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Case Nos: HC10C04779, HC11C00553, HC1101095

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 22 March 2012

Before :

THE HON MR JUSTICE ARNOLD

- -

Between :

(1) TEVA UK LIMITED **(2) TEVA PHARMACEUTICAL INDUSTRIES LIMITED**	**Claimants in 4779**
(3) ACCORD HEALTHCARE LIMITED **(4) INTAS PHARMACEUTICALS LIMITED**	**Claimants in 553**
(5) HEXAL AG **(6) SANDOZ LIMITED**	**Claimants in 1095**
- and - **ASTRAZENECA AB**	**Defendant**

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Daniel Alexander QC and **Tom Mitcheson** (instructed by **Pinsent Masons LLP**) for the **Claimants in 4779**
Daniel Alexander QC and **Adrian Speck** (instructed by **Taylor Wessing LLP**) for the **Claimants in 553 and 1095**
Piers Acland QC and **Mark Chacksfield** (instructed by **Bristows**) for the **Defendant**

Hearing dates: 20-23, 27 February 2012
Further written submissions 15 March 2012

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Judgment

MR JUSTICE ARNOLD :

Contents

Introduction

1. The Claimants in these three claims all seek revocation of European Patent (UK) No. 0 907 364 ("the Patent") in the name of the Defendant ("AstraZeneca"). The Patent is for a sustained release formulation of an anti-psychotic drug known as quetiapine (marketed by AstraZeneca under the trade mark Seroquel). Supplementary protection certificates for quetiapine based on European Patent No. 0 240 228 ("228") will expire on 23 March 2012, hence the timing of the present claims. The Claimants contend that the Patent is invalid on the ground of obviousness over an item of prior art referred to as Gefvert, other objections not having been pursued at trial. There is no challenge to the claimed priority date of 31 May 1996.. AstraZeneca applied to make two alternative sets of amendments to the claims of the Patent, but did not pursue those applications. If claim 1 is invalid, the only claim which AstraZeneca asserted to be independently valid is claim 15.

The skilled team

2. A patent specification is addressed to those likely to have a practical interest in the subject matter of the invention, and such persons are those with practical knowledge and experience of the kind of work in which the invention is intended to be used. The addressee comes to a reading of the specification with the common general knowledge of persons skilled in the relevant art, and he or she reads it knowing that its purpose is to describe and demarcate an invention. He (or she) is unimaginative and has no inventive capacity. In some cases the patent is addressed to a team of persons with different skills.

3. In the present case there was little dispute by the end of the trial as to the identity of the skilled team to whom the Patent is addressed. It is common ground that the Patent is addressed to a team comprising a clinician, a pharmacologist, a formulation scientist and a pharmacokineticist.

4. The clinician would be a trained psychiatrist, specialising in the diagnosis and treatment of patients with psychotic illnesses, and in particular schizophrenia. The pharmacologist would have specialist knowledge concerning the effects of psychiatric drugs on the body, in particular their interaction with receptors in the brain. It is clear from the evidence that there would be an overlap between the common general knowledge of the clinician and pharmacologist members of the skilled team. For present purposes, it is not necessary to distinguish between them, and I shall refer to the clinician and the pharmacologist simply as "the clinician".

5. The formulation scientist would have experience in developing pharmaceutical formulations. Pharmacokinetics is concerned with what happens to drugs in the body, particularly with reference to their absorption, distribution, metabolism and excretion. In the context of a drug development programme, a pharmacokineticist develops protocols for and analysis of data from animal and patient studies. The formulator will need to have sufficient knowledge of the basic principles of pharmacokinetics to understand the likely effects of any formulation on the pharmacokinetics of the drug in question. Accordingly, for

present purposes it is again not necessary to distinguish between them, and I shall refer to them simply as "the formulator".

6. The only dispute between the parties was as to which member of the team should be regarded as the leader. The Claimants contend that the Patent is a primarily directed to the formulator. AstraZeneca contends that the development of a new formulation of quetiapine would be primarily driven by clinical considerations and to that extent would be led by the clinician. The formulator would then use his knowledge and experience to try to prepare an appropriate formulation and method of manufacture for that formulation in accordance with the clinician's instructions as to what was required. In my judgment these contentions are not inconsistent with each other: AstraZeneca is looking at the position prior to the Patent, whereas the Claimants are looking at the position after the Patent. I therefore accept both contentions. Either way, as both sides accept, there would be a notional conversation between the members of the team, in which the advantages and disadvantages of potential formulations would be considered.

The witnesses

7. Each side called two experts, a clinician and a formulator. The Claimants' clinician was Professor Paul Harrison, who is presently a Professor of Psychiatry at Oxford University, an Honorary Consultant in General Adult Psychiatry at Oxford Health Foundation NHS Trust and a Governing Body Fellow of Wolfson College, Oxford. He graduated with a BA (First Class) in Physiological Sciences from Oxford in 1982 and qualified in medicine in 1985. From 1985-1988 he trained in psychiatry. From 1988 to 1991 he continued part-time clinical training whilst a research fellow in London. He became a Member of the Royal College of Psychiatrists in 1989, Clinical Lecturer in Psychiatry in 1991, a Wellcome Trust Senior Fellow in 1995, was appointed to his present post in 1998 and became a Fellow of the Royal College of Psychiatrists in 2002. His work combines research, clinical practice and teaching.

8. The Claimants' formulator was Dr Peter Rue. He graduated with a BSc degree in Pharmacy in 1973 from the University of Aston in Birmingham, and was awarded his PhD in 1978. From 1977 to 1999 he worked in various positions in industry, including Head of the Pharmaceutical Development Department at Glaxo Group Research from 1990 to 1996. Since 2001, he has been a Visiting Lecturer at the Department of Pharmacy at Aston, and he currently holds a Visiting Chair there. In addition, he has acted as a consultant. It is relevant to note that Dr Rue had previously acted as an expert witness in a patent case concerning a sustained release formulation of fluvastatin, *Actavis UK Ltd v Novartis AG* [2009] EHWC 41 (Ch), on appeal [2010] EWCA Civ 82, [2010] FSR 18.

9. AstraZeneca's clinician was Professor Stuart Montgomery, who has been Emeritus Professor of Psychiatry at the Imperial College of Science, Technology and Medicine, London since 1996. He received a Bachelor of Science degree from the University of London in 1960, a Bachelor of Medicine and Bachelor of Surgery from University College Hospital in 1963, a Diploma

in Psychological Medicine from the Royal College of Physicians and Surgeons in 1973 and a Doctor of Medicine degree from the Karolinska Institute in 1978. Having held posts at various institutions from 1973 to 1979, he has been successively senior lecturer, reader and professor at St Mary's Hospital School since 1979. He was a Member of the Council of the Royal College of Psychiatrists from 1980 to 1982, President of the British Association of Psychopharmacology from 1990 – 1992, and the President of the European College of Neuropsychopharmacology from 1992 to 1995. He was a Member of the Committee on the Safety of Medicines from 1987 to 1993. Over the last 30 years his work has combined clinical practice, research and teaching. He also has experience in consulting, and providing licensing approval reports, for the pharmaceutical industry.

10. AstraZeneca's formulator was Dr Chris Moreton. He holds a Bachelor of Pharmacy degree from the University of Nottingham, a Master of Science degree in Pharmaceutical Analysis from the University of Strathclyde, and a Doctor of Philosophy degree from the University of Wales, College of Cardiff (now the University of Cardiff). From 1973 to 1986 and from 1992 to 2007 he held various positions in industry, and in particular from 1992 to 2001 he was employed in positions ranging from Technical Services Manager to Senior Director Technical Operations by Penwest Pharmaceuticals Co. Since 2007 he has run his own consulting business.

11. All four were good expert witnesses whose evidence was of assistance. On many points there was little difference between each of the respective pairs.

Common general knowledge

12. I reviewed the law as to common general knowledge in *KCI Licensing Inc v Smith & Nephew plc* [2010] EWHC 1487 (Pat), [2010] FSR 31 at [105]-[112], concluding at [112]:

> "It follows that, even if information is neither disclosed by a specific item of prior art nor common general knowledge, it may nevertheless be taken into account as part of a case of obviousness if it is proved that the skilled person faced with the problem to which the patent is addressed would acquire that information as a matter of routine. For example, if the problem is how to formulate a particular pharmaceutical substance for administration to patients, then it may be shown that the skilled formulator would as a matter of routine start by ascertaining certain physical and chemical properties of that substance (e.g. its aqueous solubility) from the literature or by routine testing. If so, it is legitimate to take that information into account when assessing the obviousness of a particular formulation. But that is because it is obvious for the skilled person to obtain the information, not because it is common general knowledge."

That statement of the law was approved by the Court of Appeal [2010] EWCA Civ 1260, [2011] FSR 8 at [6].

13. In the present case there was a good deal of common ground with regard to common general knowledge by the end of the trial, but there are also three areas of dispute. I will set out the common general knowledge which is uncontroversial before turning to the disputed areas.

Clinical common general knowledge

14. *Schizophrenia*. Schizophrenia is a type of psychosis, a severe psychiatric disorder, which is found in approximately 1% of the population. Patients exhibit a range of symptoms, some referred to as "positive", such as delusions, hallucinations, disorganised speech and thought disorder and grossly disorganised behaviour, and others as "negative", such as reduced emotions, reduced motivation, personality and interest in social interactions, and poverty of speech or thinking. It was also known in 1996 that cognitive dysfunctions such as impaired attention and memory were associated with schizophrenia, but they were not part of the definition of the disease or the diagnostic criteria for it.

15. Schizophrenia is usually a chronic condition with intermittent acute episodes. Acute episodes often have to be managed by urgent admission to a psychiatric hospital, whereas chronic schizophrenia can normally be managed by drug therapy in the community. In 1996 schizophrenia was a condition which was known to require long-term regular medication. Antipsychotic drugs generally took between two and six weeks to be effective.

16. *Causes of schizophrenia*. In 1996, as indeed today, the precise causes of schizophrenia were not fully understood. It was known to have genetic, developmental and social precipitants, but the roles of these had not been fully elucidated. There was a prevailing view that schizophrenia was associated with excessive levels of the neurotransmitter dopamine being released in certain areas of the brain (the so-called "dopamine hypothesis").

17. *The "typical" antipsychotics*. The first drugs to treat schizophrenia were introduced in the 1950s, and included chlorpromazine and haloperidol, amongst others. By the priority date these drugs had come to be known as the "typical" antipsychotics. These drugs revolutionised the treatment of schizophrenia, and contributed to the deinstitutionalisation of patients. They were, however, only effective in about 70% of patients, and only against positive symptoms. They had minimal effect on the negative and cognitive symptoms of schizophrenia.

18. Unfortunately, typical antipsychotics caused many serious side effects. The most serious were known as extrapyramidal side effects (EPS), including parkinsonism (tremor, slowness of movements), akathisia (an unpleasant restlessness), acute dystonia (which can take the form of the twisting of the neck, arching of the back, or rotation of the eyes), tardive dyskinesia (involuntary movements of the tongue, head or limbs) and tardive distonias (chronic distortions of posture). These drugs also caused non-EPS side effects, such as cardiac arrhythmias, postural hypotension, weight gain and disorders of sexual function. The "tardive" side effects were particularly serious in that, although the side effects would typically not manifest themselves until after several months (or even years) of exposure to the drug, once established the effects were difficult, or even impossible, to reverse. The non-EPS side effects

were viewed as very distressing by patients, and were a frequent cause of non-compliance.

19. All of the typical antipsychotics had approximately the same efficacy profile, although differing side effects. Some, the "high potency" drugs (which tended to bind the dopamine D2 receptors with high affinity and were dosed in small mg amounts), caused worse EPS; whereas the "low potency" drugs (lower D2 affinity, and therefore dosed in higher mg amounts) tended to cause more of the non-EPS side effects.

20. *The "atypical" antipsychotics*. Clozapine, which was discovered in the 1960s, was the first antipsychotic that did not cause significant EPS. It was first introduced into clinical practice in the early 1970s, but was soon withdrawn in most countries because of the high risk (1-2%) of agranulocytosis (a lowered white blood cell count resulting in a compromised immune system). In a study in 1988, however, Kane *et al* showed that clozapine also had greater efficacy than typical antipsychotics, and that about a third of patients unresponsive to (or intolerant of) the typical antipsychotics responded to clozapine. It was therefore reintroduced in about 1989 or 1990 for treatment-resistant schizophrenics, and with rigorous blood monitoring of the patients.

21. The beneficial properties of clozapine in terms of therapeutic effect and low EPS led to an interest by the pharmaceutical companies in producing similar drugs, but without the drawbacks of clozapine (which in addition to agranulocytosis included marked sedation, excess salivation, weight gain and other rare but serious side effects). Many analogues of clozapine, which was a dibenzodiazepine, were investigated. This led to the discovery of a number of drugs which, together with clozapine, had become collectively known by the priority date as the "atypical" antipsychotics.

22. The next atypical to be launched was remoxipride, in the early 1990s, although this drug was subsequently withdrawn in 1993 due to the unacceptably high incidence of the serious side effect, aplastic anaemia.

23. A third atypical antipsychotic, risperidone, was launched in 1994. This was believed to be comparable in efficacy to the typical antipsychotics, with lower EPS, at least at lower doses. By 1996 it was the most commonly used atypical antispyschotic after clozapine.

24. By the priority date, a number of other potential atypical antipsychotics – including olanzapine (Lilly), sertindole (Lundbeck), ziprasidone (Pfizer) and quetiapine (AstraZeneca) – were known to be in clinical trials.

25. *Theories as to the mechanism of action of antipsychotic drugs.* As mentioned above, it was widely accepted that an excess of dopamine in certain areas of the brain was involved in schizophrenia, and that its antagonism was an important aspect of the action of antipsychotic drugs. As to the details of that hypothesis, and exactly how typical and atypical drugs worked to produce a therapeutic effect or their various side effects, things were far less clear.

26. Receptor occupancy can be measured by positron emission tomography (PET), a technique by which it is possible to "visualise" how drugs interact with their receptors in the living brain. PET was an established technique in 1996, and had been used to derive occupancy values for the D2 and 5HT-2A receptors. Receptor occupancy is not directly related to or predictive of efficacy in the sense that, even if receptors are occupied, it does not follow that they will have efficacy. On the other hand, if a drug has no occupancy of a receptor, it cannot be efficacious via that receptor.

27. In 1996 it was thought that, for typical antispsycotics, a D2 receptor occupancy in excess of about 65% was needed in order for the drug to have efficacy, but that if the occupancy exceeded about 75%, then EPS would be likely to result. Consistent data of this type had been obtained for a number of typical antipsychotics, and this data was the core foundation of the dopamine hypothesis.

28. Clozapine was known to achieve levels of D2 occupancy in the region of 20-60% at therapeutic doses. It was widely thought that clozapine was an exception to the general rule that an antipsychotic needed greater than 60% D2 occupancy to be effective.

29. There were a number of theories as to how clozapine achieved a therapeutic effect with little EPS. The best known theory was the D2-5HT2A theory, according to which D2 occupancy was responsible for the therapeutic effect, while 5HT2A occupancy prevented EPS, but there were a number of other competing theories. None of these theories had achieved general acceptance.

30. It was generally assumed that other atypical antipsychotics had a similar mechanism of action to clozapine, although little was known about the details of this. The clinician would have considered that it was necessary to have a significant level of D2 occupancy to achieve therapeutic efficacy and that, if there was no D2 occupancy, one would not expect the drug to be efficacious at all.

31. *Metabolism of antipsychotics*. It was well known in 1996 that the typical antipsychotics used in the treatment of schizophrenia were largely metabolised in the liver i.e. were subject to high first pass metabolism. The benchmark was chlorpromazine, 75% of which was metabolised in this way. With some typical antipsychotics the percentage was higher, while for others the percentage was lower. It does not appear that there was any common general knowledge as to whether the atypical antipsychotics were similar or different in this respect.

32. *Quetiapine*. At the priority date the clinician would have been aware from his common general knowledge that quetiapine was an antipsychotic agent which was showing promise in clinical trials and therefore was likely to show adequate efficacy, tolerability and safety in the treatment of schizophrenia. A surprising amount of time was spent at trial in considering the various clinical trials, but in my view the upshot was clear and not really in dispute. The clinician would not have known the details of all the trials, but would be likely to have read a review of them by Hirsch *et al*, "ICI 204,636: A New Atypical Antipsychotic Drug" published in a supplement entitled "Current Issues in the

Development of Atypical Antipsychotic Drugs" to the May 1996 issue of the *British Journal of Psychiatry*. The authors' conclusion was as follows:

> "In summary, ICI 204,636 [i.e. quetiapine] is effective in the treatment of the positive and negative symptoms of schizophrenia. It is generally well tolerated, with an incidence of emergent EPS not different from that with placebo. … These data are consistent with the hypothesis that ICI 204,636 has properties characteristic of an atypical antipsychotic profile."

Overall, the clinician would have agreed that the available data appeared to support this assessment, although one of the trials reviewed was more persuasive of this than another.

Formulation common general knowledge

33. *Routes of administration.* Drugs can be administered by a variety of routes, but for present purposes it is only necessary to consider formulations for oral administration.

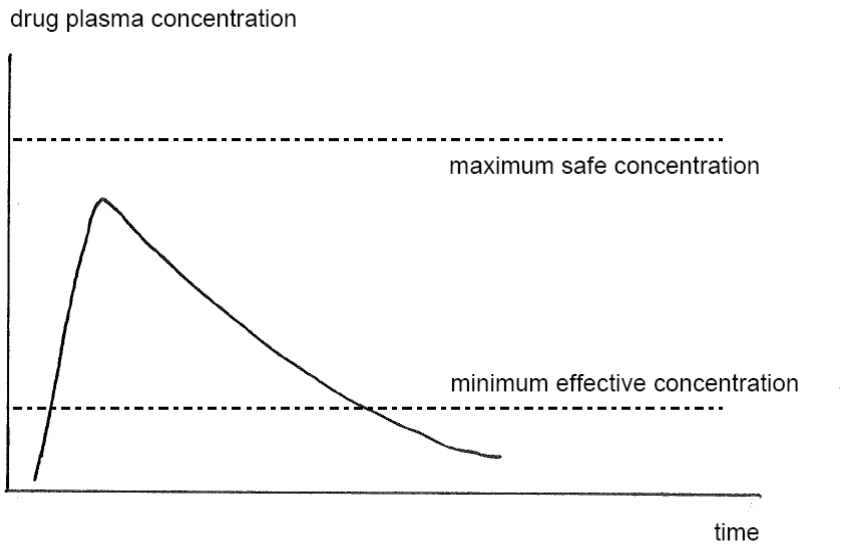
34. *Basics of drug absorption and action.* Pharmaceuticals taken orally are released from the dosage form and absorbed through the intestine into the bloodstream. That leads to levels of the drug in the blood plasma. There are several stages to this process. First, the release of the drug from the dosage form into the intestinal fluid. Next, the absorption of the drug across the intestine wall into the hepatic portal vein. This carries the drug to the liver from where it is passed into the systemic blood system. This initial journey from intestine through the liver is where some metabolism may occur, called "first pass metabolism". The proportion of drug that is metabolised in this way never reaches the systemic bloodstream in its original form.

35. Once in the bloodstream, drugs normally have to be present at a concentration high enough to give a therapeutic effect. But they must not be too high or undesirable side effects may occur. These two levels are known as Minimum Effective Concentration (MEC) and Maximum Safe Concentration (MSC). Thus, there will be a desirable band of concentrations (determined empirically for each drug) in which the drug would ideally be present.

36. While it is in the bloodstream, the amount of drug present in the blood will gradually diminish as more of it is broken down into metabolites. The standard measure of this is the drug plasma half-life: the length of time it takes for half of the drug in the plasma to be metabolised.

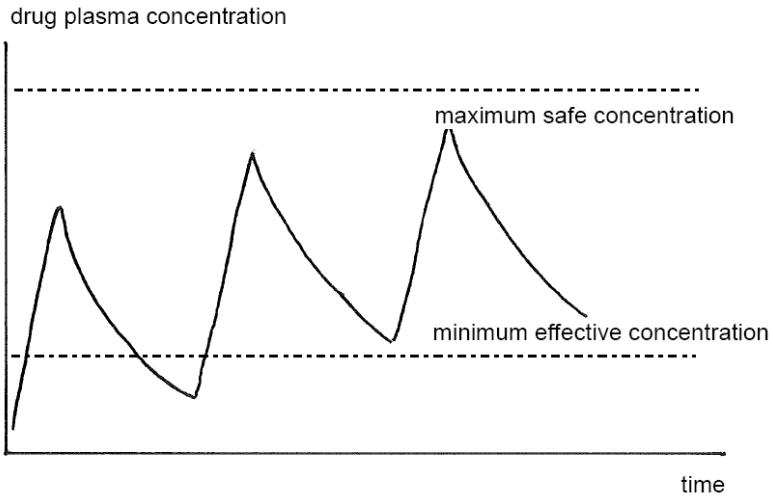
37. *Immediate release formulations.* An immediate release formulation is designed to release all the drug substantially immediately. Accordingly, early on the blood plasma levels increase as the drug is rapidly released from the dosage form and it is absorbed at the intestine wall, transported to the liver and released into the blood stream. As the amount of drug in the formulation decreases, the rate of release will slow down and eventually stop. At some point, the rate of metabolism will be greater than the rate of arrival of drug in the blood plasma. That point will signal a maximum in the blood plasma level and thereafter the

rate of metabolism will be dominant and the level of drug will decrease. The blood plasma levels look something like this:



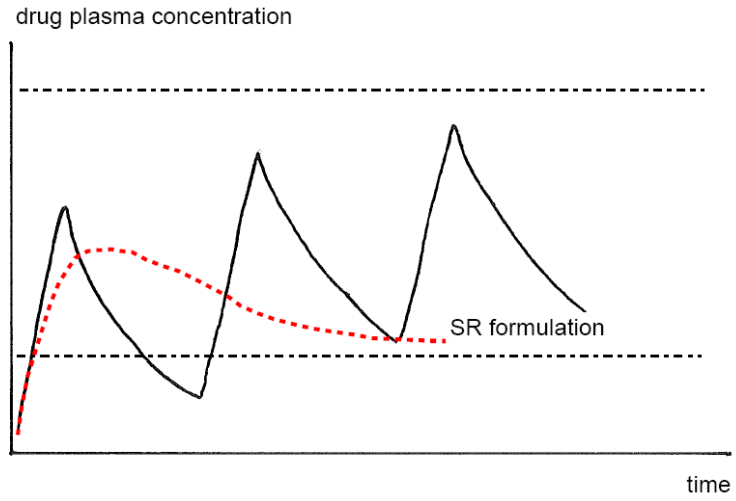
38. The peak value is often called C_{max}. It is the highest level that a drug exists in the blood plasma. The width of this peak will depend upon the rate at which the drug is metabolised. The drug levels may drop in a matter of an hour or so or it may drop very slowly – say over a whole day or more . The diagram also shows two dotted lines which notionally show the level above which the drug must be for therapeutic effect and the level above which side effects are seen.

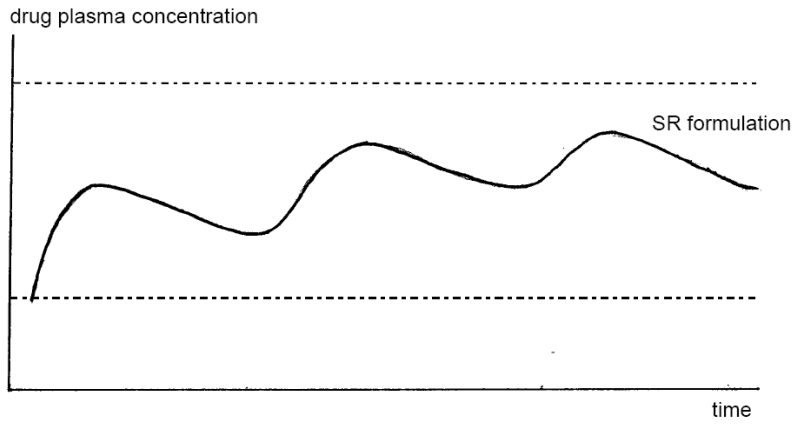
39. Where a patient takes a series of immediate release formulations the blood plasma level looks like this – each peak corresponding to each new dose.



40. *Sustained release formulations.* Sustained release formulations have been known for many years. The aim of such formulations is, as the name implies, to release the drug over a longer period of time than an immediate release formulation, thus maintaining the blood plasma level above the MEC for longer and reducing the number of times the patient has to administer the drug. If the drug is released from the tablet over a sustained period of time the profile will

look more like the figures below. The first illustration shows a single sustained release dosage in red overlaying the curve for three immediate release doses. The second illustration shows the curve where multiple sustained release doses are taken over an extended period:





41. The default formulation for the oral administration of pharmaceuticals is an immediate release formulation. From the formulator's perspective there must be some clinical need or rationale, however slight, for any new formulation, including a sustained release formulation.

42. The main advantages of sustained release formulations are as follows:

i) Blood plasma levels of drug following administration are prolonged compared to an immediate release formulation. This can be important when plasma levels have to be maintained.

ii) The variations in the maximum and minimum drug plasma levels seen at quasi-steady state are reduced. This helps avoid over- or under-dosing when the patient fails to stick to the prescribed dosing schedule.

iii) The frequency of dosing may be reduced compared to the immediate release formulation. I will return to this point below.

iv) There can be a reduction in local gastrointestinal side effects because the rate of release of the drug is reduced compared to an immediate release formulation.

43. There are a number of limitations of sustained release formulations, including the following:

i) Drugs which are only absorbed from a restricted region of the gastrointestinal tract present a problem for developing a sustained release formulation.

ii) Sustained release formulations are less suitable for drugs that have a half life of less than 1 hour or more than about 12 hours.

iii) Sustained release formulations are less suitable for very insoluble drugs.

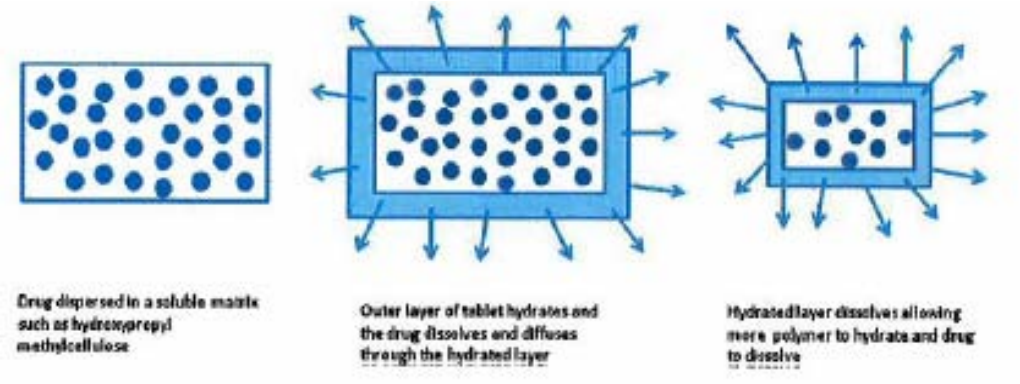
iv) Sustained release formulations are less suitable for drugs which need to be administered cumulatively in order to have a therapeutic effect or where precise dose titration is required.

v) Sustained release products usually contain more of the drug than the single dose administered in an immediate release dose form. If the sustained released formulation does not work properly and the drug is released too quickly (referred to as "dose dumping"), there is a risk of overdosing. I will return to this point below.

vi) Since more drug is required, the size of the tablet tends to be larger, which may present problems for the patient. If need be, however, the dose can be split between two tablets.

vii) There is a potential for side effects and drug-drug interactions to be increased.

44. In 1996 there were three basic types of types of sustained release tablets: matrix systems, membrane diffusion-controlled systems and osmotically-controlled systems. Matrix systems may be further divided into soluble matrices, insoluble matrices and eroding matrices. The way in which a soluble matrix works is schematically illustrated in the following diagram:



45. A well known way of formulating a sustained release oral dosage form was to use a soluble matrix made from a hydrophilic polymer (i.e. a gelling agent). A standard polymer for this purpose was hydroxypropyl methylcellulose (HPMC).

A widely available brand of HPMC in 1996 was Methocel, which was made by Dow. Dr Rue exhibited to his first report a 1995 Dow brochure entitled "Formulating for Controlled Release with METHOCEL Premium cellulose ethers". It is common ground that this brochure is the kind of publication that the ordinarily skilled formulator would have on his shelf. The first two pages of the brochure explain that matrix systems are highly resistant to dose dumping, relatively easy to formulate, easy to produce, economical and very versatile. The brochure goes on to describe a number of different grades of Methocel and to explain how dissolution rates can be controlled by, among other things, selecting and blending grades so as to change the viscosity of the gel.

46. *Excipients.* Drug formulations are conventionally formulated with pharmaceutically acceptable excipients such as lactose and cellulose derivatives (fillers) and stearic acid derivatives (lubricants).

Compliance and convenience

47. The Claimants contend that, both generally with regard to drugs which were orally administered and specifically with regard to antipsychotics, the general view of clinicians and formulators in 1996 was that administration once daily was preferable to more frequent administration because it improved patient compliance and was more convenient for patients and carers (such as nurses in a hospital environment). AstraZeneca accepts that once or twice daily dosing was regarded as significantly better than three or four times daily, but disputes that once daily was regarded as significantly different to twice daily. There was quite a lot of evidence on this topic. I do not consider it necessary to review all of the evidence, but the salient points are as follows.

48. *Compliance from the clinician's perspective.* A textbook an extract from which was exhibited by Professor Harrison to his first report as exemplifying the common general knowledge, namely Gelder *et al*, *Oxford Textbook of Psychiatry* (3rd ed, 1996), states at 537:

> "Psychotropic drugs have often been given three times a day, even though their duration of action is such that most can be taken once or twice a day without any undesirable fall in plasma concentrations between doses. Less frequent administration has the advantage that out-patients are more likely to be reliable in taking drugs. In hospital, less frequent drug rounds mean that nurses have more time for psychological aspects of treatment."

49. There are a number of papers in evidence which specifically address the question of compliance. I am not persuaded that any of these were themselves common general knowledge, but nevertheless I will consider them to see what light they shed on the matter.

50. First, a review article by Blackwell, "Treatment Adherence", *Brit. J. Psychiat.* (1976), 129, 513-31 considered the problem of adherence (compliance) in the context of use of medication in psychiatry. When surveying the risk factors contributing to non-adherence, the author said at 522:

> "There is clear evidence that adherence is adversely affected when multiple medications are prescribed or drugs are given in frequent divided doses.… These observations and increasing knowledge about the metabolism of psychotropic drugs has led to the widespread popularity of once daily therapies as a means of improving adherence…."

In the course of making recommendations to deal with adherence problems, the author said at 526:

> "The medication itself plays an obvious part in management. The complexity of the regimen should be kept to a minimum by prescribing the least possible number of medications and daily dosages."

51. Secondly, a review by Greenberg, "Overview of Patient Compliance with Medication Dosing: A Literature Review", *Clinical Therapeutics* (1984), 6, 592-599 considered 26 studies the literature of compliance with pharmaceuticals generally and concluded that once-a-day and twice-a-day regimens were associated with significantly better compliance (73% and 70% respectively) than were three-times-daily (52%) and four-times-daily (42%) regimens. Professor Montgomery pointed out that once a day was not statistically significantly better than twice a day. On the other hand, Professor Harrison explained that the data in Greenberg was quite weak because of the nature of the studies being reviewed.

52. Thirdly, Razali and Yahya, "Compliance with treatment in schizophrenia: a drug intervention program in a developing country", *Acta Psychiatr. Scand.* (1995), 91, 331-335 investigated compliance by schizophrenia patients in Malaysia. The authors found that compliance was significantly better in those who were treated for less than five years, received daily or twice-a-day doses and who viewed the medication as valuable to them. The authors commented that this finding was consistent with Greenberg's conclusion.

53. Finally, AstraZeneca relied upon a review by Fenton *et al*, "Determinants of Medication Compliance in Schizophrenia: Empirical and Clinical Findings", *Schizophrenia Bulletin*, (1997), 23, 637-651. This was not published until after the priority date of the Patent, however. If one puts that on one side, the authors state at 642:

> "**Complexity of regimen.** Although the complexity of a medication regimen is associated with compliance across a broad range of medical disorders (Haynes 1976), only one (Razli and Yahya 1995) of four empirical studies that focused exclusively on schizophrenia identified a statistically significant association between complexity of regimen and compliance. Hoffman et al. (1974), Hogan et al. (1983), and Buchanan (1992) found no such association."

54. Professor Harrison's evidence was that non-compliance (and partial compliance) is a major cause of relapse in schizophrenia. For patients with

schizophrenia, non-compliance has three main types of cause. First, illness-related factors e.g. their lack of insight means they do not believe they are ill and thus do not need treatment. Secondly, treatment-related factors. Antipsychotic drugs cause side-effects (EPS, sedation, and many others) such that the patient chooses not to take them. Thirdly, for some patients, it may simply be forgetfulness. His view was that dosing once a day would be likely to lead to better compliance than twice a day, and his opinion was that the majority of clinicians working in schizophrenia in 1996 would have said the same. He drew a comparison with SSRIs, a class of antidepressants which could be prescribed once a day, whereas older drugs were often twice a day, and said that that was regarded as attractive to prescribers and patients. He accepted, however, that there was no firm evidence to support his view.

55. Professor Montgomery's evidence was that both the scientific literature and his own clinical experience supported the conclusion that twice a day was just as good for compliance as once a day. As he put it:

> "... logically, once a day, as you say, it is obvious, but our studies showed that there was no disadvantage to twice a day."

56. *Compliance from the formulator's perspective*. Dr Rue exhibited to his first report as exemplifying the common general knowledge extracts from two textbooks on formulation science which address this question. First, Rubinstein, "Tablets", in *Pharmaceutics: The Science of Dosage Form Design* edited by Aulton (1988) states at 315:

> "**Sustained-release tablets**
>
> *Advantages and disadvantages as a dosage form*
>
> In recent years there has been a large increase in the development and use of sustained-release tablets which are designed to release the drug slowly after ingestion. The main factor in the more widespread use of these types of dosage forms is that patient compliance is improved since only one or two tablets need to be taken daily. … A single daily dosage has advantages with psychiatric patients, since this patient group generally forgets to take their medication regularly, and for patients in hospital a decrease in the number of doses administered can result in a time saving for nurses."

57. Secondly, Chang and Robinson, "Sustained Drug Release from Tablets and Particles Through Coating" in, *Pharmaceutical Dosage Forms: Tablets* (2nd ed, vol 3) edited by Lieberman, Lachman and Schwartz states at 200:

> "Aside from the enormous advantage of overcoming compliance problems, well-designed sustained-release dosage forms offer considerable potential in terms of the temporal and spatial delivery of drug and the resulting maintenance of drug levels in tissues of the body."

58. Dr Rue was clear that once daily dosing was preferred:

> "...once daily dosing is the gold standard. That is what we are in industrial formulation attempting to achieve whenever possible. So given that that is what we would normally be aiming for, if twice daily dosing was effective, then clearly one would be looking at improving it to once daily."

59. Dr Moreton, on the other hand, said that all the data that he had ever come across on compliance suggested that there was no real difference between once a day and twice a day.

60. *Prescribing practice*. Both sides appealed to prescribing practices as supporting their respective cases. AstraZeneca relied on the fact that, with two exceptions, the recommended dosing regimen in the UK for all drugs used in the treatment of schizophrenia in 1996 was three or more times a day, notwithstanding that many of them had terminal half lives which made them suitable for dosing once a day. Professor Harrison's evidence, however, was that he tried to use once a day whenever he was confident either that the patient did not need the medication more frequently or that it might make a difference to their compliance. He also pointed out that pharmaceutical companies might not always think it cost effective to secure regulatory approval for a change to the dosing regime.

61. The Claimants pointed out that prescribing practice in the USA was different. Thus one of the standard texts in the US, Kaplan and Sadok's *Synopsis of Psychiatry* (7th ed, 1994) states at 944:

> "Although the pharmacokinetic properties of the antipsychotics vary widely (for example, their half-lives range from 10 to 20 hours), the most important clinical generalisation is that all the antipsychotics currently available in the United States (with the exception of clozapine) can be given in one daily oral dose once the patient is in a stable condition and has adjusted to any adverse effects."

As Professor Harrison observed, this implies that once daily dosing is regarded as advantageous.

62. *Convenience*. Apart from the question of whether once a day leads to better patient compliance than twice a day, several of the materials referred to above recognise that once a day is more convenient, particularly for carers, than twice a day. As the Claimants pointed out, this was an advantage which pharmaceutical companies capitalised on when marketing antipsychotics in 1996. Thus an advertisement for Serdolect (sertindole) in the *British Journal of Psychiatry* in September 1996 listed seven advantages including "once daily dosing" and once for Zyrexa (olanzapine) in December 1996 referred to "a simple once-daily dosage". Both of these appeared after the priority date of the Patent, but there is no suggestion that the thinking changed during this period.

63. *The Patent*. The Patent says at [0004] (quoted in paragraph 72 below) that

sustained release formulations "provide the advantageous property of allowing the active medicament to be administered less frequently e.g. once a day".

64. *Conclusion*. The conclusion which I drawn from the evidence as a whole is that the perception of the skilled team would have been that once daily dosing was to be preferred to twice daily both because it might lead to better patient compliance, although there was no hard evidence that it did so, and because it was more convenient to patients and, particularly, carers. Furthermore, the skilled team would have been well aware that one of the advantages of sustained release formulations was that they enabled less frequent administration, and in particular once a day rather than twice a day.

High first pass metabolism

65. It is common ground that the formulator would be aware that the fact that a drug is subject to a high first pass metabolism presents a problem for developing a sustained release if the liver enzymes are saturated by a clinical dose. In principle, the effect of high first pass metabolism will be the same for both an immediate release formulation and a sustained release formulation, namely to reduce the bioavailability of the drug. In those circumstances bioavailability will be dose-dependent: doubling the dose will double the bioavailability. If the liver enzymes are saturated by a clinical dose of an immediate release formulation, however, then some of the drug will escape being metabolised in the liver before reaching the systemic circulation. In those circumstances bioavailability will not be dose-dependent. Sustained release of the same dose over a longer period of time will result in more of the drug being metabolised, leading to lower bioavailability than the immediate release formulation, and hence lesser efficacy.

66. There is a dispute, however, as to whether the formulator would expect the first pass metabolism of the drug he was working on to be saturated at clinical doses. Dr Rue was clear that he would not:

> "I think it was common general knowledge that most drugs do not saturate the first pass metabolic pathways in the liver within the clinical dose, and that is important. Clearly, most drugs will saturate the liver enzymes at some point. But in my opinion it was generally known that there were relatively few drugs that caused this problem."

67. Counsel for AstraZeneca submitted that this evidence was contradicted by passages from two textbooks. Dr Rue did not agree with this, however, and the answer I have just quoted was given when the second passage was put to him in cross-examination. I have no difficulty in accepting his evidence on this point. Thus the key part of the second passage (from Welling and Dobrinska, "Dosing Considerations and Bioavailability Assessment of Controlled Drug Delivery Systems" in *Controlled Drug Delivery* edited by Robinson and Lee (2^{nd} ed, 1987)) states at 258:

> "After oral dosing, on the other hand, drug reaches the liver via the portal vein at far greater concentrations than normally

> found in the systemic circulation. In fact, the levels may be high enough to exceed the capacity of the hepatic metabolising enzymes. Thus, the higher the oral dose the greater the possibility of saturating hepatic drug metabolising enzymes. Conversely the smaller the dose, or the slower the dose is released from the formulation, the smaller the possibility of saturating first pass metabolism. The potential for reduced drug availability due to first-pass metabolism is therefore greater with controlled or sustained release formulations than conventional designs."

In my judgment this is consistent with Dr Rue's evidence.

68. As for Dr Moreton, although he regarded a high first pass metabolism as more of a potential problem than did Dr Rue, he agreed that saturation was the key issue, and he did not go so far as to say that the formulator would expect the first pass metabolism to be saturated at clinical doses.

69. Both experts made it clear that the formulator would be alert to any information which was available concerning the extent to which the specific drug under consideration saturated the liver enzymes. Furthermore, it was Dr Rue's evidence that, if no information was available, routine testing would be carried out to ascertain whether the bioavailability was dose-dependent.

70. I conclude that the formulator would not approach the task of formulating a drug with a general expectation that the first pass metabolism would be saturated by a clinical dose. But if there was information available suggesting that the first pass metabolism was saturated by a clinical dose of an immediate release formation of the particular drug which the formulator was being asked to formulate, then he would regard developing a sustained release formulation of that drug as problematic.

pH modifiers

71. It is common ground the use of pH modifying excipients such as sodium citrate in sustained release formulations was an established practice in 1996. It is also common ground, however, that the only commonly known use of such pH modifiers was to increase the solubility of the drug. Although pH modifiers had also been used to reduce the solubility of the drug, Dr Rue accepted that that use was not common general knowledge. On the other hand, he maintained that the general principle of using a buffer to control pH whether in acidic conditions or neutral conditions, and thus obtain pH independent drug-release, was well-known. That evidence is supported by some of the textbooks and articles in evidence, and I therefore accept it.

The Patent

72. Having said at [0001] that the invention relates to a sustained release pharmaceutical composition comprising quetiapine or a pharmaceutically acceptable salt thereof, the specification states:

> "[0002] It is desirable in the treatment of a number of diseases, both therapeutically and prophylactically, to provide the active pharmaceutical ingredient in a sustained release form. Desirably the sustained release provides a generally uniform and constant rate of release over an extended period of time which achieves a stable and desired blood (plasma) level of the active ingredient without the need for frequent administration of the medicament.
>
> [0003] While there are numerous sustained release formulations known in the art which utilize gelling agents, such as hydroxypropyl methylcelluloses, it had been found to be difficult to formulate sustained release formulations of soluble medicaments and gelling agents, such as hydroxypropyl methylcellulose, for several reasons. First of all, active ingredients which are soluble in water tend to generate a sustained release product which is susceptible to a phenomenon known as dose dumping. That is, release of the active ingredient is delayed for a time but once release begins to occur the rate of release is very high. Moreover, fluctuations tend to occur in the plasma concentration of the active ingredient which increases the likelihood of toxicity. Further, some degree of diurnal variation in plasma concentrations of the active ingredient has also been observed. Finally, it has been found to be difficult to achieve the desired dissolution profiles or to control the rate of release of the soluble medicament.
>
> [0004] Accordingly a need exists for sustained release formulations of soluble medicaments, such as [quetiapine] or a pharmaceutically acceptable salt, which overcome, or at least alleviate, one or more of the above described difficulties and which further provide the advantageous property of allowing the active medicament to be administered less frequently e.g. once a day, while achieving blood (plasma) levels similar to those attained by administering smaller doses of the medicament more frequently, e.g. two or more times daily."

73. Thus the problems identified in the Patent as being the problems to which the invention is addressed are those identified in [0003]. These are various problems which are said to have been encountered in making sustained release formulations of "soluble medicaments" with gelling agents such as hydroxypropyl methylcellulose.

74. The specification goes on at [0007]-[0008] to say that quetiapine may be used as an antipsychotic agent, that it is of particular interest since there is a substantial reduction in the potential for EPS, and that its preparation and properties are described in three patents, including 228. It then says in [0009]:

> "According to the present invention there is provided a sustained release formulation comprising a gelling agent,

> preferably hydroxypropyl methylcellulose, and [quetiapine], or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients. …"

75. At [0013] the specification states that hydroxypropyl methylcellulose "is commercially available under several trademarks e.g. METHOCEL® E, F, J and K from Dow …"

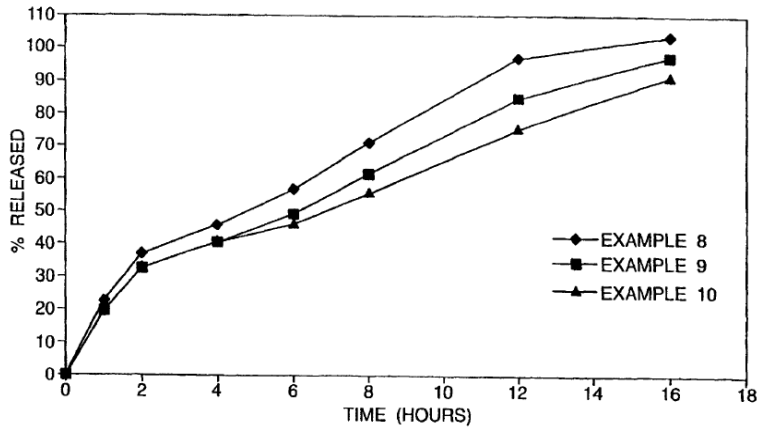
76. At [0017] the specification states that the formulation will, in general, include one or more excipients, including:

> "… pH modifiers which include suitable organic acids or alkali metal (e.g. lithium, sodium or potassium) salts thereof, such as benzoic acid, citric acid, tartaric acid, succinic acid, adipic acid and the like or the corresponding alkali metal salts thereof, preferably the alkali metal salts of such acids and in particular the sodium salt of citric acid (i.e. sodium citrate)…"

77. At [0042]-[0060] the specification describes 12 examples. Example 1 is a formulation consisting of 57.6% quetiapine, 15.0% Methocel E50LV Premium, 19.1% lactose, 6.3% microcrystalline cellulose and 2.0% magnesium stearate. Example 2 is a formulation consisting of 57.6% quetiapine, 15.0% Methocel E50LV Premium, 5.0% Methocel E4M Premium CR, 10.2% lactose, 10.2% microcrystalline cellulose and 2.0% magnesium stearate. Examples 8, 9 and 10 are formulations containing 43.2% quetiapine, 12.5% sodium citrate, varying proportions of lactose and microcrystalline cellulose, 2.0% magnesium stearate and the following hydroxypropyl methylcelluloses: 15.0% Methocel K100V Premium CR (example 8), 25.0% Methocel KL100V Premium CR (example 9) and 25.0% Methocel KL100V Premium CR plus 5.0% Methocel K4M Premium CR (example 10). Example 12 is a comparative example consisting of an immediate release formulation.

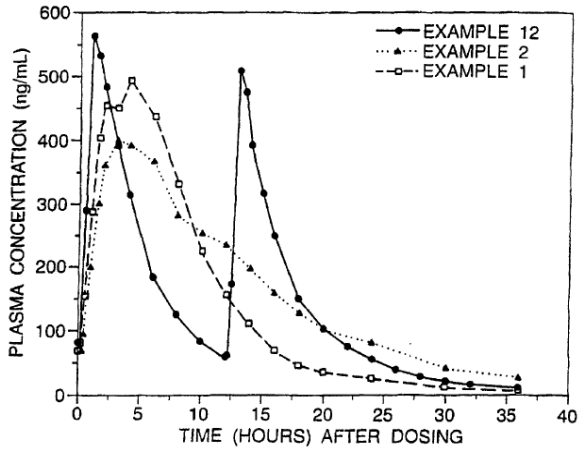
78. Figure 1 shows the release (dissolution) profiles of the sustained release formulations of examples 8, 9 and 10:

Fig.1.



79. Figure 2 shows the plasma concentration versus time profiles of quetiapine for the sustained release formulations of examples 1 and 2 compared to the immediate release formulation of example 12:

Fig.2.



80. The procedure by which the profiles shown in Figure 2 were obtained is described at [0038]. In summary, 16 patients were assigned to Group A and 16 to Group B. To begin with all patients were given the immediate release formulation of example 12. Thereafter Group A was treated according to a regime which included the administration of the sustained release formulations of example 2, while Group B was treated according to a regime which included the administration of the sustained release formulations of example 1. The following table shows the mean area under the curve (AUC) values for a 24 hour dosing interval and the mean maximum blood concentration (C_{max}) values which were found:

	Group A		Group B	
Example No	AUC_{0-24}	C_{max}	AUC_{0-24}	C_{max}
1	-	-	4886	565
2	5609	433	-	-
12	5347	703	4818	563

81. It can be seen that the values reported for the sustained release formulations are similar to those reported for the immediate release formulation. Thus there is no problem with the bioavailability of the sustained release formulation due to the first pass metabolism.

The claims

82. Claim 1 is as follows:

> "A sustained release formulation comprising a gelling agent and [quetiapine] or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients."

83. Claims 14 and 15 are as follows:

> "14. A formulation according to anyone of claims 1-13 wherein one of the one or more pharmaceutically acceptable excipients is a pH modifier.
>
> 15. A formulation according to claim 14 wherein the pH modifier is sodium citrate."

Gefvert

84. Gefvert is an abstract by Gefvert *et al* entitled "Time course for dopamine and serotonin receptor occupancy in the brain of schizophrenic patients following dosing with 150mg Seroquel™ tid" published in *European Neuropsychopharmacology*, volume 5, issue 3 in September 1995. It is sufficiently short to quote in full:

> "SEROQUEL™ (ICI 204,636) is an atypical dibenzothiazepine antipsychotic agent in Phase III development by Zeneca Pharrnaceuticals. Dosing of SEROQUEL in the Phase II/III programme was TID [*ter in die* i.e. three times daily] and QID [*quater in die* i.e. four times daily] based partly on preliminary phermacokinetic data for the parent compound (Tmax approximately 1.5 h, plasma elimination half-life approximately 3 h). Given the importance of compliance with medication in schizophrenics, a more convenient dose regimen would be beneficial.
>
> This was an open, non-randomised trial to determine whether receptor occupancy data is consistent with BID [*bis in die* i.e. twice daily] dosing. Schizophrenic patients (DSM IIIR) were dosed with 150 mg SEROQUEL three times a day for four weeks and examined using Positron Emission Tomography (PET) at 2, 8, 12 and 24 hours after their final dose of 150 mg SEROQUEL. Plasma ICI 204,636 concentrations were measured. PET scans used the radio-ligand [11C]-raclopride (RAC: a specific dopamine D2 antagonist) or [11C]-n-methylspiperone (NMS: a less selective dopamine D2/serotonin 5HT2 antagonist) PET data analysis followed the methods of Nordstrom et al (1992). Eleven subchronic or chronic schizophrenic subjects (age 20-43 years, mean 33.9) were entered and eight completed the PET assesssments. There were no serious adverse events. No extrapyramidal side effects (EPS) were reported during the dosing phase.

Time post 150 mg SEROQUEL (h)	2	8	12	26
Putamen D2 occupancy (n)	44% (4)	30% (4)	27% (4)	0% (3)
Frontal Cortex 5HT2 occupancy (n)	72% (4)	65% (4)	58% (4)	50% (4)
plasma ICI 204,636 ng/ml (n)	402.8 (8)	102.2 (8)	47.0 (8)	7.2 (8)

D2 ligand binding at 26 h was similar to values for neuroleptic-naïve patients published by Nordstrom et al (1993), hence Seroquel D2 receptor occupancy assumes zero occupancy at 26 h. 5HT2 ligand binding at 26 h was 50% of published values for the drug naïve state; SEROQUEL 5HT2 receptor occupancy calculation assumes the value from Nordstrom et al (1933). Mean plasma elimination half-life was approximately 5.3 hours (range 2.7-9.3 hours).

Once to twice daily dosing may therefore maintain sufficient 5HT2/D2 receptor occupancy for therapeutic benefit with low incidence of EPS in schizophrenic patients. A large efficacy study in 622 patients (SAFARI) comparing BID and TID dosing regimens is in progress."

85. Gefvert discloses the following points to the skilled team:

i) Seroquel (quetiapine) is in Phase III development. The dosing regimen in the Phase II/III programme was TID and QID.

ii) Given the importance of compliance with medication in schizophrenics, a more convenient dose regimen (i.e. more convenient than TID/QID) would be beneficial. The object of the study was to determine whether receptor occupancy is consistent with BID dosing.

iii) The patients used in Gefvert's study were given 150 mg quetiapine TID (i.e. total of 450 mg/day). Although not explicitly stated, it is common ground that the skilled team would appreciate that this was in an immediate release formulation. Receptor occupancies and plasma concentrations were measured 2, 8, 12 and 26 hours after the final dose.

iv) The D2 occupancy at 2-12 hours was 44-27% (i.e. within the range of therapeutic efficacy if quetiapine has a similar mode of action to clozapine), whereas at 26 hours it was 0% (a level at which no therapeutic efficacy would be expected).

v) The mean plasma half-life was approximately 5.3 hours (i.e. close to the middle of the range suitable for a sustained release formulation).

vi) No EPS were reported.

vii) Gefvert concludes that once to twice dosing may maintain sufficient receptor occupy for therapeutic efficacy with low EPS. A large efficacy study comparing BID and TID regimens is in progress.

What would the skilled team find out about quetiapine?

86. It is common ground that, if considering a new formulation of a drug, the formulator would as a matter of routine carry out a literature search to try to ascertain the relevant properties of the drug, in particular its (i) solubility profile and dissociation constant, (ii) partition coefficient, (iii) dose required, (iv) stability, (v) absorption, (vi) distribution, (vii) metabolism and (viii) elimination and half-life. To the extent that these were not available from the literature, then the formulator would have to carry out some routine tests.

87. Dr Moreton carried out such a literature search for the purposes of his first report. As he explained, he searched two electronic databases which were available in 1996 using the search term "quetiapine". As Dr Rue pointed out, Dr Moreton omitted to use the search terms "Seroquel" and "ICI 204, 636". The limitations of Dr Moreton's search can be seen from the fact that it would not have turned up Gefvert.

88. Dr Moreton set out in his report a convenient table of the information he ascertained in this way, and the sources from which he obtained it:

Property	**Information**	**Source**
Dose size	Doses of up to 750mg/day being trialled	Wetzel et al (1995)
Absorption	Well absorbed	Casey (1996)
Metabolism	Extensively metabolised (<5% excreted unchanged)	Casey (1996)
	Extensive first-pass metabolism (animal studies). The authors therefore presume that at least one metabolite must be active.	Wetzel et al (1995)
Bioavailability	Low bioavailability (5-15%) (animal studies)	Wetzel et al (1995)
Elimination half-life	6 hours (longer in some elderly patients)	Casey (1996)
	1-3 hours (animal studies)	Wetzel et al (1995)
	Approximately 3 hours (human studies)	Fabre et al (1995)
Solubility profile	Ranges from 18.5 mg/ml at pH1 to 2.3 mg/ml at pH7	AstraZeneca

89. The only part of this table which is controversial is the section on metabolism. The source referred to as "Casey (1996)" (Casey, "'Seroquel' (quetiapine): preclinical and clinical findings of a new atypical antispsychotic", *Exp. Opin. Invest. Drugs* (1996), 5(8), 939-957) was not published until after the priority date, so the formulator would not have found that.

90. Wetzel *et al*, "Seroquel (lCI 204 636), a putative "atypical" antipsychotic, in schizophrenia with positive symptomatology: results of an open clinical trial and changes of neuroendocrinological and EEG parameters", *Psychopharmacology*, (1995) 1191, 231-238 states:

> "Seroquel undergoes extensive first-pass metabolism via ring hydroxylation, sulfoxidation, *N*- and *O*-dealkylation and side

> chain oxidation (Seroquel Investigator's Brochure 1993). Presumably, at least the 7-hydroxylated is pharmacologically active and may contribute to seroquel's clinical effects."

It is common ground that it is unclear whether this is reporting results from animals or Phase I human studies. Even if the former is the case, as Dr Moreton assumed, Dr Rue accepted that the skilled team would proceed on the basis that there could be high first-pass metabolism in humans. He did not accept, however, that the skilled team would conclude from this that saturation was likely.

91. Dr Rue said in his second report that the skilled team "would conduct literature searches to confirm that [quetiapine's] pharmacokinetics are linear i.e. pre-saturation of the enzymes". In a footnote he stated that "pharmacokinetic data was published in an abstract by Wong *et al*, 'Multiple dose pharmacokinetics and dose proportionality study of 'Seroquel' (ICI 204,636) in male schizophrenic patients', 34th Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico (1995) [which I will refer to as "Wong I")] - see Exhibit PR-18". Counsel for AstraZeneca demonstrated in cross-examination of Dr Rue that the document which was exhibited as PR-18 was in fact a different document, namely a duplicate publication by the same authors at a different meeting after the priority date (which I will refer to as "Wong II"). Indeed, the description of exhibit PR-18 in the index to the relevant trial bundle did not correspond to Dr Rue's description of Wong I. As counsel for the Claimants demonstrated by producing a copy of Wong I during his cross-examination of Dr Moreton, however, apart from the reference to PR-18, Dr Rue's statement in his footnote was entirely accurate.

92. Counsel for AstraZeneca accepted in his closing submissions that Wong I had been made available to the public before the priority date, but submitted that the Claimants had not established that it would have been found by means of a literature search at the relevant date. In support of this submission, he relied in particular on the fact that this had not been put to Dr Moreton in cross-examination. I do not accept this submission. Counsel for AstraZeneca got Dr Rue to accept in cross-examination that *Wong II* could not have been accessed "by way of a literature search of the kind described by Dr Moreton" on or before 31 May 1996. Counsel did not actually challenge Dr Rue's evidence that *Wong I* would have been found by a literature search. Furthermore, his question to Dr Rue was in any event too limited, since as noted above Dr Moreton's search only used the term "quetiapine" and Dr Rue had by this stage already pointed out the omission of the other search terms. A search using the term "quetiapine" would not have turned up Wong I, whereas either of the other terms suggested by Dr Rue would have done. Yet further, as counsel for the Claimants pointed out, the accessibility of Wong I is corroborated by the fact that it is cited in the Casey (1996) article referred to and exhibited by Dr Moreton himself, which was published later in 1996. In these circumstances I do not consider that it was incumbent on counsel for the Claimants to put it to Dr Moreton that Wong I would have been found by means of a literature search at the relevant date: he was entitled to assume that that point was not in issue.

93. Turning to the content of Wong I, this reports a pharmacokinetic study of quetiapine which found that both C_{max} and AUC increased proportionally with

dose over the range 100 mg to 375 mg. Thus it supports Dr Rue's evidence that the skilled team would have discovered that the pharmacokinetics of quetiapine were linear. Accordingly, they would not have been concerned about saturation of the first pass metabolism.

Obviousness

The law

94. A patent will be invalid for lack of inventive step if the invention claimed in it was obvious to a person skilled in the art having regard to the state of the art at the priority date. The familiar structured approach to the assessment of allegations of obviousness first articulated by the Court of Appeal in *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd* [1985] RPC 59 was re-stated by Jacob LJ in *Pozzoli v BDMO SA* [2007] EWCA Civ 588, [2007] FSR 37 at [23] as follows:

> "(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) 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?"

95. What matters is whether or not the invention was technically obvious, not whether it was commercially obvious: see *Hallen Co v Brabantia (UK) Ltd* [1991] RPC 195 at 213. This does not necessarily mean that commercial considerations are irrelevant. The mindset of the skilled person may be conditioned by commercial considerations only to consider certain types of technical solutions, as in *Dyson Appliances Ltd v Hoover Ltd* [2001] EWCA Civ 1440, [2002] RPC 22.

96. It is sometimes relevant to consider whether the step in question was obvious to try. In *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] RPC 28 Lord Hoffmann explained the correct approach to this question at [42] as follows:

> "In the Court of Appeal, Jacob L.J. 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 L.J. in *Johns-Manville Corporation's Patent* [1967] R.P.C. 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] R.P.C. 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.'"

97. It is also sometimes relevant to consider whether the addressee would have a prejudice against taking a particular step which might otherwise appear obvious. As Jacob LJ explained in *Pozzoli v BDMO*, invention can lie in demonstrating that an established technical prejudice is unfounded, and so an apparent "lion in the path" is merely a paper tiger. In *Dyson Technology Ltd v Samsung Gwangju Electronics Co Ltd* [2009] EWHC 55 (Pat), [2009] FSR 15 at [153]-[157] I considered *Glaxo Group Ltd's Patent* [2004] EWHC 477 (Pat), [2004] RPC 43, *Pozzoli v BDMO* and *Conor v Angiotech* and concluded that it was not necessary for the patent to explain how or why, contrary to the prejudice, the invention worked or was practical, but only for the disclosure in the patent to make it plausible that the invention would work or be practical. I added:

> "… I do not believe that the patent must expressly address the prejudice, although a failure to mention any prejudice in the specification may be of evidential significance."

Neither side in the present case took issue with this analysis.

98. Counsel for the Claimants relied strongly upon the subsequent decision of the Court of Appeal in *Actavis v Novartis* (cited above). As previously mentioned, this concerned a patent for a sustained release formulation of fluvastatin. Counsel relied both on Jacob LJ's consideration of the law of obviousness at [17]-[50] and, particularly, on his application of the law to the facts of the case at [51]-[66]. The latter passage is too long to quote in full, but since counsel submitted that there was a precise parallel between the present case and that one, I must cite enough to show Jacob LJ's reasoning:

> "51. … Before going to the Judge's conclusions, it is worth noting that Actavis put its case higher than it needed to. It advanced a case that a sustained release form of fluvastatin would be expected not only to be a more convenient formulation for patient compliance but would be likely to have significant

> medical advantages, namely improved therapeutic effect and fewer side effects. Hence, the argument ran, there was a strong motive to create a sustained release form and a strong expectation that all three types of benefit would be obtained, the two medical and the convenience.
>
> 52. On the facts the Judge rejected the 'medical advantage' motivation as having a significant enough expectation of success. But he did accept the 'more convenient' advantage point. …
>
> …
>
> 54. So the whole basis for the invention as set out in the Patent was destroyed. The Patent says the skilled man would think the solubility of fluvastatin was so high that the skilled man would think a sustained release form could not be made. But that was not so. The skilled man would not think that, based on his common general knowledge alone. The problem presented in the Patent was illusory (Lloyd LJ's happy choice of word) – it was in reality a non-problem because fluvastatin is not so highly soluble that the skilled person would expect it to be impossible or difficult to make a sustained release form.
>
> …
>
> 56. Mr Meade had to accept that the basis of the invention as presented by the patentee would not in reality have been seen as a problem by the skilled person. So he pointed to the PSA, submitting that this clearly allowed for a reformulation of the problem. It would be good enough to support the Patent if there was another problem in the way. That problem, he suggested was this: that the skilled person would not have a sufficient expectation of success to make it worthwhile trying to make a sustained release formulation. This case should be considered on an 'obvious to try' basis. And because of an insufficient expectation of success Actavis should fail.
>
> …
>
> 61. I start with Mr Wyand's challenge. He submitted that the Judge had made an error in assessing what was meant by 'success' in terms of the Patent. It was not improved clinical efficacy or the same efficacy with fewer side effects. It was simply a sustained release formulation which one would expect to work. Moreover if one wanted a motive, there was one – improved patient compliance. Whether it was worth actually developing such a formulation (there would be costs of testing and compliance with regulatory requirements) was irrelevant. As the Patent said at [15] there was a need for a slow release formulation which it was possible to prepare.

> 62. I accept that submission. Once the obstacle put forward in the Patent against being able to make a sustained formulation was shown to be illusory, then a sustained release formulation is obvious. You might get better efficacy or fewer side effects, but you would certainly get better compliance. In *Pozzoli* terms the only difference between the prior art and the claim is the idea of making a sustained release formulation. For that there was a technical motivation and no difficulty, real or apparent.
>
> 63. The [problem and solution approach] gives the same answer. What is the objective problem? Why that which the patentee himself stated – to produce a sustained release form of fluvastatin. Was the solution obvious? Yes, any of the standard methods for such formulations would clearly work: there is no reason why they would not.
>
> 64. There is no need and it would be wrong to re-formulate the problem as suggested by Mr Meade. This is not a case where some prior art unknown to the patentee has turned up. Nor is it right to reformulate the problem as one of looking for better medical effects when that was not the problem as seen by the patentee or to reformulate the solution as having found such effects when the patentee has not promised any."

The skilled team and the common general knowledge

99. I have identified these above.

The inventive concept of claim 1

100. There is no dispute as to the inventive concept of claim 1. It is a sustained release formulation of quetiapine comprising a gelling agent. Although claim 1 is not limited to HPMC, HPMC may be taken as the paradigm gelling agent.

The difference between Gefvert and claim 1

101. It is common ground that the difference between Gefvert and claim 1 is that Gefvert does not disclose a sustained release formulation of any kind.

Would it have been obvious?

102. As mentioned above, counsel for the Claimants contended that there was a precise parallel between the present case and *Actavis v Novartis*. He submitted in both his opening and closing submissions that the problems identified by the Patent at [0004] were illusory: it was well within the competence of an ordinarily skilled formulator in 1996 successfully to formulate a sustained release formulation of a soluble drug using a gelling agent, and in particular HPMC. In particular, although it was known that dose dumping could be a problem if the formulation work was not done properly, this was not in practice a difficulty, and certainly not with quetiapine. Counsel for AstraZeneca did not

challenge this submission. In any event, on the evidence of Dr Rue and Dr Moreton, it is clearly well founded.

103. In these circumstances, counsel for the Claimants submitted that the reasoning of Jacob LJ in *Actavis v Novartis* was equally applicable to the present case. That reasoning, however, was predicated upon the trial judge's findings of fact. Accordingly, I must turn to the facts of the present case.

104. The Claimants' case is straightforward. They contend that: (i) the skilled team would conclude from Gefvert that once daily dosing of 450mg of an immediate release formulation of quetiapine was unlikely to be efficacious; (ii) the skilled team would consider that a sustained release formation was likely to be efficacious and would offer advantages in terms of compliance and convenience; and (iii) the skilled team would expect to be able successfully to formulate a sustained release formulation of quetiapine using HPMC, which would be a routine choice of matrix, and would in fact achieve success without difficulty.

105. AstraZeneca contends that: (i) the skilled team would not consider developing a sustained release formulation of quetiapine unless there was some clinical need or rationale for one; (ii) Gefvert would not provide any such need or rationale, since the skilled team would conclude that, if once daily dosing was required, it could be achieved with a larger dose of immediate release formulation; and (iii) even if the skilled team was lead by Gefvert to consider developing a sustained release formulation of quetiapine, it would be deterred from doing so by quetiapine's high first pass metabolism, or at least would not have a reasonable expectation of success.

106. I accept AstraZeneca's first point, which is not really disputed. Turning to the second point, Professor Harrison's evidence was that Gefvert suggested that twice daily dosing of an immediate release formulation looked promising, but it was unlikely that once a day would be. The D2 occupancy data indicated that D2 dropped below 20% sometime between 12 and 26 hours, suggesting that there would be a 9-10 hour period during the day when occupancy was too low for therapeutic effect. The same conclusion was suggested by the plasma half-life. This evidence is supported by the fact reported by Gefvert that a large trial was underway to compare the efficacy of twice-a-day with three-times-a-day, but not once-a-day.

107. Professor Montgomery agreed that Gefvert indicated that a single 450 mg dose of an immediate release formulation daily would not be efficacious. His evidence was that his suggestion would have been to try a much higher dose, from twice to six times, and see what the occupancy was. As he accepted, however, that would carry an increased risk of side effects. He agreed that a sustained release formulation was one way to go, but considered that it would be logical first to try a higher dose in an immediate release formulation.

108. My conclusion from this evidence is that the skilled team would conclude from Gefvert that a single 450 mg dose of an immediate release formulation daily would not be efficacious. The skilled team would regard once daily administration as desirable for the reasons given in paragraph 64 above.

(Incidentally, there is no evidence before me that sustained release quetiapine in fact has any other advantage.) To achieve once daily administration, a sustained release formulation and a higher dose of an immediate release formulation would both be obvious possibilities.

109. Turning to AstraZeneca's third point, for the reasons given above, the skilled team would neither expect from its common general knowledge nor conclude from the formulator's literature search that quetiapine was likely to saturate the first pass metabolism. It would therefore not be deterred from developing a sustained release formulation. Nor would its expectation of success be adversely affected. I therefore agree with the Claimants that the skilled team would expect to be able successfully to formulate a sustained release formulation of quetiapine using HPMC, which would be a routine choice of matrix. There is no dispute that it would in fact achieve success without difficulty.

Claim 15

110. Counsel for AstraZeneca argued that claim 15 was independently valid because it was not obvious to use a pH modifier, and in particular sodium citrate, to decrease the solubility of a drug in a soluble matrix since that was not common general knowledge. I do not accept this argument. Claim 15 covers the use of sodium citrate as a pH modifier for any purpose. It is not limited to its use to decrease solubility. Addition of a pH modifier such as sodium citrate to increase solubility was common general knowledge and thus obvious. In any event, as I have already held, the formulator would know that the general principle is the same whether the effect of the pH modifier is to increase or reduce solubility in particular circumstances. Thus, even if it is assumed that the problem to which claim 15 is addressed is that quetiapine has high solubility in the low pH conditions of the stomach and that the solution is to add a pH modifier to reduce that solubility (despite there being no mention of this in the Patent), the solution was an obvious one.

<u>The Dutch judgment</u>

111. On 7 March 2012 the District Court of the Hague (Judges Kalden, Blok and de Vries) gave judgment on a parallel claim by Sandoz BV and three other parties ("Sandoz") to revoke the Dutch counterpart of the Patent (Case 397921/HA ZA 11-1977). In a careful and detailed judgment of 26 pages (in translation), the Dutch court rejected Sandoz's argument that the Patent was obvious over Gefvert. It summarised its reasons at [5.47] as follows:

> "The aforementioned findings lead to the following conclusion. On the filing date, quetiapine had not yet been proven to be sufficiently effective without having serious side effects in large-scale and extended use. The average person skilled in the art had at most a very limited motivation to choose that particular substance to create a sustained release formulation. Therapy compliance does not materially improve by substituting a twice daily dose with a once daily dose. The side effects of quetiapine known on the filing date were not serious,

> but were limited to sleepiness and drowsiness, side effects that occur in all anti-psychotics. The optimum dose of an immediate release formulation was not yet known, just as the concentration effect for quetiapine was not known, so that the average person skilled in the art was in the dark about the dose needed in a sustained release formulation. On the other hand, in the District Court's opinion, the average person skilled in the art did not have high expectations about his chances of successfully developing a sufficiently effective sustained release formulation of quetiapine. The pH-dependent solubility of quetiapine and the possibly variable kinetics, in view of the varying half-life values reported, result in the average person skilled in the art taking problems in formulating into account. In addition, the average person skilled in the art is unsure whether a sustained release formulation will have sufficient therapeutic efficacy because such a formulation lowers the peak plasma concentration when compared to the peak reached with an immediate release formulation. Due to a combination of a high first-pass metabolism, high serum protein binding and a low D_2 receptor level, the average person skilled in the art will realise that there is a risk that the reduced bio-availability results in insufficient therapeutic efficacy of the formulation, in particular for the treatment of an attack."

112. It is clearly a matter of regret that different European courts considering the validity of the same patent should reach opposite conclusions. Both for this reason, and because of the respect that a judgment of the District Court of the Hague merits in any event, I have carefully considered the Dutch court's reasoning. It does not persuade me that the conclusion I have reached is incorrect, however. My main reasons are as follows.

113. First, the evidence before the respective courts was different. In the Netherlands the witnesses were different to those before me (save that Dr Rue filed reply evidence in place of Sandoz's first formulator Dr Rawlins). Furthermore, the hearing before the Dutch court lasted one day, and there was no cross-examination. I had the advantage of hearing all four experts cross-examined in the course of a hearing lasting about four days (though spread over parts of five).

114. Secondly, although a lot of the same articles and textbooks appear to have been placed before the Dutch court as before me, there are certain differences. By way of example, the Dutch court does not refer to Wong I. Either this was not placed before the Dutch court or the Dutch court did not appreciate its significance.

115. Thirdly, the Dutch court proceeded on the basis that the Patent was not entitled to priority (see [5.1]). As a result, it relied upon a number of articles which were published after the priority date. In particular, it referred no less than seven times to Casey (1996). By contrast there was no challenge to priority before me, and it was common ground that Casey (1996) was post-published.

116. Fourthly, the arguments before me were different to those before the Dutch court. In particular, in its closing submissions before me the only "lion in the path" relied upon by AstraZeneca was high first pass metabolism, whereas before the Dutch court AstraZeneca also advanced a number of others. Some of these were accepted by the Dutch court, notably high serum protein binding (see [5.38]-[5.40]) and pH-dependent solubility (see [5.41]-[5.43]).

117. Fifthly, in the light of the evidence and arguments before me, I am unable to agree with the Dutch court's conclusions with regard to either motivation or expectation of success. It would lengthen this judgment unduly to go through all of the Dutch court's reasons explaining why I differ, but I will give two examples. With regard to motivation, the Dutch court found at [5.9] that the fact that the immediate release formulation of quetiapine had not yet proved itself in clinical practice meant that the skilled person would be reluctant to develop an alternative formulation and would only proceed if he was strongly motivated to start developing a sustained release formulation or had a high expectation of success. No such argument was advanced by AstraZeneca before me, and the evidence before me does not support that conclusion.

118. With regard to expectation of success, the Dutch court concluded at [5.31]-[5.37] that a high first pass metabolism was a counter-indication for the development of a sustained release formulation. In this connection, it found at [5.35] that "Linear pharmacokinetics indicate that saturation point of the enzymatic breakdown process has been reached". On the evidence before me, that is incorrect: linear pharmacokinetics indicates the exact opposite.

119. Finally, the Dutch court appears to have attached no weight to the facts that the problems described in the Patent are illusory and that the "lions in the path" relied upon by AstraZeneca are not mentioned in the Patent: see [5.50]. In my view these points are of significance, albeit not conclusive.

Conclusion

120. I conclude that the Patent is invalid.