entity within the patch controls the release rate of the drug. There can be no doubt that forming a multilaminate will significantly affect drug delivery, as will placing two slabs side by side to form a binary system. In my judgment the skilled person would understand monolithic in the context of the Patent to mean a patch which has one functional layer as far as drug delivery is concerned. It excludes multilaminates and binary systems.

contain an amount of fentanyl sufficient to induce and maintain analgesia in a human for at least three days

57. This is an important integer and it has a bearing on the allegations of anticipation, obviousness, insufficiency and infringement.

58. The defendants' primary position is that the integer is completely unclear and accordingly the claim cannot be infringed and is insufficient. The Patent itself recognises that patients vary widely in their individual pharmacokinetic and pharmacodynamic response to opioids. They have different drug clearance rates and pain itself is highly subjective. Over time, tolerance to opioids may increase and the severity of the pain may change. Moreover, there is up to a five fold variation in skin permeability between individuals and a three fold variation in permeability across the body of any one individual.

59. The defendants also say that the difficult issues which arise are exemplified by a consideration of the allegedly infringing products, the Osmach and Mezolar Matrix patches. The product literature for these makes clear that any particular patch may:

    i) provide no pain relief in some patients;

    ii) provide pain relief, but only for a shorter period in other patients;

    iii) provide a full three day's worth of pain relief for yet other patients;

    iv) and be dangerous to use for a fourth class of patients.

60. In these circumstances, the defendants contend it is impossible to determine conclusively whether any particular patch contains an amount of fentanyl sufficient to induce and maintain analgesia in a human for at least three days. A patch may induce analgesia for three days in one patient but not in another. A patch which induces analgesia in a particular patient when first administered may fail to do so at a later date. The defendants say all of this produces a hopeless degree of uncertainty.

61. Alza has taken different positions during the course of the action. Dr Enscore explained in his first report, and I accept, that the skilled person would be very familiar with the three day treatment regimen of Durogesic. The patches are applied and replaced in sequence, such that a sufficient level of drug is maintained in the blood to ensure that the induced analgesia is sufficient to treat the level of pain experienced by the particular patient. He also explained, and again I accept, it was well understood that there is an initial period during the first three day application when the blood concentration is rising but is below the minimum level required for

analgesia; and further, it was well understood that it might be necessary to try different patch sizes and to titrate upwards to find the correct dosage level for any individual.

62. Dr Enscore concluded the skilled person would understand the patch of the invention had to be capable of use in a multi-day regimen like that used for Durogesic. Dr Enscore also explained that *in vivo* tests are necessary to show whether the three day requirement was satisfied, a view supported by Alza in opening because, it said, *in vitro* tests can only ever be predictive of *in vivo* performance. In particular, a patch that exhibits a particular *in vitro* flux profile may give an unexpected *in vivo* profile. Further, the amount of time that any particular patch remains stuck to a person will play a large part in determining how much drug that person will receive. Overall, Alza argued, the patches of the invention must be comparable to Durogesic.

63. During the course of its opening submissions and again in closing, Alza accepted that the claim is broader than patches which are bioequivalent to Durogesic, and submitted it is enough that a patch causes analgesia in some humans in a three day cycle of applications.

64. In my judgment this modified construction contended for by Alza is correct. The skilled person would not understand the claim to be limited to patches which are bioequivalent to Durogesic, nor to patches which induce analgesia over three days in *all* humans. The range of humans and their inherent variability means that no patch could ever satisfy this requirement. The specification would be understood to mean that the patches of the invention must contain sufficient analgesic to induce and maintain analgesia in *some* patients for three days. It matters not that other patients may suffer breakthrough pain or that analgesia in such other patients may not last for the whole three days.

65. The next question is how the skilled person is to determine whether this requirement is satisfied. I accept that the specification envisages this may be determined by *in vivo* tests on healthy volunteers and determining the plasma levels generated. In this regard the specification provides various normalised and standardised ranges in paragraphs [0063] and [0064] and, more importantly, the skilled person would know that the Physicians Desk Reference (also known as the PDR) specifies that minimum effective plasma concentrations of fentanyl in opioid naïve patients range from 0.2 to 1.2 ng/ml. So long as the plasma levels remain above this level in at least some humans then the skilled person knows that analgesia will be induced in at least some humans.

66. In closing, Alza made a further concession. It accepted for the purposes of these proceeding only and on the basis of the evidence at trial, that *in vitro* skin permeation studies on monolithic patches provide an alternative method for the skilled person to assess whether such patches satisfy the three day requirement. In my judgment this concession was rightly made. The expert evidence was clear that the measurement of flux in properly conducted and validated *in vitro* skin permeation studies provides a sufficiently accurate indicator of the *in vivo* flux, and hence of the plasma levels. As to the lower limit on the flux that will cause analgesia in some humans, Dr Enscore thought it to be about 1 μg/hr, as described in paragraph [0065] of the Patent. I am satisfied that this is the extreme edge of the

claim and that commercial patches are designed to produce a flux which is a good deal higher.

Infringement

67. There is only one issue on infringement, namely whether the three day requirement of the claim is (or can be) satisfied. The defendants say Alza has not established that the Osmach and Mezolar Matrix patches contain sufficient fentanyl to induce and maintain analgesia in a human for at least three days.

68. Both the Osmach and Mezolar Matrix patches have obtained marketing approval on the basis of their bioequivalence to the Durogesic patch. I have no doubt that any patch which meets the requirements of European marketing approval on the basis of bioequivalence to Durogesic will induce and maintain analgesia in some humans for at least three days and this was confirmed by both experts. These products fall right in the centre of the claim. Infringement is therefore established.

Validity – Insufficiency

69. In the light of my conclusion on construction, I can deal with the allegation of insufficiency quite shortly. There can be no doubt that in certain circumstances ambiguity in the claims can render a patent insufficient. As Lord Hoffmann explained in the *Kirin Amgen* case at [121] to [131], ambiguity may not simply throw up the possibility of doubtful cases but make it very difficult, if not impossible, to carry out the invention at all.

70. The defendants contend that this is not a case where there are puzzles at the edge of the claim. Rather, they say, the requirement that the patch must contain an amount of fentanyl sufficient to induce and maintain analgesia in a human for at least three days is so unclear as to be insufficient. I am unable to accept this submission. The Patent contemplates *in vivo* tests on healthy volunteers and observing the plasma levels generated. If they are above 0.2 ng/ml then, as I have indicated, the skilled person knows that analgesia will be induced in some patients. Likewise the Patent contemplates *in vitro* tests to determine the level of flux a patch will generate. If it is above the lower limit of 1 μg/hr then, once again, the skilled person knows that the patch will induce analgesia in some patients. I would also emphasise that these are the extreme edges of the claim and that those seeking to practise the invention are likely to work substantially above them, as the alleged infringements in this case demonstrate.

71. In my judgment the claims are broad but not ambiguous and no undue burden is imposed on the skilled person in determining whether a patch falls within their scope.

Validity – Novelty

General

72. The decision of the House of Lords in *Synthon v SKB* [2006] RPC 10 makes clear there are two requirements for a patent claim to be anticipated by an earlier published document: it must disclose the invention claimed in the patent, and the

skilled person must be able to perform the claimed invention without undue effort by using the matter disclosed and his common general knowledge.

73. The disclosure requirement is a strict one. The earlier document must give clear and unmistakeable directions to do what is claimed. As the Court of Appeal explained in *General Tire v Firestone* [1972] RPC 457 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 of 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 if 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…
>
> 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 unmistakeable directions to do what the patentee claims to have invented… 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."

74. In the present case there are two novelty citations, Samyang and Roy.

Samyang

75. Samyang was filed on 6 October 2000 but not published until April 2001, shortly after the priority date of the Patent. It is therefore a novelty only citation under section 2(3) of the Patents Act 1977.

76. The invention of Samyang is a transdermal patch comprising two adjacent drug containing adhesive layers which have different solubilities for the drug in question. This difference affects the rate of drug release from each. By selecting appropriate polymers for each reservoir, patches can be made so as to provide an initial rapid dose of drug from the first, low solubility, reservoir and a delayed but more sustained drug release from the second, high solubility, reservoir.

77. Samyang describes a number of examples of patches in accordance with its invention (Examples 1-5) and two comparative examples of patches not made in accordance with its invention (Comparative Examples 1 and 2).

78. The defendants contend the Patent is anticipated by Examples 1 and 4 and by Comparative Example 2, but particular attention was focused on Example 4 and Comparative Example 2. The first of these, Example 4, discloses a fentanyl patch made up of two adhesive slabs side by side. One is a silicone adhesive slab which will release drug at a rapid rate. The other is an acrylate adhesive slab which releases the drug more slowly. Comparative Example 2 discloses a patch containing a single acrylate adhesive slab.

79. The defendants have carried out experiments based on Example 4 and Comparative Example 2 to support their argument that they each release enough fentanyl to induce and maintain analgesia for three days and, in the case of Example 4, the defendants made up a patch comprising only the acrylate slab of the example. In the light of these experiments I do not understand it to be seriously disputed that the patches tested in the experiments do indeed release enough fentanyl to satisfy the three day requirement. Accordingly, the issues which remain to be determined have been helpfully identified by Alza as follows:

    i) whether Examples 1 and 4 disclose monolithic transdermal patches;

    ii) whether polyacrylate patches made in accordance with Examples 1 and 4 satisfy the three day requirement. It is to be noted that this is not the same question as whether the patches of the experiments satisfied the three day requirement - the reason being that the patches of the experiments contained a polyacrylate slab but not the silicone slab of the Example 4;

    iii) whether a polyacrylate patch made according to Example 1 would have a reservoir which was a single phase polymeric composition free of undissolved components.

80. As for point (i), the defendants contend that the fact that Examples 1 and 4 describe a binary system does not prevent a finding of anticipation because it is trite law that the addition of an additional element (here a silicone slab) does not take something out of the claims; and in any event the claim uses the word “comprising”.

81. It follows from my conclusion on construction that the defendants’ submission must be rejected. The claim is directed to a monolithic patch. It is a characteristic of such patches that a single entity within the patch controls the release rate of the drug. The binary systems of Examples 1 and 4 have two adhesive slabs, not one. This is not a case where the prior art discloses a patch which falls in the claim and which has another feature as well. The presence of two adhesive slabs in the binary system means it does not fall in the claim at all.

82. Turning to point (ii), the three day requirement, Alza submits that there is insufficient evidence for the court to decide whether this requirement is satisfied in relation to Examples 1 and 4. The experiments conducted in relation to Example 4 showed that a patch containing the polyacrylate part of the example would deliver a flux of at least 10 μg/hr over 72 hours, which is plainly sufficient. However, says Alza, the amount of drug in the polyacrylate slab may have decreased had it been placed next to the silicone slab due to its partitioning sideways between the two polymers. This contention was supported by the evidence of Dr Walters who

accepted under cross examination that fentanyl would partition between the two polymers until they were at equilibrium.

83. The defendants respond that the point taken by Alza is a bad one because if the polyacrylate slab anticipated the claim when it was cast, it is no defence to argue that on storage the position may have become different.

84. I have some concern about the way this point was advanced by Alza because it was not foreshadowed in the reports of Dr Enscore. Nevertheless and not without some hesitation, I have come to the conclusion it is a good one. The experiment was not adequate to determine whether the three day requirement would have been met had the acrylate and silicone slabs been placed side by side. It is simply not possible for me to determine on the evidence whether it would or not. Moreover the defendants' response does not meet the point. The patch must be such that it will deliver sufficient fentanyl to induce analgesia over three days. The fact that it may deliver enough fentanyl to induce analgesia at the moment it is cast is not sufficient. It must do so over the whole three days and so after the reservoirs have become partially depleted.

85. The case on Example 1 relied upon the experiment conducted in relation to Comparative Example 2. Dr Enscore considered it was possible to extrapolate from 12 %wt fentanyl (Comparative Example 2) to 10 wt% (Example 1) and likewise from 10 cm^2 to 7 cm^2. Hence the resultant steady state flux from the polyacrylate patch would be about 17 µg/hr and the final flux would be expected to be about 7 µg/hr. Dr Walters broadly agreed. Alza sought to put to Dr Walters that it was not possible to make a quantitative prediction because the patches were of different thickness, the patch of Comparative Example 2 having a thickness of 50 µm and that of Example 1 having a thickness of 40 µm. Dr Walters accepted that it would make a difference but believed it would not be a very big one. I agree and do not think there is anything in this particular point. Nevertheless, the partitioning point referred to above in relation to Example 4 is an equally valid objection in relation to Example 1.

86. It follows that the defendants have not established that polyacrylate patches made in accordance with Examples 1 and 4 satisfy the three day requirement.

87. Finally, I must deal with point (iii). Alza has never been asked to agree and has never agreed that anything made in accordance with Example 1 would have a reservoir which was a single phase polymeric composition free of undissolved components. The defendants led no evidence on this and asked no questions about it. It has not been established this element of the claim is satisfied.

88. That leaves Comparative Example 2. This is a patch comprising a single slab of acrylate material containing fentanyl and so the side by side objection does not arise. I am satisfied in the light of the evidence that this patch would provide a flux at least as high as that of the commercial 12 µg/hr patches and it therefore falls right in the heart of the claim.

89. In conclusion, the allegation that the Patent lacks novelty over Comparative Example 2 of Samyang succeeds. However, it is accepted by the defendants this invalidity can be cured by amendment.

Roy

90. Roy was published in 1996 and describes work done on various forms of drug in adhesive fentanyl patches, using polyisobutylene (PIB), polyacrylate (GELVA 737) and silicone adhesives and the production of a number of patches and tests done on them.

91. The purpose of the work was explained by Roy in the following passage upon which Alza places particular reliance:

> "In recent years, various pressure-sensitive adhesives were considered for fabricating transdermal delivery systems. To fabricate such a transdermal device, the drug was either dissolved or dispersed in a polymeric solution, and a thin film of desired thickness was then prepared by the solvent-cast method. The rate of release of drug from such an adhesive matrix is governed by drug solubility and diffusion coefficients in polymer. Usually, these parameters were greatly influenced by the physicochemical properties of the polymer or adhesive. Therefore, it is important to evaluate the physicochemical parameters of an adhesive to design a suitable transdermal system that would eventually deliver a drug at a desired rate through skin for an extended period. …"

92. I think it is fair to say that the reader would therefore understand Roy to be describing the results of an investigation into the properties of various polymers and adhesives rather than the production of finished patches.

93. As Dr Walters explained, Roy reports that skin fluxes from 2% fentanyl in PIB, polyacrylate and various silicones were all in the region 0.9 – 6.3 $\mu g/cm^2/h$, with steady state fluxes achieved over at least 24 hours. More specifically in relation to polyacrylates, Roy made patches from GELVA 737 containing 2% and 4% fentanyl by weight. The *in vitro* skin permeation tests were performed with 1.3 cm^2 patches. Alza accepts that these patches were single phase patches free of undissolved components.

94. In the light of all his results, Roy concludes:

> "In summary, the diffusion coefficient of fentanyl in silicone-2920 adhesive was the highest among the four pressure-sensitive adhesives examined. The silicone-2920 with 2% drug loading provided the highest skin flux. Because of low drug solubility, a high diffusion coefficient, and a low Kp/w, the silicone-2920 adhesive appears to be a very promising adhesive candidate for designing a transdermal device with minimum drug loading to sustain the delivery of fentanyl at a desired rate to induce analgesia in humans for the relief of acute and chronic pain."

95. The defendants contend that Roy anticipates the Patent because it teaches the production of acrylate patches made of GELVA 737 which satisfy all the elements of the claim. Alza says there are two respects in which the attack must fail:

    i) Roy does not specify the thickness of the acrylate adhesive so it cannot be assumed it fell within the claim limits of 0.0125mm to 0.1mm.

    ii) The experimental data based upon the Roy patches show that they do not satisfy the three day requirement.

96. It is correct that Roy does not give the thickness of the acrylate adhesive which he used in his skin permeation tests. However, he also carried out a membrane permeation test and for that he used an acrylate reservoir thickness of 70µm.

97. Dr Walters explained in his report that, unless stated otherwise, the skilled person would presume the same thickness had been used in both experiments. Thus, he said, the value of 70 µm would seem to him to be the correct one to use and he believed the skilled formulator would have done likewise. However, in cross examination he accepted the skilled person could choose a different thickness, and one outside the limits of the claim (Day 4 at 439):

> "Q. If you want to make an acrylate patch with fentanyl in, Roy does not specify a thickness to use that acrylate layer, does he?
>
> A. No.
>
> Q. Mr. Watson put to Dr. Enscore, the day before yesterday, a paragraph in the Permatec patent -- I don't know if you remember that -- where there was a suggested preferable range for the adhesive layer of 50 to 150 microns.
>
> A. Yes.
>
> Q. And Dr. Enscore agreed with Mr. Watson that those were reasonable thicknesses traditionally used in transdermal devices. You would agree with that?
>
> A. Yes.
>
> Q. If you wanted to make an acrylate patch with fentanyl in having read Roy, one could choose a thickness in the range of 100 to 150 microns.
>
> A. One could, but 150 microns is getting a bit on the thick side and would take a long time to dry."

98. In my judgment it is plain that Dr Walters did not consider it inevitable that the skilled person would make a patch falling in the claim by following the teaching of Roy. This was confirmed by the way the case was put to Dr Enscore in cross examination (Day 2 at 248):

> "Q. As I understand it, you agree that while Roy does not tell you what thickness his two Gelva patches are to be rolled at, I think you agree that 70 microns would be a reasonable place - not inevitable but would be a reasonable thickness to make.
>
> A. 70 microns is within the range of reason, yes."

99. Turning to the three day requirement, the defendants relied upon an experiment to show the flux achieved by a 4 wt% patch. I am satisfied that the skilled person would not take a single result to determine the flux and that the approach taken by the defendants in their experiments was appropriate. This gave a flux of 0.9334 µg/hr from 48-60 hrs and 0.91 µg/hr from 60-72 hrs. It was therefore below the lower limit of 1 µg/hr described in paragraph [0065] of the Patent and once again outside the scope of the claim. It is clear that the Roy 4 wt% patch does not satisfy the three day requirement as the flux is below 1 µg/hr for the final period of 24 hours.

100. I conclude Roy does not contain clear and unmistakeable directions to make a patch falling within the claim. The allegation of lack of novelty over Roy therefore fails.

Invalidity - Obviousness

General

101. It is convenient to address the question of obviousness by using the structured approach explained by the Court of Appeal in *Pozzoli v BDMO* [2007] EWCA Civ 588; [2007] FSR 37. This involves the following steps:

(1) (a) Identify the notional "person skilled in the art".

(b) Identify the relevant common general knowledge of that person.

(2) Identify the inventive concept of the claim in question or, if that cannot readily be done, construe it.

(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed.

(4) Ask whether, when viewed without any knowledge of the alleged invention as claimed: do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

102. The last question requires the court to take into account all the relevant circumstances. It is also helpful to consider the nature of the obviousness case. Here the defendants say that there were three obvious routes for a designer of a fentanyl transdermal patch to consider, one of which was drug in adhesive without a rate controlling membrane. I think it is fair to characterise this as being an 'obvious to try' case, and so it is one of the kind considered by the House of Lords in *Conor v Angiotech* [2008] UKHL 49. There Lord Hoffmann said at [42]:

> "In the Court of Appeal, Jacob LJ dealt comprehensively with the question of when an invention could be considered obvious

> on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, by saying that the notion of something being obvious to try was useful only in a case in which there was a fair expectation of success. How much of an expectation would be needed depended upon the particular facts of the case. As Kitchin J said in *Generics (UK) Ltd v H Lundbeck A/S* [2007] RPC 32 , para 72:
>
> > "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success.""

103. As part of its response to the allegation of obviousness, Alza submits that invention may lie in overcoming the preconceptions and prejudices of the skilled workers in the field and showing that which was thought would not work, in fact would work. I accept that is so. As Jacob LJ said in *Pozzoli* at [27]:

> "A patentee who contributes something new by showing that, contrary to the mistaken prejudice, the idea will work or is practical has shown something new. He has shown that an apparent lion in the path is merely a paper tiger. Then his contribution is novel and non obvious and he deserves his patent."

104. Alza also properly warns me of the danger of allowing 'obvious to try' arguments to invalidate commercially valuable patents in research-intensive fields.

105. I must also avoid hindsight. This is particularly important where, as here, there is an allegation of obviousness based upon the common general knowledge. I put it this way in *Abbott v Evysio* [2008] EWHC 800 at [180]:

> "It is also particularly important to be wary of hindsight when considering an obviousness attack based upon the common general knowledge. The reason is straightforward. In attacking a patent, attention is focussed upon the particular development which is said to constitute the inventive step. With this development in mind it may be possible to mount an attack which is unencumbered by any detail which might point to non obviousness: *Coflexip v. Stolt Connex Seaway* (CA) [2000] IP&T 1332 at [45]. It is all too easy after the event to identify aspects of the common general knowledge which can be combined together in such a way as to lead to the claimed invention. But once again this has the potential to lead the court astray. The question is whether it would have been obvious to

> the skilled but uninventive person to take those features, extract them from the context in which they appear and combine them together to produce the invention."

106. The allegation of obviousness is also founded on a number of prior publications. Each of these must be deemed to be read properly and with interest and the public has a right to make anything which is an obvious development of what is disclosed. But I accept Alza's submission that the fact that a document is published does not mean it necessarily forms a realistic starting point for an obviousness attack. As I said in *Eli Lilly v Human Genome Sciences* [2008] RPC 29 at [295]:

> "I am unable to accept either of these submissions. In my judgment the first is a wholly artificial approach and it is not one which the law requires. I accept that the skilled person must be deemed to consider any piece of prior art properly and in that sense with interest. This emerges clearly from the decision of the Court of Appeal in *Asahi Medical Co Ltd. v. Macopharma (UK) Limited* [2002] EWCA Civ 466 and is necessary to prevent a patent from depriving the public of their right to make or do anything which is merely an obvious modification of what has been done or published before. But the law does not deem the skilled person to assume the prior art has any relevance to the problem he is addressing or require him to take it forward. Having considered it, he may conclude that it is simply not a worthwhile starting point and so put it to one side."

107. More recently, in *Dr Reddy's v Eli Lilly* [2008] EWHC 2345 Floyd J emphasised the danger of focussing on one prior publication to the exclusion of the prior art as a whole at [170]:

> "…there is nothing to single out Chakrabarti's work from all the other work being conducted contemporaneously to solve that problem. An approach which focuses unduly on Chakrabarti and examines what the skilled person could or might do with that document, to the exclusion of the prior art as a whole, is therefore tainted to some degree with hindsight."

108. In my judgment all these principles are relevant to the allegations of obviousness advanced in this case and I have them well in mind.

Obviousness over the common general knowledge

109. It is common ground that in 2001 it was obvious to seek to develop a fentanyl patch which was bioequivalent to Durogesic. The case of obviousness over the common general knowledge then runs as follows. A monolithic drug in adhesive patch was one option available to the skilled person and, due to its simplicity, probably the preferred option. Such a patch would inevitably have a backing layer with a reservoir disposed on it. A subsaturated patch would be one of the two options available to the skilled person and, due to the manufacturing and stability issues of saturation plus excess patches, probably the preferred option. It would be necessary

for any generic alternative to Durogesic to be therapeutically equivalent to Durogesic and hence it must contain sufficient drug to induce analgesia for at least three days. Polyacrylates were one of the three commonly used classes of adhesives at the priority date and would probably have been the skilled person's most favoured class. Finally, a thickness of up to about 100μm was typical for the reservoirs of a drug in adhesive patch. It was therefore obvious to make a patch falling within the claims of the Patent.

110. Alza's answer is equally straightforward and comprises two elements. First, it contends that the prevailing attitude of the skilled person was that a rate controlling membrane was required in order to produce a fentanyl patch that displayed acceptable safety characteristics similar to those of Durogesic. The skilled person was well aware that fentanyl posed significant risks due to its narrow therapeutic window, and therefore the primary objective in developing a patch was to ensure that the maximum dose it could deliver would not put the patient at risk. Moreover, it was also well known that in some people the skin at the site of application would absorb fentanyl at an unusually high rate, and that in order to minimise the risk to these people it was believed that a patch must have a rate controlling membrane so as to provide an upper limit on the rate of drug flux.

111. Secondly, the prevailing attitude of those skilled in the art was that in order to achieve a sustained fentanyl release rate that achieved the same therapeutic effect in humans as Durogesic, the patch would have to contain fentanyl at saturation plus excess. The skilled person would have been aware of the importance of chemical potential in determining the flux of drug through the skin. He would also have been aware that in a subsaturated patch, the chemical potential in the reservoir and hence the flux begins to drop off as soon as the patch starts to deliver drug. By contrast, in a saturation plus excess design, the excess drug continually tops up the reservoir and thereby maintains the chemical potential and hence a relatively steady drug delivery rate. The skilled person knew that Durogesic achieved this by using a saturation plus excess design, in combination with a rate controlling membrane.

112. Accordingly, says Alza, it was not obvious to the skilled person that an effective generic version of Durogesic could be made by developing a subsaturated patch that did not use a rate controlling membrane.

113. In assessing these rival submissions, it is convenient to begin by summarising some of the main aspects of the common general knowledge.

114. At a general level I am satisfied the skilled person would have known there were essentially three transdermal systems, namely liquid reservoir with a rate controlling membrane, polymer laminates with a rate controlling membrane and drug in adhesive without a rate controlling membrane.

115. The liquid reservoir system has two principal design features which were known to bring advantages. Saturation plus excess tends to ensure that the chemical potential remains constant throughout the period of administration and this is plainly a desirable feature in a system for the delivery of a drug such as fentanyl with a relatively narrow therapeutic index and potentially serious side effects. The rate controlling membrane sets an upper limit to the system flux and so provides safety, acts to increase the resistance of the system relative to the skin, so reducing the

effect of the inherent variability in skin permeability, and assists in limiting flux drop off over time.

116. Nevertheless, by 2001, the drug in adhesive systems, commonly comprising polyacrylate adhesives, were undoubtedly very popular and were perceived to have the advantages of being thinner, cosmetically more appealing, more robust, less open to abuse, having better skin adherence and avoiding instability problems sometimes associated with saturation plus excess designs. I am also satisfied that it was known that drug in adhesive patches could deliver drugs over a period of a day and, indeed, that the available estradiol patch (a drug with a similar permeation coefficient to that of fentanyl) was effective for seven days. The skilled person was well aware of techniques to address a fall off in drug delivery, such as by making the patch thicker or selecting an adhesive with a higher solubility for the drug to be delivered, and so permitting an increase in the drug loading. He would also have known that the composition of the reservoir affects the release rate.

117. More specifically, the experts agreed the skilled person would have known that fentanyl is a potent opioid with potentially serious side effects of respiratory depression and that it was therefore only used to treat chronic pain. He would also have known that for any given individual, fentanyl had a relatively narrow therapeutic index. As for patients, he would have known that there are significant variations both between and within individuals in terms of skin permeability, even disregarding damaged skin. He would have known of Durogesic and its component elements, that it was a saturation plus solid excess design with a rate controlling membrane and that it was the only transdermal fentanyl patch available at the priority date. He would have appreciated that the rate controlling membrane was a safety feature which mitigated uncontrolled drug release, reduced the effect of skin variability and limited flux drop off over time.

118. Against this background I come to the heart of the issue, namely whether it was obvious to develop a fentanyl drug in adhesive patch. Here I found the evidence of the experts particularly helpful. In his reports, Dr Enscore suggested that in 2001 the skilled person would not have thought that a drug in adhesive system could be made safely and effectively in a patch required to be used for the same indication and broadly in the same way as Durogesic. However, under cross examination, Dr Enscore frankly accepted that there were advantages associated with both approaches, namely liquid reservoir and drug in adhesive systems, and that it was perfectly reasonable to favour either, as shown by this interchange on Day 2 at 161:

> "Q. Now, Dr. Walters I would suggest to you very fairly pointed out that whereas he would favour a subsaturated patch, there may have been those that would have favoured a suspension patch. Now, would you agree that it is one of those things where reasonable men can differ?
>
> A. Oh, absolutely.
>
> Q. So you are not suggesting that Dr. Walters' attitude was atypical of a significant part of those in this field in 2001 that you would aim for sub-saturation if you could achieve it?

> A. There are advantages associated with both approaches. A skilled formulator would examine both approaches, examine the advantages and disadvantages offered by each and make a decision.
>
> Q. As everything in this art, it is all a trade off, is it not, in the sense that if you go subsaturated you are probably going to need a thicker patch for a given adhesive?
>
> A. To avoid fall off, yes.
>
> Q. Again, how much thicker? Can we live with it? It is a matter of judgment and trial and error that the skilled formulator -- that is what he does.
>
> A. Correct."

119. Moreover, testing a drug in adhesive matrix and then adjusting the formulation to modify its drug release characteristics was a basic skill, as Dr Enscore accepted on Day 2 at 165:

> "Q. Now, there are a number of points arising. First, you agree, I assume, that when you have produced a particular adhesive drug matrix, you can easily test it to see what its release characteristics are and then by adding enhancers, perhaps less drug, perhaps a different adhesive, you can adjust the release rates up or down. That is all basic skill, is it not?
>
> A. Yes."

120. He gave similar evidence to like effect a little later on the same day at 238:

> "Q. Nevertheless, if your instinct is to go for a drug-in-adhesive, you would trial various adhesives, various concentrations, carry out in vitro tests, vary the thickness, until you arrived at the profile you wanted. The Duragesic generic would be designed in exactly the same way as all the other drugs that have been drug-in-adhesives.
>
> A. That would be the way you would design a drug-in-adhesive patch, yes.
>
> Q. And the designer would be doing nothing untoward. He would be carrying out using his normal abilities and knowledge to formulate a suitable patch
>
> A. To formulate a patch he hopes eventually is suitable, yes."

121. As for the rate control membrane, Dr Enscore accepted this was just one of the matters to be evaluated, on Day 2 at 193-4:

> "Q. Now, I read those two paragraphs as you telling my Lord that in your view nobody would think of putting fentanyl into a drug-in-adhesive because of the concern about not having the rate-controlling membrane. Now, that just is not accurate, is it, doctor?
>
> A. It is my opinion that clearly people have thought about doing it, as evidenced by the passages we have been reading.
>
> Q. So it is not the case that the skilled man would have been put off putting fentanyl into a drug-in-adhesive by concerns that there was not the safety of the rate-controlling membrane. It was not a concern. The absence of a rate-controlling membrane would not have been a concern to the skilled man in 2001?
>
> A. It might have been a concern, but it didn't dissuade them from doing it.
>
> Q. It is just one of the evaluation points that you have to look at?
>
> A. (Nodding). …. The answer was yes."

122. In the end, Dr Enscore accepted that the skilled person would consider drug in adhesive and he would experiment with the known adhesives like the acrylates, on Day 2 at 240-241:

> "Q That the skilled man is trying to make a three day patch for fentanyl, you agree he would consider a drug-in-adhesive patch. You agree he would experiment with the known adhesives like the acrylates. Yes?
>
> A. Yes.
>
> Q. And he would find out that he could do it. All the patent says is, "We have done it," but the skilled man, without seeing the patent, would have arrived at that conclusion simply through routine trials, would he not?
>
> A. Once he had made a patch and actually conducted a bioequivalence study against Duragesic, had he made a patch that was bioequivalent, it would have been shown to be bioequivalent.
>
> Q. Yes, but if he is trying to make a patch that is bioequivalent, that is going to be his design goal. He wants to make a drug-in-adhesive. He will experiment with different acrylates until he finds the right combination of thickness. It is just all routine, is it not?
>
> A. It depends on how you define routine. I mean, it is ---

> Q. Nobody arrives at a drug, sorry - I didn't mean to cut across. Did you finish?
>
> A. That is OK.
>
> Q. Nobody designs a drug-in-adhesive just "there it is". For all the different drugs, you run trials with different adhesives, different concentrations, different thicknesses. That is what the doctors and the Walters and people working at Alza are paid to do [sic]. That is routine.
>
> A. You apply a design method to the patch and you develop a patch. I can't argue against that."

123. If he did so, he would make a patch within the claim, and he would find it worked.

124. Dr Walters expressed the opinion in his reports that it was well known at the priority date that formulators knew how to exercise control over drug release profiles through the choice of adhesive used and that a rate controlling membrane was not necessary for sustained release or for safety. Moreover he would always start with a preference for a subsaturated patch so as to avoid long term problems with stability. The subsaturated patches also had advantages in that they were less susceptible to misuse and risk of rupture and were the simplest to make. He believed the skilled person would try a drug in adhesive system and he would find that it worked.

125. Under cross examination Dr Walters recognised the importance of rate control and that a rate control membrane had always been used for fentanyl and there was no general understanding it could be dispensed with. He also accepted that zero order kinetics was the ideal for sustained delivery and accepted that this could not be achieved with a subsaturated patch. He also accepted that one would not have expected to be able to match the Durogesic *in vitro* flux profile using a subsaturated drug in adhesive patch. Nevertheless, he maintained that he would still conduct *in vitro* tests on a drug in adhesive design because of the advantages of such systems and because he thought what was important was to deliver drug in the therapeutic window and he considered that could be achieved. In re-examination he elaborated his reasoning by explaining that an increase in drug concentration or patch thickness would alleviate any tail off in the rate of flux. In considering this evidence I think it important to have in mind that Durogesic does not itself provide a consistent flux over the whole three day period, as Figure 3 of the Patent demonstrates. Moreover, and importantly, bioequivalence does not demand an exact match of the profiles but only a reasonable one. Indeed, as the Patent explains, bioequivalence is concerned with substantially the same pharmacokinetic effects as demonstrated by the AUC and C_{max}. The fact that the skilled person would expect a greater fall off in flux over time with a drug in adhesive patch, again as shown in Figure 3 of the Patent, is therefore by no means inconsistent with bioequivalence.

126. I have come to the conclusion in the light of the evidence as a whole that it was obvious at the priority date to try to develop a patch which was bioequivalent to Durogesic and for that purpose to make and carry out *in vitro* tests on a drug in adhesive subsaturated fentanyl patch. In so doing it was obvious to make a patch falling within the scope of the claims. The skilled person would have recognised the

advantages and disadvantages associated with both liquid reservoir and drug in adhesive patches and he would have considered them both well worth trying. He would not have regarded the presence of a rate controlling membrane and an excess of drug to be essential features of any design for the transdermal delivery of fentanyl.

127. The attack of obviousness over the common general knowledge therefore succeeds.

Obviousness over Roy

128. I have discussed the general disclosure of Roy earlier in this judgment. I concluded it does not give clear and unmistakeable directions to make a patch having a thickness of 0.0125 mm to 0.1 mm, nor to make a patch which satisfies the three day requirement. I must therefore consider whether these differences constitute steps which would have been obvious to the person skilled in the art or whether they involved any degree of invention.

129. The defendants contend it would have been perfectly apparent to the skilled person that he could take the idea of a polyacrylate fentanyl patch forwards and that he would be encouraged by the data in relation to a subsaturated PIB matrix which shows little tail off over 72 hours. If he had done so he would not have encountered any difficulty in producing something in accordance with the claims. In particular, the 1.3 cm^2 patches used by Roy were obviously only for the purposes of the reported experimental investigation and could be increased in size to give the rate of administration required. Roy evaluated, inter alia, 4 wt% and 2 wt% fentanyl patches made of the acrylate GELVA 737. Increasing the 4 wt% experimental patch to 20 cm^2 (still a small patch) would give an administration rate of 26 µg/h (equivalent to the smallest commercial Durogesic patch). Likewise, increasing the 2 wt% patch to 40 cm^2 (still well within the typical range of up to 100 cm^2) would give the same flux. Alternatively, or in addition, the skilled person could increase the concentration of fentanyl in the patch, to produce yet higher fluxes. Moreover, the thickness requirement of the claim is entirely standard.

130. Alza submits Roy does not claim to be teaching the skilled reader how to make a finished patch at all. Rather its teaching is limited to one element (the reservoir) in a transdermal patch and does not extend to any of the other functional elements that may be needed. It therefore does nothing to lead the skilled person away from his belief that a rate control membrane was necessary for safety reasons and a saturation plus excess design was necessary to achieve sustained release. Further, the teaching of Roy is clear as to the adhesive which should be used to fulfil the aim of sustained delivery of fentanyl transdermally; and that is silicone-2920.

131. Dr Walters explained in his reports why he considered it was obvious to take the steps necessary to make a patch in the claims. In particular, he said that the skilled formulator would typically aim for a patch of up to 100µm thickness and if the level of analgesia was not enough the skilled person could easily change the size or drug content of the patch to produce something with a higher flux. Moreover, the data in Roy show that silicone-2920 has a high flux rate and a low solubility for fentanyl which would raise a concern that a silicone-2920 patch might run too low on fentanyl to function properly over a three day period. By contrast, the other adhesives would not run the risk of being exhausted in this way.

132. Under cross examination he maintained this position. It was suggested to him that Roy's teaching is entirely sound and that the conclusions are justified on the basis the authors are proposing silicone-2920 on the basis of its low solubility for fentanyl which means that a high chemical potential can be generated with little drug. Flux can then be maintained over an extended period by using a saturation plus excess design with a rate control membrane. Dr Walters did not agree. As he understood the paper, the authors had in mind sustained delivery from silicone for only about one day. If, on the other hand, the skilled person had a preference for sustained delivery over three days with a subsaturated patch, so avoiding long term instability and adhesion problems, then it would be plain to the skilled person that silicone-2920 was not suitable and he would investigate the polyacrylates.

133. Dr Enscore expressed the opinion in his first report that the skilled reader would have assumed the conclusions in Roy were justified on the data presented and the skilled person would have moved forward with silicones as the preferred adhesive, with PIBs as a possible back up. He would have had no incentive to investigate polyacrylates further, and indeed would have had a positive disincentive to do so.

134. Under cross examination, Dr Enscore adopted a rather different position, as is apparent from the following revealing, if rather lengthy, exchange on Day 2 at 244-246:

> "Q. Now, this is published in 1995. Six years later, Dr. Walters and other workers in the field have a wide variety of adhesives which they can experiment with, including increasingly acrylics. Now, you are not suggesting to my Lord that there is anything other than a routine investigation to compare acrylics to PIB for potential use in a three day patch.
>
> A. It appears to be what Roy and Cleary did in this paper.
>
> Q. But you would want to try it. He only tried Gelva 737. Six years later, you would want to try it with Durotak 4098 and 2287. There are whole new kids on the block in terms of acrylics.
>
> A. I have no idea when those adhesives were introduced. I don't know if they were available in 1995 or not.
>
> Q. Doctor, you are a skilled man. You are using your experience, the knowledge that you have to test a variety of formulations to get the best combination. Are you suggesting to my Lord that it would require anything other than mere routine investigation to try dissolving fentanyl in some of the known popular polyacrylates existing in 2001 and to test them for their in vitro flux?
>
> A. No, that would be a common thing to do.

> Q. And if you did that, you would find that 4098, for example, would give you a flux of the type that we see in the experiments.
>
> A. That is likely.
>
> Q. That would be something that you could then test in vitro against Duragesic. If the comparison was close enough, you could go forward into in vivo tests.
>
> A. Yes.
>
> Q. So what does the patent tell you that the skilled man would not have arrived at by routine investigation in the light of Roy?
>
> A. My answer would be that it worked.
>
> Q. The skilled man would anticipate from his in vitro investigations that it would work, would he not?
>
> A. If he matched Duragesic flux and managed to do that with a reasonable mass loading of fentanyl at a reasonable thickness and did not see much greater variability in the permeability across the skin dermas he was using compared to Duragesic, that would give him great hope that it would work in vivo.
>
> Q. Granted the task of "make me a generic Duragesic and I would like it to be drug-in-adhesive if you can", if the skilled man had not thought of a way to do it from his common general knowledge, Roy clearly points the way - don't need a rate-controlling membrane, choose the right adhesive and you will be there.
>
> A. Given that you don't care what the thickness is going to be, and fentanyl content, yes, absolutely.
>
> Q. You would experiment to see whether the thickness was acceptable or not.
>
> A. Yes.
>
> Q. But it would certainly be worth trying.
>
> A. Sure."

135. I understood Dr Enscore to accept that the skilled person interested in making a three day fentanyl patch would not simply focus on the silicones and that in the light of Roy it would have been routine and, indeed, a common thing to do, to investigate the available polyacrylates and test their *in vitro* flux. They could then be tested against Durogesic. If the comparison was close enough the skilled person would proceed to *in vivo* tests. Moreover, the Patent teaches no more than that patches made in the course of this routine investigation would work.

136. In my judgment the arguments advanced by Alza are artificial and involve an unduly narrow and blinkered approach by the skilled person which was not reflected in the evidence of the experts. I believe Roy is encouraging and that the skilled person would have considered the available polyacrylates for a sustained release subsaturated fentanyl in adhesive patch without a rate control membrane. It was obvious to investigate the polyacrylates for this purpose and to make a patch falling within the claims. The allegation of obviousness over Roy therefore succeeds.

137. There was a further argument on Roy which I can dispose of shortly. The defendants say the skilled person is entitled to repeat Roy and cast a large patch of 4% drug in GELVA 737 at any sensible thickness. From that patch he can then cut subpatches for further experiment. Even if the 1.3 cm^2 patches Roy describes do not fall in the claims because the flux is too low, the skilled person could cut out from his large patch subpatches to whatever size he needed for his particular experiment and such patches would fall in the claims.

138. I am not satisfied this argument adds anything to the general attack of obviousness. It assumes the skilled person thinks it worth repeating Roy and, more importantly, making a patch as opposed to a polyacrylate membrane. Had I rejected the general attack, I do not believe this attack could have succeeded.

Obviousness over the Yu Poster

139. The Yu Poster reports studies done by employees of Samyang into a binary system in which a patch is made up of two different adhesive blocks side by side.

140. On page 2, the poster refers to the use of fentanyl as an analgesic and to its transdermal delivery by the known Durogesic patch.

141. On page 4, the poster sets out its "Objective". It recites that transdermal fentanyl could be administered easily without the aid of a physician, is very useful for chronic pain treatment, has a long duration of action and can be applied twice per week. It continues that, in contrast to Durogesic, the solid matrix system composed of "monolayer adhesive gives good touches and comfort to patients due to its thin and compact size". It then states:

> "To fabricate such a matrix transdermal device, several pressure sensitive adhesive polymers (acrylate and silicone) were characterised with respect to fentanyl's solubility, diffusion coefficient and permeability coefficient. In addition, the skin flux of several combinations of these adhesives were evaluated to optimize the matrix formulation adequate for inducing sufficient analgesia in a human."

142. Experimental methods are described on page 5. Six adhesives were tested: three silicones and three polyacrylates, namely Durotak 87-2196, 87-2287 and 87-4098. The defendants fairly emphasise that all of these are listed as suitable adhesives in paragraph [0050] of the Patent, and that Durotak 87-2287 is the specific acrylate used in the examples of the Patent.

143. Importantly, hairless mouse skin was used for the *in vitro* permeation tests, and it was agreed this is a poor model for human skin.

144. The results appear from page 7. *In vitro* skin permeation studies are reported for two of the polyacrylates (Durotak 87-2287 and 87-4098) and two of the silicones. It is apparent from page 10 that the silicones gave rapid drug release over the first 24 hours, but very little thereafter. By contrast, the polyacrylates gave sustained release over 50 hours, the period of the studies.

145. Figure 6 on page 14 is a graphical representation of the results of a comparative study between Durogesic and a binary patch of silicone and polyacrylate. This shows that the binary patch delivers significantly more fentanyl over the first 24 hours and that delivery from the two patches then gradually converges over the next 48 hours.

146. It is apparent that the difference between what is disclosed and the alleged invention is the use of a single polyacrylate matrix and a direction to make a subsaturated patch without a rate control membrane.

147. The defendants accept that the binary patch described in the poster would not be ideal for a Durogesic equivalent due to the initial spike given from the silicone element of the patch. They contend, however, that the obvious step to take would be to remove that element and just use the acrylate layer, which is shown in the poster to give sustained release matching that of Durogesic over 72 hours, and to incorporate it in a subsaturated patch.

148. Alza says this approach involves hindsight and, most importantly, relying on results obtained from hairless mouse skin, a notoriously poor model for human skin. It then requires the skilled person to reject the teaching of the document itself (using silicone and acrylate polymers side by side) and perceive that he might be able to use acrylate polymers alone to produce a three day patch.

149. Further, it requires the skilled person to decide to avoid a saturation plus excess design and a rate control membrane despite the well known Durogesic design and the fact there is nothing in the poster to demonstrate to him that subsaturated and non rate controlled patches could be made to work effectively and safely in humans.

150. Dr Walters recognised in his reports that the *in vitro* data is obtained in hairless mouse skin but explained that historically this had been used for permeation studies even though it was known to be a poor model for human skin. He thought the skilled person would treat the results with circumspection but nonetheless read the document with interest. He also believed the data in the poster suggest that the silicones released fentanyl quickly but that the polyacrylate gave steady release over a much longer period. He also found Figure 6 of interest in teaching that the dual patch initially released more fentanyl than Durogesic, but over time the profiles of the two tended to converge. This would have suggested to the skilled person interested in a patch which was bioequivalent to Durogesic that the initial burst was not a good thing and that the constant release provided by the polyacrylate would be likely to produce a profile closer to that of Durogesic.

151. In cross examination Dr Walters again readily accepted that hairless mouse skin is a poor model, indeed he would not trust it at all. He also accepted that it was not possible to say the difference in profiles in Figure 6 was entirely attributable to the silicone and he was not clear as to whether the drug was present at saturation plus excess. Nevertheless he maintained the poster does teach that the solubility of fentanyl in silicone is lower than in acrylate and that if long term delivery was required then an acrylate would probably be more suitable.

152. Dr Enscore explained in his first report that he did not think the skilled team interested in developing a transdermal patch for use in the same indication as Durogesic would have considered the Yu Poster useful for three reasons. First, it does not address the instability problem with any patch made up of a combination of adhesives, namely that drug will tend to migrate between the reservoirs to achieve equilibrium. Second, the patches are designed to decrease the time required to achieve analgesic plasma concentrations – a consideration relevant for the treatment of acute pain but not chronic pain. Third, the patches are tested on hairless mouse skin. As to the first point, Dr Enscore considered that binary patches suffer from the serious flaw that they are inherently unstable if the chemical potential in the two contiguous polymeric reservoirs is different. As to the second point, he observed that the initial burst of analgesia required by Yu is achieved by using two reservoirs made of different polymers; the silicone to release the initial burst of fentanyl and the polyacrylate to release the fentanyl over a longer time. As to the third point, hairless mouse skin was known to be a poor predictor of flux in humans.

153. In cross examination Dr Enscore adopted a much more pragmatic attitude. He accepted that one perfectly clear approach to making a generic Durogesic would have been to drop the silicone, as appears from this interchange on Day 2 at 251-252:

> "Q. If you were tasked to produce a generic Duragesic and you were wanting to make it bioequivalent to get the shortcut regulatory approval, you would know that the initial hit aspect would have to be avoided because you wouldn't have bioequivalence, would you?
>
> A. Correct.
>
> Q. Would it not be perfectly clear that if you were not trying to make an improved fentanyl patch, if all your task was to match Duragesic, to simply dispense with the silicone layer and just use fentanyl dissolved in Durotak?
>
> A. That would be one approach. You could dispense with the acrylate and use silicone and adjust the loading and pick one with the solubility you wanted and possibly achieve the same result.
>
> Q. So if you were tasked with making a bioequivalent Duragesic, and you had the Samyang abstract, it would suggest to you two ways forward. Both would be drug-in-adhesive. Yes?

A. Yes.

Q. No rate-controlling membrane?

A. They do not use a rate-controlling membrane.

Q. And it would then be a matter of design choice whether you experimented to get the flux as close to Duragesic as you wished with the polysilicone or with the acrylic.

A. Yes."

154. A little later he accepted it would be clear that a way forward would be to use fentanyl in polyacrylate without a rate control membrane, at 253-254:

"Q. The point is, how do I make a bioequivalent patch to Duragesic? In the Samyang poster, and particularly in figure 6, there is your answer, is it not? It is demonstrated that acrylic will give you a reasonable in vitro match. You are going to have to fine tune it and ----

A. Clearly you have to fine tune it because there is more of a difference between the two curves. There is more difference between the two curves than can be accounted for with the amount of drug in the silicone layer.

Q. Yes. Following on from that, you have to fine tune, but with the task of the generic Duragesic, the Samyang poster and in particular figure 6, it would be clear that a way forward would be drug-in-adhesive, polyacrylate adhesive, no rate-controlling membrane.

A. A way forward, yes.

Q. And as to whether you would make it saturated or subsaturated, you would wish to make it subsaturated if you could accommodate that in an acceptable thickness.

A. I wouldn't, but ----

Q. Others would.

A. Others might."

155. These are important passages. In the end there was practically nothing between the experts. One of the obvious ways forward in the light of the Yu Poster was to make a polyacrylate subsaturated patch without a rate control membrane. The Patent is obvious in the light of this citation.

Obviousness over the Yu Abstract

156. The Yu Abstract reports an evaluation of the diffusion characteristics of several adhesives with a view to designing a novel transdermal delivery system for fentanyl, in which two adhesive matrices are positioned in parallel.

157. Three polyacrylates were tested, namely Durotak 87-2196, 87-2287 and 87-4098, and three polysilicones. *In vitro* fentanyl flux through human skin from adhesive matrices was conducted using modified Franz diffusion cells at 32ºC. It was found that the solubility of fentanyl in the polyacrylate adhesives was about 10 times higher than those in the silicone adhesives. The section headed results reads:

> "In vitro drug permeation through skin from adhesive matrices was highly dependent on the kind of adhesives. In the case of silicone matrix, fentanyl permeated the skin fast, resulting in the high permeation rate and short time lag. On the other hand, acrylate matrices showed a relatively lower and sustained skin flux over 72 hours."

158. The defendants say that based upon this teaching the skilled person would have known that he could achieve 72 hour sustained release of fentanyl from a polyacrylate adhesive patch. Alza counters the skilled person is not taught whether the patches were saturated or subsaturated and the Yu Abstract does nothing to dissuade him from adopting that which he would have thought necessary, namely a saturation plus excess design with a rate control membrane.

159. In his report, Dr Walters accepted that one cannot tell from the abstract the patch thickness, nor the area, nor whether it was saturated or subsaturated but the information that acrylate drug in adhesive patches provide sustained delivery for 72 hours would be encouraging and the skilled person would appreciate that one option would be to make a subsaturated patch.

160. In the course of his cross examination, Dr Walters maintained there was enough information here to convince him to carry out further experiments on the acrylates to see if success was achievable, as appears from the following exchange on Day 3 at 413-414:

> "MR. TAPPIN: So, doctor, this abstract would not persuade you that you could make something equivalent to Duragesic just using an acrylate drug-in-adhesive patch, would it?
>
> A. This abstract tells me that I could probably get sustained delivery, maybe not zero order, but I could get sustained delivery, from an acrylate for 72 hours. I would do my own experiments from there to see what kind of levels I would get.
>
> Q. Doctor, would it be fair to say that if you were given this abstract, before taking any decisions on it, you would really want to see the poster or the presentation of which it was an abstract?

> A. Well, that is what one normally does, if you go to a conference and you have read the abstracts beforehand and decided which posters you are going to go to.
>
> Q. I mean, you would want to see the actual data, would you not, before making any decisions?
>
> A. I would like to see the human data, yes.
>
> Q. Would it be fair to say really, doctor, there is not enough data in this abstract on which to make any decision?
>
> A. I think there is enough data there to convince me to consider using the acrylates to do some further experiments with.
>
> Q. But, doctor, you would not think, on the basis of this, that you could make something bioequivalent to Duragesic using acrylate drug-in-adhesive.
>
> A. To the experiment - and find out.
>
> Q. But if you were asked, doctor, would you, on the basis of this, expect to succeed, you would have to say that really you would have no idea.
>
> A. Of course I would have no idea. I would want to try it myself and find out."

161. Dr Enscore explained in his third report that the abstract simply does not contain enough information to allow any decisions to be made as to patch design. But under cross examination he again accepted that the abstract teaches that polyacrylates will deliver fentanyl at acceptable rates for up to 72 hours, as appears from these answers on Day 2 at 255-256:

> "Q. Again, if you are trying to make a generic Duragesic, this document is also telling you polyacrylates will deliver fentanyl at acceptable rates for up to 72 hours.
>
> A. OK, they deliver 1 to approximately 4 for up to 72 hours.
>
> Q. That is in the Duragesic ballpark, is it not? 4 mcg per centimetre squared means that you can get to 100 mcg an hour with a 25 square centimetre -- it is all right for everybody else, they are just standing listening, but Dr. Enscore and I have been humming away.
>
> A. Yes, they don't speak about system sizes, but one presume they could select a system size.
>
> Q. If you were dithering, "How on earth do I make a generic Duragesic?", here is the answer on a plate for you.

> A. Stick your acrylate adhesive and hope that you get lucky relative to matching the Duragesic transdermal flux profile with acceptable error with acceptable residual drug at the end of 72 hours.
>
> Q. But remember the claim is not limited to Duragesic. We are simply showing that it would be obvious to make a patch containing fentanyl which will deliver sufficient fentanyl over 72 hours to give analgesia and here it is reported that a polyacrylate adhesive will give up to 72 hours in the range of, let us say, 3 mcg per hour centimetre squared. That is clearly in any sensible size patch, 10, 20 cm squared, going to be giving you the flux of fentanyl that you would need for analgesia for chronic cancer pain.
>
> A. In some patients.
>
> Q. Yes. So what has the patent given you that you could not readily work out for yourself from the abstract?
>
> A. Again, I can only say that all the things came together and that the patch of the patent worked."

162. I think it is clear from this that Dr Enscore was contemplating a subsaturated drug in adhesive and without a rate control membrane. The abstract encourages the skilled person to investigate the polyacrylates which have been shown to provide extended release of fentanyl over 72 hours at a level sufficient to induce analgesia in some patients. The skilled person would not have known the investigation would be successful; but it was obvious to try.

163. In my judgment the Patent is obvious over the Yu Abstract.

Obviousness over Permatec

164. Permatec describes an invention relating to a novel composition for sustained and controlled transdermal drug administration comprising a combination of saturated and unsaturated fatty acids or alcohols of different chain lengths as permeation enhancers. It contemplates the use of monolithic patches for multi-day release over a period of up to seven days.

165. A long list of drugs which can be used in the invention appears in paragraph [0055], of which fentanyl is one, although it is not singled out for particular attention. Similarly, many different adhesives are identified in paragraph [0059], including polyacrylates.

166. The preferred range of thickness of the reservoirs is described as being between 50-150μm and those of the examples have thicknesses varying from 80-100 μm.

167. In the light of this disclosure, the defendants say the skilled person would understand that a polyacrylate adhesive subsaturated patch may be made for the

transdermal delivery of many drugs, including fentanyl, and that sustained delivery can be achieved for up to seven days. This was supported by Dr Walters both in his second report and under cross examination. I have carefully considered that cross examination and do not consider the position taken by Dr Walters persuasive. I believe it is tolerably clear he has simply picked out the parts of Permatec which, together, can be said to point to a patch falling in the scope of the claims of the Patent.

168. Dr Enscore gave evidence in his first report that a skilled person seeking to design a fentanyl patch would not have been interested in Permatec, a view which was not challenged effectively in cross examination.

169. In my judgment any obviousness case founded on Permatec must rely heavily on hindsight to identify the aspects of the disclosure which, when pieced together, may be said to teach a patch falling in the claims of the Patent. It adds nothing to the case based upon the common general knowledge.

Obviousness over Cygnus

170. Cygnus is directed to resilient patches with improved skin adhesion. More specifically it relates to patches that include a number of spaced resilient structural laminates that enable the patches to stretch in concert with the area of skin to which they are adhered and which facilitate their handling prior to application. It also teaches that propylene glycol monolaurate (PGML) can be used as a permeation enhancer to increase the transdermal delivery rate of fentanyl.

171. The defendants focus particular attention on the paragraph bridging columns 7 and 8 which addresses the lifetime and thickness of typical estradiol and fentanyl patches:

> "When layer 17 is the primary reservoir for drug, its thickness will depend on the intended lifetime of the device. Thicker layers (and hence more drug and, when present, enhancer) will be used to increase the lifetime. In the case of estradiol …; whereas with fentanyl the effective lifetime will be about 1 to 7 days. In estradiol …; whereas in fentanyl embodiments [the reservoir layer] will normally be about 25 to 150 microns thick."

172. They also rely on the passage in column 8, lines 6 – 25, which refers to the absence of a rate controlling membrane in a fentanyl patch, and states:

> "Device 11 does not include means for controlling the rate at which either drug or enhancer is administered to the skin. Instead, in the case of an estradiol or fentanyl device employing PGML as enhancer, estradiol/fentanyl is presented to the skin at rates in excess of that which the treated area of the skin is able to absorb, while PGML is presented to the skin in quantities sufficient to allow necessary skin interaction. The system does not control either the rate of administration of estradiol/fentanyl or GML. Unlike ethanol, increasing the concentrations and thermodynamic activities of the PGML in the system does not

> increase estradiol/fentanyl flux appreciably beyond a limiting PGML concentration in the range of 6% to 10% in the adhesive layer. At PGML concentrations equal to or above this level, estradiol/fentanyl skin permeation becomes essentially constant and independent of PGML driving force in the system or estradiol loading above the limiting level necessary to provide equilibrium saturation in all layers and components of the composite."

173. The defendants then turn to Examples 20 and 21 which describe polyacrylate patches with different backing layers, one being occlusive and the other non occlusive. These are said to consist of a drug reservoir lamina consisting of 2.5% fentanyl base, 1.5% PGML and 96% acrylate polymer, and a pressure sensitive adhesive consisting of 1.5% fentanyl base, 1.5% PGML, 2.5% silicone oil and 94.5% amine resistant polydimethylsiloxane. In relation to these, Cygnus states:

> "Fentanyl skin flux from the occlusive system was 2.96 µg/cm2/hr, whereas the nonocclusive system gave 0.37 µg/cm2/hr. The lower flux of fentanyl from the nonocclusive system is due to the dehydration of the skin. Although the fentanyl flux decreased significantly from the nonocclusive system, a steady-state flux of 0.37 µg/cm2/hr was maintained up to 72 hours."

174. Based upon this disclosure, the defendants say the skilled person would appreciate that the occlusive patch provides a steady drug release over 72 hours, and at a rate that if made at, say, 72 cm^2 would be expected to provide the same total drug flux as the 25 µg/hr Durogesic patch then on the market.

175. Dr Walters supported this conclusion in his third report. However, under cross examination he accepted there was nothing to tell the skilled person how thick the fentanyl containing siloxane layer was. Moreover there was nothing to suggest it was there simply as a thin layer of adhesive to adhere the acrylate to the skin. Indeed, he considered the siloxane layer would have an effect on drug release, that the flux would depend upon the partition coefficient of fentanyl as between the skin and the siloxane and on the chemical potential of the fentanyl in the siloxane, that it would partition between the siloxane and the acrylate and that, in a sense, the acrylate was acting as a reservoir to top up the siloxane.

176. Dr Enscore was cross examined on these examples and the highlight was this interchange on Day 2 at 266:

> "Q. But if somebody came to you and said, we have had a brilliant idea, everything is good about this patch, but we have found that the adhesive that we have been recommended from 3M, in fact it is sticky enough on its own, we are going to do away with that extra adhesive layer and compensate by putting a little bit more fentanyl into the polyacrylate layer, you would say, mmm, that is a pretty straightforward modification. Try it.
>
> A. One could try it.

Q. It is something that would occur to one of ordinary skill.

A. Yes."

177. It is notable the question was put on the basis that the skilled person had been presented with a different adhesive and told to do away with the siloxane layer.

178. I think it plain that the allegation of obviousness over Cygnus relies on substantial hindsight to modify the multilaminate systems described so as to produce a patch falling within the claims. This citation therefore adds nothing to the allegation of obviousness over the common general knowledge.

Obviousness over Hercon

179. The obviousness case based upon Hercon was not pursued and I need say no more about it.

Conclusion

180. The Patent is anticipated by Comparative Example 2 of Samyang and is obvious over the common general knowledge, Roy, the Yu Poster and the Yu Abstract.