Neutral Citation Number: [2008] EWHC 2345 (Pat)

Case No: HC07C00963

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 13/10/2008

Before :

THE HON MR JUSTICE FLOYD

- -

Between :

DR REDDY'S LABORATORIES (UK) LIMITED	**Claimant**
- and -	
ELI LILLY AND COMPANY LIMITED	**Defendant**

- -
- -

Mr Henry Carr QC, Mr Andrew Lykiardopoulos and Mr James Whyte (instructed by **Powell Gilbert LLP**) for the **Claimant**
Mr Simon Thorley QC, Mr Andrew Waugh QC, Mr Colin Birss QC and Mr Miles Copeland (instructed by **Howrey LLP**) for the Defendant

Hearing dates: 8, 10, 11, 14-18, 22-24 July 2008

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Judgment

Mr Justice Floyd :

1. Dr Reddy's Laboratories (UK) Limited ("DRL") brings this action to seek revocation of European Patent (UK) No 0 454 436 ("the Patent") which belongs to the Defendant Eli Lilly and Company Limited ("Lilly").

2. The Patent has a priority date of 25th April 1990. It concerns Lilly's drug olanzapine which is a widely prescribed anti-psychotic agent used for the treatment of schizophrenia. Claim 3 is a claim to olanzapine alone. The case raises issues as to the validity of patents for individual compounds selected from a prior class.

Witnesses

3. DRL called three expert witnesses: Professor John Geddes, Professor Peter Jenner and Professor Stanley Roberts.

4. Professor Geddes is a psychiatrist. He is currently a Senior Clinical Research Fellow and Professor of Epidemiological Psychiatry at the University of Oxford. He is also an Honorary Consultant Psychiatrist for the Oxfordshire & Buckinghamshire Mental Health Foundation Trust. In such positions he spends approximately 60% of his time on research and 40% of his time in clinical practice as a consultant psychiatrist. He has been involved in the treatment of patients with a wide range of psychotic illnesses and has conducted research into the efficacy and effectiveness of drug treatments.

5. Lilly said that Professor Geddes was not really qualified to give evidence about the detail of toxicological pre-clinical studies. Professor Geddes accepted that his expert knowledge was based on reviewing, rather than conducting such trials which was not really his area. To the extent that it matters, I have kept this in mind. Lilly had a more general criticism of Professor Geddes, based on his tendency to give long answers to questions. I do not think there is anything in this. Professor Geddes was indeed a very fluent witness, and displayed a commendable anxiety to ensure that his evidence was explained and understood. I do not think that he can be accused of becoming an advocate for DRL's case as Lilly suggested.

6. Professor Peter Jenner is a pharmacologist and currently Emeritus Professor of Pharmacology in the School of Health & Biomedical Sciences, King's College London. He is also Director of the Neurodegenerative Disease Research Group at King's College, Director of the National Parkinson Foundation Centre of Excellence and Director and Chief Scientific Officer of Proximagen Neurosciences plc (a drug discovery and development company) and a Director of Primagen Limited (a pharmaceutical consultancy company). Professor Jenner's particular expertise lies in the assessment of movement disorders amongst (inter alia) those suffering from psychotic illness or as a result of the treatment thereof.

7. Lilly submitted that Professor Jenner's expertise was somewhat circumscribed, making it difficult for him to express views on some aspects of the case. Where this was the case Professor Jenner very fairly acknowledged that this was so. I have taken this into account in reaching my conclusions.

8. Professor Stanley Roberts is currently an Honorary Visiting Professor in the School of Chemistry at Manchester University. He is also a Director of Oxyrane Limited, a

company involved in the development of biopharmaceuticals, and a Scientific Advisor to York Pharma Limited, a speciality pharmaceutical company. From 1980 to 1986, he was Head of Chemical Research at Glaxo Group Research in Greenford where his research focused on the development of new pharmaceuticals as head of a team of around 80 employees. Since leaving Glaxo he has been Professor of Organic Chemistry at Exeter, Liverpool and now Manchester Universities.

9. Lilly suggested that Professor Roberts was poorly placed to give expert evidence on the medicinal chemistry aspects of the case as his primary expertise was that of a synthetic chemist, and even then, not in the field of anti-psychotic agents. I think it is fair to say that Professor Roberts comes to this case as someone with general experience of working with drug development teams in the pharmaceutical industry, and therefore with first hand knowledge of how such teams operate. He was not properly described as a medicinal chemist when he arrived at Glaxo; but by the time he left he had gone up the steep learning curve to become one. I am satisfied that he was well able to assist me on the approach of a medicinal chemist, albeit without any specific experience of research into anti-psychotics.

10. Lilly also called three expert witnesses: Professor David Nichols, Professor Guy Goodwin and Dr Ronald James.

11. Professor David Nichols is a medicinal chemist whose research interest is studying the structure activity relationships of central nervous system drugs and drug design. The particular focus of his research has been hallucinogenic and anti-dopaminergic drugs, the latter being of particular relevance here. He holds the Robert and Charlotte Anderson Distinguished Chair in Pharmacology at Purdue University, Indiana, USA and has been the Professor of Medicinal Chemistry at Purdue since 1984 and Professor of Pharmacology since 1985. From 1990 to 1996 he taught graduate chemists a course on medicinal chemistry and structure activity relationships of drugs.

12. DRL criticised the evidence of Professor Nichols in a number of ways. First DRL drew attention to Professor Nichols' lack of experience in industry. It is correct that he had not been employed in industry, but he had experience of working with industry. I have taken this lack of hands-on experience into account, to the extent that it matters. Secondly DRL pointed to the fact that this was not the first time Professor Nichols had assisted Lilly on its olanzapine patents: he had given evidence, either orally or in writing, on a number of previous occasions. DRL suggested that this had led to a lack of objectivity.

13. Two principal matters were relied on by DRL in support of this criticism: Professor Nichols' evidence about the general knowledge on the need for electron-withdrawing substituents in effective atypical anti-psychotics, and some differences between his evidence in the United States and here. As to the first point, that is a matter to which I will have to return in its proper context. I think Professor Nichols may have stated his proposition too broadly. But, that said, I do not think that this affected the weight I should attach to other parts of his evidence As to the second point, it is true that there was, on the face of it, a stark difference between the evidence given by Professor Nichols in relation to the 1989 Chakrabarti paper in the United States and these proceedings. But this difference was explained by the fact that he had been asked different questions in the two jurisdictions. Here, rather bizarrely, his instructions had restricted him to considering progressing the identified compounds only. It is perhaps

unfortunate that he did not make this aspect of his instructions clear, particularly as his instructions more or less precluded a conclusion of obviousness. But once it is accepted, as it must be, that he was answering different questions, the force of the criticism falls away. Overall, I found Professor Nichols a helpful witness.

14. Professor Goodwin has since 1996 been W.A. Handley Professor of Psychiatry at Oxford University, a role that incorporates his clinical practice at the Warneford Hospital in Oxford. Earlier he held positions as Honorary Consultant Psychiatrist, Honorary Senior Lecturer and Professor of Psychiatry at the University of Edinburgh. I found him to be a first rate expert witness, giving his evidence entirely fairly.

15. Dr James is an experienced animal toxicologist, having worked for Huntingdon Life Sciences and, in an interval from 1980-1984, the Wellcome Foundation.

16. DRL criticises Dr James in three respects. Firstly DRL says that Dr James was answering rather different questions from those that arise in the action, namely whether Lilly's commercial decisions were reasonable rather than whether evidence existed for the claims made in the patent as to the advantages of olanzapine. DRL are correct as to the approach that Dr James was taking, but I must evaluate the effect of his having taken that approach in its proper context: it is not a criticism of him as a witness. Secondly DRL criticise Dr James for having included a table in his second report which included a treatment of the data which he was not inclined to support in his oral evidence, except on the basis that it was a kind of tit-for-tat response to a sentence in Professor Geddes' report. This did not, in my judgment, reflect well on Dr James, who should never have embarked on this potentially misleading exercise. His justification for doing so does not hold water. Finally DRL says that Dr James admitted to severe reservations in respect of an MPI study which he had relied on (without making those reservations clear) in his reports. I think there is force in that criticism as well.

17. I concluded that I should exercise caution before relying too heavily on Dr James' evidence.

18. Lilly also called two factual witnesses whom I mention here and who both gave their evidence fairly: Dr Pullar, who was involved in the research leading to the synthesis of olanzapine, and Ms Carlisle who gave evidence about olanzapine's sales figures.

Background

19. Schizophrenia is a debilitating psychiatric disorder. Its symptoms include delusions and hallucination, withdrawal, lack of motivation and disorganisation of mental function and deficits in memory, attention and executive function. It is treated with antipsychotic agents.

20. **Chlorpromazine** was the first effective antipsychotic agent. Its antipsychotic effect was discovered in 1953. Later experiments by Carlsson & Lindqvist measured metabolism of dopamine in mouse brain tissue and showed that chlorpromazine led to a significant increase in turnover of dopamine in the brain. This led to the theory that chlorpromazine blocked the actions of dopamine as a brain neuro-transmitter. The theory is known as the dopamine hypothesis of schizophrenia.

21. Chlorpromazine has the chemical structure set out below:

Chlorpromazine

Chlorpromazine is a phenothiazine, so called because it has two phenyl rings (on the left and right) in the structure around a thiazene central ring.

22. Whilst, by 1990, the dopamine hypothesis was the main scientific theory underlying the mechanism of action of chlorpromazine and other antipsychotics, it was also known that a number of neurotransmitters interacted with dopamine and so contributed to a variety of its CNS functions.

23. A more or less contemporaneous SCRIP publication entitled 'Current Trends in Antipsychotic Research' (1990) ("the SCRIP report") describes the other neurotransmitters that were implicated at the time. The introduction to Chapter 2 states that:

> "The pathological changes responsible for the symptoms of schizophrenia are essentially unknown. Nevertheless, hypotheses on the roles of particular neurotransmitters abound and it could be stated that the number of such theories grows proportionally to the number of neurotransmitters discovered."

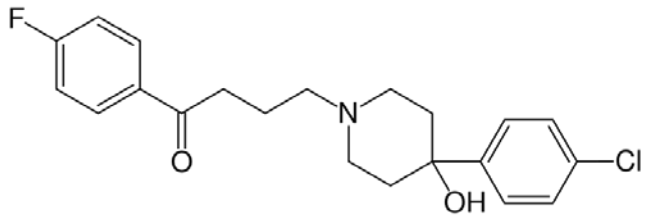
The chapter concludes by quoting a 1987 paper:

> "Schizophrenia is most likely a multi-neurotransmitter-system disease, caused by a factor or factors that could be acting on any of these systems."

24. The discovery of chlorpromazine's antipsychotic properties led companies to synthesise other phenothiazine derivatives with similar properties and to the development of other agents on new chemical backbones: thioxanthenes and butyrophenones. All these drugs were essentially designed to be like chlorpromazine in their pharmacological activity profile. By 1990 the drugs of this type that were available were phenothiazines (such as a thioridazine) thioxanthenes (such as flupenthixol) and butyrophenones (such as haloperidol).

Perphenazine (a phenothiazine)

Flupenthixol (a thioxanthene)



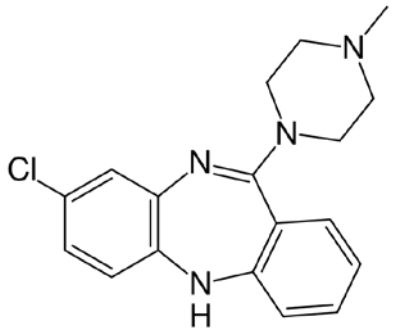
Haloperidol (a butyrophenone)

25. These various compounds are (at least now) grouped together as the typical, classical, or first generation antipsychotics (FGAs). Whilst they undoubtedly demonstrated valuable therapeutic efficacy, the FGAs shared a number of unpleasant side effects, most notably motor side effects referred to collectively as Extra Pyramidal Symptoms (EPS)**.** EPS included Parkinsonism, akathisia (a type of motor restlessness), acute dystonia (which can take the form of arching of the back, standing in strange positions or staring with the eyes turned up), tardive dyskinesia (which consists of involuntary movements of the face, head, limbs and even body) and tardive dystonias (which are disabling, chronic distortions of posture and are often untreatable).

26. The term “tardive” means that the side effect manifests itself only some time after exposure to the drug and, once established, tardive effects can continue even after discontinuation of treatment.

27. Classical antipsychotics also caused an elevation of the hormone **prolactin** in both men and women.

28. A breakthrough in antipsychotic drug therapy came with **clozapine:**



Clozapine

29. The advantage of clozapine was that it proved to be just as effective against the positive symptoms of schizophrenia as the earlier drugs, but did not produce their range of EPS or prolactin elevation. Hence clozapine was designated the first of the "atypical" antipsychotic drugs.

30. Clozapine was discovered in 1959. Unfortunately, following its clinical introduction in the early 1970s, clozapine was implicated in the death of a number of patients who developed a fatal suppression of white blood cells (agranulocytosis) after taking the drug. It was accordingly withdrawn. The drug was eventually re-licensed in the UK (in 1989) but only under the strict condition that patients were required to undergo weekly blood tests. This enforced regime made clozapine an expensive (and inconvenient) drug to prescribe.

31. The need in 1990 was thus for a safe and effective antipsychotic which shared clozapine's lack of EPS but which did not share its agranulocytotoxicity.

32. In 1990 it was not known what precisely gave clozapine its property of avoiding EPS. As the SCRIP report stated in 1991:

> 'In addition to the antidopaminergic effects, clozapine has a multiplicity of receptor interactions including muscarinic, α-adrenergic, serotonergic, and histaminergic receptors. It is at present unclear whether any specific combination of these contributes to its unique properties.' (Page 39, first paragraph).

33. In addition there was no explanation for the agranulocytosis observed with clozapine in clinical use.

34. In subsequent research, when a new chemical entity was synthesised with a view to discovering a new antipsychotic agent, it was tested for its neuroleptic activity. The term "neuroleptic" describes the pharmacological activity of compounds characterised by their ability to induce a particular profile of behaviour by blocking dopaminergic receptors. Mechanisms employed to assess neuroleptic activity included different ligand binding assays (dopaminergic, serotonergic, histaminergic, muscarinic) to establish a range of receptor affinities, and behavioural studies in animals e.g. a conditioned avoidance response, or "CAR" test" and a catalepsy test or "CAT" test. The idea of the latter tests was to see whether a given dose of the test substance could block the conditioned response (e.g. avoiding a shock which the rat was conditioned

to know followed a buzzer) without producing catalepsy (i.e. a total blockade). I shall have to return to the CAR and CAT tests in connection with one of the citations.

35. The view expressed in the SCRIP report as of 1990 (page 62) was that:

> "the chances for a major breakthrough in the field of drug treatment of schizophrenia to occur in the near future are rather slim. Progress is impeded by our profound ignorance of the real cause(s) and pathogenesis of schizophrenia".

36. There was no new registration for an atypical antipsychotic like clozapine, from clozapine itself in 1960 until the introduction of risperidone and olanzapine in the 1990s.

37. **Olanzapine** was launched under the name ZYPREXA in 1996. It has the structure

38. Points to note about the structure of olanzapine are (a) the absence of any substituents on the phenyl ring (on the left as depicted) and (b) the methyl substituted thieno-group (on the right).

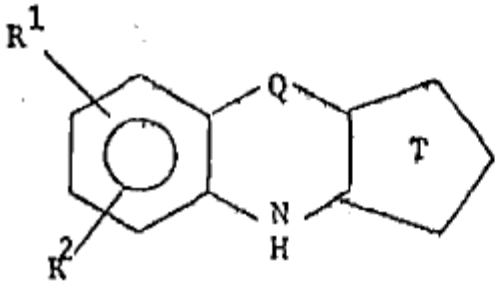
Lilly's research leading to olanzapine

39. The facts concerning Lilly's work towards olanzapine are not, save in one respect, in dispute. I have summarised the history in Appendix 1 to this judgment. I will return to the significance of this history when considering the question of inventive step.

40. It is convenient to deal now (in chronological order) with the Lilly prior art, that is to say the Lilly documents relied upon by DRL in their lack of novelty and/or obviousness attacks on the Patent.

The 235 Provisional

41. On 26th November 1974 Lilly filed a provisional application for a patent claiming a wide class of thieno-benzodiazepines "having useful central nervous system activity". The provisional specification was published together with the complete specification on 22nd November 1978. The class was defined first by reference to a general formula:



(I)

42. The values attributed to each of the variables R^1, R^2, Q and T were wide. Professor Nichols calculated that the general formula was wide enough to encompass 10^{19} compounds, 10 billion billion. More significantly, the draftsman of the 235 Provisional also indicated that there were preferred values for the substituents, which he lists on pages 7-8. This preferred group of compounds amounts to some 86,000 compounds. The specification also lists some 100 compounds by name, but without giving details of physical properties, indicating that they have not been made. The provisional specification contains 15 synthetic examples for a selection of compounds. Olanzapine is not listed in the 100 compounds or the subject of any examples.

43. The necessary values of the substituents for olanzapine are, however, amongst those specifically mentioned as possibilities for each of the variables in the preferred group. Thus R^1 and R^2 are both explicitly permitted to be hydrogen, Q can be arranged so as to create a diazo- central ring with a methyl-piperazine substituents, and T arranged to be a thieno- group with a methyl substituents.

44. The provisional specification claims in respect of all the compounds of formula (I) as follows:

> "Specifically they are potent centrally acting compounds with neuroleptic, sedative or relaxant effects. These properties, coupled with their high therapeutic index, render them useful in the treatment of mild anxiety states and certain kinds of psychoses."

45. Beyond the statement as to "high therapeutic index", which would convey qualitatively low side effects, no statements are made as to specific side effects and there is little or no biological information. In addition to olanzapine, the preferred class includes flumezapine and ethyl flumezapine. It also includes ethyl olanzapine.

The 235 Patent

46. The complete specification of 235 is not cited as prior art, but Lilly relies on it as it argues that the skilled reader would read both the provisional and complete specifications together, because they were published together. The complete specification was published in November 1978. I have assumed in DRL's favour that such an exercise is not permissible for an attack based on lack of novelty. The complete specification is not (and could not be) referred to in the provisional. However, when considering obviousness, which includes a consideration of what the skilled person would do when confronted with a document, I think it is legitimate to

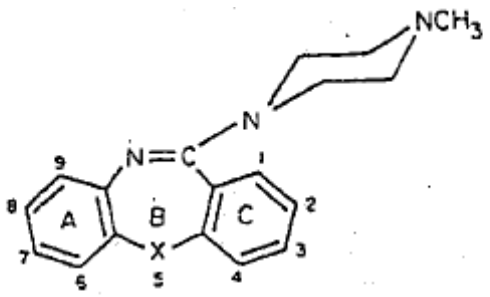
take a more realistic approach and assume that the skilled reader would read the complete specification as well.

47. For present purposes it is enough to note that R^1 and R^2 are now defined in the preferred class in the complete specification in such a way as to exclude the possibility that they are both hydrogen, as would be the case for olanzapine. Moreover the document has identified flumezapine as a particularly active compound.

Chakrabarti 1980

48. Dr Chakrabarti was leader of the team at Lilly with the responsibility for developing novel anti-psychotic drugs.

49. In 1980, with co-authors from Lilly, Dr Chakrabarti published a paper in the Journal of Medicinal Chemistry entitled "4-piperazinyl-10-H-thieno[2,3-b][1,5]benzodiazepines as Potential Neuroleptics". This was Part 3, and not the final part, of a series of papers. The article was impressive in that it reported the synthesis of some 59 compounds. The article notes, early on, the fact that clozapine differs from other dibenzoepines in having a reduced incidence of EPS. The authors produce a figure and chart like this:



	X	substituent
loxapine	O	2-Cl
clothiapine	S	2-Cl
HF-2046	NH	2-Cl
clozapine	NH	8-Cl

50. The authors drew attention to the fact that the atypical clozapine differed chemically from typical neuroleptics in having a chlorine substitution in position 8 in ring A, as opposed to position 2 in ring C. This effect had also been reported in the case of another classical neuroleptic, octoclothepin. The authors discuss the reasons for this change in activity in the following way:

> "There is no definitive explanation as to how the transposition of this halogen substitution can result in a profound change in activity. Molecular topography of clozapine and HF-2046, as determined by X-ray crystallography, does not reveal any significant difference. Electron transfer reactions have been often implicated in reversible attachment of biologically active molecules at a receptor site. Such a shift in nuclear substitution, as above, can contribute to the electronic imbalance

between the two benzene rings of the asymmetrical tricyclic system."

51. The authors surmise that, if an electron withdrawing group such as chlorine, can shift the electronic balance of the molecule to advantage, the same effect might be achievable by replacing ring C (the right hand ring as shown above) with a suitable heterocyclic ring i.e. a ring in which carbon is replaced by another atom, such as nitrogen or sulphur. Such a ring would be electron-rich, and thus create or contribute to the electron imbalance in a different way. In particular, the authors propose replacing benzene ring C with a thieno- ring, a five-membered ring with a sulphur hetero-atom:

52. In order to test this theory, a series of individual compounds is recorded as having been synthesised. The compounds selected use a range of values of R_1, R_2 and R. Compound 6 is ethyl olanzapine: in other words a compound identical to olanzapine but with a ethyl rather than a methyl substituent on the thieno- ring. Olanzapine is not included in the list.

53. The compounds recorded as synthesised were tested for neuroleptic activity by their ability to induce hypothermia in mice and by their comparative scores in conditioned avoidance response and catalepsy tests in rats. The objective (in the case of the CAR and CAT tests) is (as mentioned earlier) to find a drug which blocks the conditioned avoidance response at doses that are lower than those required to induce catalepsy.

54. The results were compared with those obtained with known anti-psychotics, clozapine, haloperidol, thioridazine and *cis*-flupenthixol.

55. From the results, the authors are able to draw certain conclusions about the relationship between structure and activity:

i) as to the substituent R on the piperazine ring, the authors say that higher alkyl substitution (i.e. anything bigger than methyl) leads to a reduction in activity. However, compounds where R is a hydroxyalkyl group such as hydroxyethyl "retain good activity";

ii) the substitution of ring A with a halogen atom at position 7 on the retained benzene ring enhanced activity;

iii) a short alkyl substitution (methyl, ethyl, iso-propyl) at position 2 on the thiophene ring seems to increase the activity, but compounds with a bulky (tertiary butyl) or long (n-hexane) group showed only minimal activity.

56. The authors conclude the article in the following way:

> "Unlike the standard neuroleptics tested, clozapine blocks the conditioned avoidance response in rats at doses which are very much lower than those required to produce catalepsy. It is thought that this profile of activity is associated with the relative lack of extrapyramidal side effects produced by this compound in the clinic. A number of compounds in the present series, e.g. 9,12,17,29, and 34, have been found to be more potent than clozapine and show a similar, if less marked, separation of activity in these two tests. This profile of activity needs further development of this class of compounds."

There are a number of things to note about this concluding paragraph.

57. Firstly, there is no mention of compound 6, ethyl olanzapine in the list of highlighted compounds.

58. Secondly, compound 34, which shares with olanzapine an unsubstituted phenyl ring, has a hydroxyethyl group attached to the piperazinyl substituent. This is a reflection of the observation made in the text, noted above, that such compounds, despite the presence of a larger group, retain good activity.

59. Thirdly, compound 9, which is singled out, is flumezapine, the compound which Lilly took on to clinical trials.

60. Lastly, the final sentence of this paragraph was argued by DRL to be an express suggestion to synthesise further compounds within the class. Lilly argued that it was simply a general statement of the potential of the class. I think it is dangerous to attach too much weight to this rather poorly constructed sentence. It seems to me to be little more than the familiar upbeat conclusion to an article of this kind, aimed at those responsible for sponsoring further research. I do not read it as a clear direction or suggestion to synthesise further compounds. Where the article would lead the skilled person depends on a wider consideration of the evidence, including the sentiment expressed in this sentence.

Chakabarti 1989

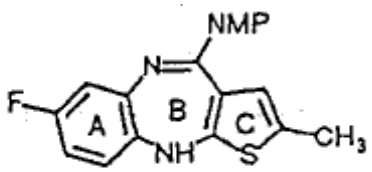
61. Chakrabarti 1989 is entitled "Synthesis and Pharmacological Evaluation of CNS Activities of [1,2,3]Triazolo[4,5-b][1,5]-, Imidazolo[4,5-b][1,5]-, and Pyrido[2,3-b][1,5]benzodiazepines. 10-Piperazinyl-4H-1,2,3-Triazolo[4,5-b][1,5] benzodiazepines with Neuroleptic Activity." It was published in 1989.

62. The article begins by recapitulating that a change in the electronic distribution in the two phenyl rings in the dibenzo-epine class of neuroleptics leads to a profound change in activity, as evidenced by the difference between clozapine (with minimal EPS) and its 2-chloro- isomer which has a classical profile of activity. The article also summarises the teaching of Chakrabarti 1980, that an effect similar to that obtained with clozapine could be obtained if ring C is replaced with an electron-rich thiophene group. The article continues:

> "One of these compounds, flumezapine (3), in which the thiophene group is substituted with an electron-donating methyl

group is more potent than clozapine and was selected as a candidate for clinical trial."

63. I think it is fair to say that the skilled reader would understand that Lilly had, for good reason, selected flumezapine as the most promising candidate from the class referred to in Chakrabarti 1980. The structure of flumezapine is given as



flumezapine (3)

where NMP is the N-methyl piperazinyl group.

64. The objective of the research reported in the article is to examine compounds where the thieno- ring reported on in Chakrabarti 1980 is replaced with other heteroarene groups. The alternative groups are (a) imidazolo [1,5]-, (b) [1,2,3]triazolo[1,5] and (c) pyrido [1,5].

65. Having introduced the purpose of their investigation the authors say:

> "Experience in the [structure activity relationship] of the thienobenzodiazepines led us to the design and synthesis of only a limited number of compounds in each series."

66. The authors summarise their results as follows:

> "The results obtained in these two tests are shown in Table II, where it can be seen that only the triazolobenzodiazepine series contains compounds with a significant level of activity. In general, the in vitro activity of the triazolobenzodiazepines on (3H)spiperone binding is about 10 times less than that obtained with similarly substituted thieno [2,3-b][l,5]benzodiazepines.
>
> "As in the case of the thienobenzodiazepines, the neuroleptic activity is enhanced by halogen substitution in the 7-posítion as in compounds 6-8, 12, and 13, although further halogen substitution as in the dichloro derivative 10 reduces the ability of the compound to compete with (3H)spiperone. ….. All the active compounds have a short alkyl group at the 2-position, with ethyl being more active than methyl."

67. Thus the alternatives to the thieno compounds investigated here proved to be less interesting than the thiophenes in general and flumezapine in particular.

The Patent

68. The Patent begins by explaining the EPS problem with classical antipsychotics. It goes on to record the introduction of clozapine and the subsequent restrictions on the

use of clozapine on the grounds of its tendency to cause agranulocytosis, as explained above.

69. The Patent then refers to the class of compounds in the 235 Patent, and records that in clinical trials of the lead compound (flumezapine) elevated liver enzyme levels were detected leading to termination of the trials. The Patent also records that in clinical trials with flumezapine, two patients showed the emergence of EPS.

70. Having introduced olanzapine, the Patent goes on to describe its properties. It claims that olanzapine has given "surprising and excellent results" in experimental screens and in clinical trials. It is said to exhibit "high activity" at "low dosage levels". The results of the (open as opposed to blind) completed clinical trial are summarised as good results. Preliminary results from three further ongoing clinical trials "appear to confirm this high level of efficacy".

71. Of importance for this case is the following passage which makes a number of claims for the compound:

> "Moreover, there is a low incidence of only mild and transient elevation of liver enzymes in patients treated with therapeutic doses, and plasma levels of creatinine phosphokinase (CPK) are lower than with flumezapine, indicating a lower adverse effect on muscular tissue. Furthermore, the compound of the invention causes lower elevation of prolactin levels than other currently used neuroleptic drugs and this suggests fewer disturbances of the menstrual cycle, and less gynecomastia and galactorrhea. No alteration of white blood cell count has been observed in clinical studies."

72. In addition the Patent claims that

> "in dog toxicity studies with a closely analogous compound [2-ethyl olanzapine] … it was observed that four out of of eight dogs showed a significant rise in cholesterol levels, whereas the compound of the invention did not show any rise in cholesterol levels."

73. The Patent concludes:

> "Overall, therefore, in clinical situations, the compound of the invention shows marked superiority, and a better side effects profile than prior known antipsychotic agents, and has a highly advantageous activity level."

The Claims

74. Claim 1 is to olanzapine (by its chemical formula) or an acid addition salt thereof. Claim 3 is to olanzapine itself. Lilly relied on a number of subsidiary claims: 4-6, 8, 11-12 and 14-18 only in relation to the plea of invalidity over a document called Schauzu, and not otherwise. These are, in general terms, use claims and claims to pharmaceutical compositions and dosage unit forms.

Novelty: Law

75. Section 2(1) of the Patents Act 1977 provides:

> "2.-(1) An invention shall be taken to be new if it does not form part of the state of the art.
>
> (2) The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way."

76. This part of the law of patents was reviewed by the House of Lords in *Synthon's Patent* [2006] RPC 10. There are two requirements for a claim to be anticipated by a prior document: disclosure and enablement. As to disclosure, Lord Hoffmann, who gave the leading judgment, began by citing passages from what he described as two judgments of "unquestionable authority": the speech of Lord Westbury LC in *Hills v Evans* (1862) 31 LJ Ch (NS) 457 at 463 and the judgment of the Court of Appeal in *General Tire and Rubber Co v Firestone Tyre and Rubber Co Ltd* [1972] RPC 457 at 485-486. In the latter case the Court of Appeal said:

> "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 be shown to lack the necessary novelty".

77. At paragraph 22 Lord Hoffmann says this:

> "If I may summarise the effect of these two well-known statements, the matter relied upon as prior art must disclose subject-matter which, if performed, would necessarily result in an infringement of the patent. That may be because the prior art discloses the same invention. In that case there will be no question that performance of the earlier invention would infringe and usually it will be apparent to someone who is aware of both the prior art and the patent that it will do so. But patent infringement does not require that one should be aware that one is infringing: "whether or not a person is working [an] ... invention is an objective fact independent of what he knows or thinks about what he is doing": *Merrell Dow Pharmaceuticals Inc v H N Norton & Co Ltd* [1996] R.P.C. 76, 90. It follows that, whether or not it would be apparent to anyone at the time, whenever subject-matter described in the prior disclosure is capable of being performed and is such that, if performed, it must result in the patent being infringed, the disclosure condition is satisfied. The flag has been planted,

> even though the author or maker of the prior art was not aware that he was doing so."

78. It follows from the above that a generic disclosure will not normally take away the novelty of a subsequent claim to a member of the class. For example disclosure of "fixing means" is not a disclosure of a nail.

79. The particular question which arises in this case concerns the effect of a particular kind of disclosure, namely that made by a chemical class formula or "Markush" formula. Such formulae are capable of encompassing many millions of compounds. In theory a person (or more likely a computer) could sit down and create a list of all possible individual compounds covered by the formula. As I have mentioned, 235 contains one such formula which extends to more than 10^{19} compounds. Does the fact that the skilled person or robot could write down all those compounds satisfy the requirements of a disclosure of an individual compound made the subject of a later claim?

80. This question is addressed on a regular basis by the EPO in deciding applications for chemical patents under the EPC. They have developed a doctrine that a chemical class disclosure does not necessarily take away the novelty of an individual compound falling within the class.

81. In Decision T 12/81 *Bayer AG Diastereomers* dated 9th February 1982, the Technical Board of Appeal had to consider whether a particular stereochemical form of a substance was anticipated by the disclosure in a prior document in circumstances where that form of the substance proved to be the inevitable result of one of a number of processes described in that document when applied to a particular starting material. It appears that the prior art described some 20 starting materials and five processes. The Board rejected an argument that only compounds described in the worked examples would suffice to deprive a later claim of novelty. Compounds could be adequately described by reference to starting materials and process parameters alone. At [11] – [13] of their Reasons the Board also rejected an argument that the novelty of the compound could be justified on the basis of "selection".

> "11. This argument cannot be accepted. The concept of substance selection pre-supposes the choosing of a single compound or a specific sub-group from a group of substances. Thus the felicitous choice of the claimed threo- compound from among the multiplicity of substances covered by Formula 1 in the cited document would, of course, be a genuine selection if the cited document did not supply any further information. The compound or sub-group chosen must, of course, also be new; but that is not the case here…
>
> 12. A substance selection can come about in various ways, e.g. if an unmentioned compound or group of compounds having a formula covered by the state of the art is found, in the absence of any information as to the starting substance or substances. The present subject-matter does not involve a selection of that kind in an area which, although marked out by the state of the art, is nonetheless virgin territory.

> 13. However, the disclosure by description in a cited document of the starting substance as well as the reaction process is always prejudicial to novelty because those data unalterably establish the end product. If on the other hand two classes of starting substances are required to prepare the end products and examples of individual entities in each class are given in two lists of some length, then a substance resulting from the reaction of a specific pair from the two lists can nevertheless be regarded for patent purposes as a selection and hence as new."

82. These passages specifically envisage two ways in which a novel selection can be made. The first is where an "unmentioned" compound from territory marked out in the state of the art is selected. There is no difficulty with that case: the compound is not disclosed. The second is where, in order to arrive at the compound, a combination of starting materials has to be chosen from "two lists of some length". The Board does not expand on its reasoning as to why in those circumstances the compound is not disclosed. One can infer that the Board considered that the need to make a choice from amongst many combinations in order to arrive at an individual compound prevented the prior disclosure from "unalterably establish[ing]" the claimed compound.

83. In Decision T 181/82 *Ciba Geigy Spiro Compounds* dated 28th February 1984 the Technical Board of Appeal was faced with a case involving the application of its rule about comparative testing with the prior art. That rule relates to inventive step, but one aspect of the rule is that the prior compound chosen as the comparator must be one which is actually disclosed in the prior document, as opposed to being simply within the scope of its claims. The Board suggested that the appropriate comparison would be with an 8-methyl derivative of the disclosed prior class of spiro compounds. The applicant for the patent contended that a disclosure of C_1-C_4 alkyl bromide in the 8-position was not a disclosure of the 8-methyl bromide (C_1 and methyl being the same thing). The contention was rejected. The Board held ([8] of the Reasons) that a consideration of the claims of the prior document led one to specific compounds which were alkylated in the 8-position by C_1-C_4 alkyl. The Board first distinguished between a compound which is covered by a definition and one which is expressly taught:

> "It cannot be denied the [*semble "that"*] the eight conceivable alkyl bromides are covered by all these definitions; a strict distinction must be drawn between this purely intellectual content of the definitions and their information content in the sense of a specific teaching with regard to technical action."

84. The Board went on to apply that definition by holding that as C_1 alkyl bromide (i.e. methyl) was specifically mentioned in the definition, and not merely included within its scope, it was disclosed:

> "When the teaching from a citation is interpreted, special attention must be paid to the material actually disclosed in the sense of a complete, specific technical rule. A group of compounds in which the substituent is characterised by a range teaches the skilled person only about the individuals

> specifically designated from the group. The formulation C1-C4 alkyl bromide in Process Claim 9, which is chosen in citation (A), therefore describes the corresponding 8-methyl derivatives in every detail in connection with the spiro derivatives according to Claims 3-7 envisaged therefor. ”

85. By contrast the reference to C_4, though explicit, left open 4 possible configurations of the butyl bromide, and was not therefore a specific disclosure of any one of them. C_{2-3} which were covered but not mentioned at all, so were also not specifically disclosed.

86. The Board’s distinction between a disclosure in the sense of “a complete, specific technical rule” in contrast to mere “intellectual content” is one which it is important to keep in mind.

87. In Decision T 0007/86 *Draco Xanthines* dated 16th September 1987 the claimed invention was a medical use of 3-propyl xanthine. Prior document (20) disclosed substituted xanthines where the two substituents were R (at position 3) and R_1 (at position 8). Each of these substituents could take a number of values, specifically including R as 3-propyl and R_1 as H (i.e. unsubstituted at the 8-position): that particular combination would yield the claimed 3-propyl xanthine. However the Board held that compound was nevertheless not disclosed. It reasoned as follows:

> “In its decision T 12/81 (Diastereomers, O.J. 1982, 296) the Board stated by way of obiter dictum that if two classes of starting substances are required to prepare a product and examples of individual entities in each class are given in two lists of some length, then a substance resulting from the reaction of a specific pair from the two lists can nevertheless be regarded as new (see in particular, paragraph 13). In the Board's view, this principle is clearly applicable not only for starting substances in chemical reactions but also for polysubstituted chemical substances where the individual substituents have to be selected from two or more lists of some length, such as in the present case. Therefore, on this basis, document (20) cannot be interpreted either as a specific disclosure of 3-propylxanthine or consequently of a pharmacological use (as a diuretic) of this compound. Thus, in the Board's judgement, document (20) cannot be regarded as being detrimental to the novelty of the subject-matter of the claims.
>
> In the application of this principle in a previous case, the Board has refused to regard those compounds, which result from the reaction of one compound arbitrarily selected from a group of generically defined reactants with a single reaction partner, as being prior disclosed. Thus, N-propyl-[substituted] heneicosane was considered to be novel since this compound (in contrast to the N-methyl compound) was not regarded as being disclosed merely by the description of the reaction of [the starting] heneicosane with one of the groups of compounds, C_1-C_4-alkyl bromides (cf. T 181/82 O.J. 1984, 401, 410). But if a mere [*semble “more”*] precisely structurally defined (described by a

> chemical reaction) class of chemical compounds with only one generically defined substituent does not represent a prior disclosure of all the theoretical compounds encompassed by an arbitrary choice of a substituent definition, it must be clearly valid for a group of chemical substances, the general formula of which has two variable groups. Therefore, in the present case, a class of chemical compounds, defined only by a general structural formula having at least two variable groups does not specifically disclose each of the individual compounds which would result from the combination of all possible variants within such groups."

88. Accordingly even where the necessary substituent values are expressly mentioned, the EPO treats the individual compound as not having been disclosed if, in order to arrive at the specific combination of substituents, a choice has to be made from two (or more) lists of some length. There is plainly a question of degree involved here when considering how the overall disclosure would be understood.

89. The Board's jurisprudence is taken a little further by Decision T 0296/87 *Hoechst Enantiomers* dated 30th August 1988. In that case the claimed class of compounds overlapped with those disclosed in a prior document. The disclosed compounds evidently had an asymmetric carbon atom, a fact which, as was well known, meant that each compound could exist in different enantiomeric forms. The patentee restricted its claim to the claimed class of compounds "with a content of at least 80% of the D-form", thus limiting each compound to one of the enantiomeric forms. The Board held that this was adequate to confer novelty. In the course of its reasoning the Board said:

> "6. The first requirement regarding novelty is to establish whether a known chemical formula evidently containing a (single) asymmetrical carbon atom destroys the novelty not only of the compound in the form of its racemate, but also of its enantiomers (d- and l-form or D- and L-form). This applies in particular to documents (1) to (3), which indisputably disclose structures overlapping those described in the contested patent, the only difference being that the latter claims D-enantiomers whereas the former makes no mention of them at all.
>
> 6.1 Here the Board is guided by the conclusions it reached in its "Spiro compounds" decision T 181/82 (OJ EPO 1984, 401) concerning the novelty of chemical entities within a group of substances of known formula. With regard to products of the reaction of specific spiro compounds with a (C1-C4)-alkyl bromide defined as a group, the Board drew a sharp distinction between the purely intellectual content of an item of information and the material disclosed in the sense of a specific teaching with regard to technical action. Only a technical teaching of this kind can be prejudicial to novelty. If any such teaching is to apply in the case of a chemical substance, an individualised description is needed. Thus, as the Board decided in that case, the purely intellectual content of the term

> (C1-C4)-alkyl comprises the eight groups methyl (C1), ethyl (C2), n- and iso- propyl (each C3), and n-, sec.-, iso- and tert.-butyl (each C4). Only the methyl group is disclosed in individualised form, however, since this is synonymous with the lower basic value C1- alkyl. In contrast, the special alkyl groups with two or three carbon atoms - included but not enumerated - are not disclosed in this way; nor are the four individual groups comprised in the upper basic value (C4), which discloses butyl groups only as a generic term.
>
> 6.2 The Board believes this principle applies in the present case to the extent that, judging by expert interpretations of the structural formulae and scientific designations to be found in the prior art, the latter describes only racemates. Given the asymmetrical carbon atom in the formula, the substances in question can indeed occur in many conceivable configurations (D- and L-enantiomers); that alone does not mean, however, that these configurations are disclosed in individualised form. The novelty of the D- and L-enantiomers is therefore not destroyed by the description of the racemates.
>
> 6.3 The situation is different if the state of the art includes enantiomers - howsoever designated (D, d, L, l or + or -) - which are specifically named and can be produced.
>
> 6.4 The Board's present view accords with its established case law on the novelty of chemical substances whereby the only technical teachings prejudicial to novelty are those which disclose a substance as the inevitable result of a prescribed method or in specific, i.e. individualised, form (cf. T 12/81, "Diastereomers", OJ EPO 1982, 296; T 181/82, "Spiro compounds", loc. cit.; T 7/86, "Xanthines", OJ EPO 1988, 381).
>
> 6.5 In taking this view the Board is aware that the two enantiomers, far from falling merely intellectually within the definition of the structure in question, actually exist unseparated in the racemate. Generally, the latter can also be separated by converting the enantiomers into a mixture of diastereomers, e.g. using optically active substances, then resolving the mixture and recovering the enantiomers from the resulting products. These considerations are immaterial to the question of novelty, however, and will be more usefully applied to the examination as to inventive step."

90. The Court of Appeal in *Generics (UK) v H. Lundbeck AS* [2008] EWCA Civ 311; [2008] RPC 19 regarded paragraph 6.2 of the reasons set out above as settled jurisprudence of the EPO and applied it: see per Lord Hoffmann at [9].

91. The notion that a prior disclosure does not take away the novelty of a claim to a specific compound unless the compound is disclosed in "individualised form" is, I believe, a sound one. I will endeavour to explain why.

92. Firstly, a general formula is an extremely powerful way of covering large number of chemical compounds: hence their frequent use in patent disclosure. It is, of course possible that someone could write down in succession all the compounds covered by all possible permutations of the variable substituents of the formula: but it is wholly artificial to suppose that anyone would. Attention would focus on compounds actually described, the remainder of the class being no more than a theoretical penumbra around those compounds.

93. Secondly, in those circumstances, I do not think it can be said that the prior document "contains a clear description of, or clear instructions to do or make, something which would infringe the patentee's claim". The description is not clear because of the need to make a combination of substituents before the compound could be regarded as "unalterably established".

94. I would accordingly hold that a general formula with multiple substituents chosen from lists of some length will not normally take away the novelty of a subsequent claim to an individual compound.

Selection patents: law

95. Patent law, at least under the Patents Act 1949, has always had a separate topic called "selection patents". So much so, that the uninitiated might have searched (in vain) for a section in the statute allowing for the grant of patents for inventions, otherwise old or obvious, in the case where an invention was the selection from a class. The classic statement on this branch of the law was that of Maugham J in *I.G. Farbenindustrie's Patent* (1930) 47 RPC 289 at 322-3.

> "Three general propositions may, however, I think, be asserted as true:- First, a selection patent to be valid must be based on some substantial advantage to be secured by the use of the selected members (the phrase will be understood to include the case of a substantial disadvantage to be thereby avoided). Secondly, the whole of the selected members must possess the advantage in question. Thirdly, the selection must be in respect of a quality of a special character which can fairly be said to be peculiar to the selected group."

96. Maugham J went on to explain the third requirement, which is that which has given rise to argument here:

> "The third proposition requires a little explanation. If there are five thousand possible members of the group, and a hundred have been selected as possessing some new and definite advantage, it is not intended to assert that such a selection patent would be bad if it were shown as the result of further research that there existed another hundred members possessing the same advantage. If, on the other hand, it were to be established that there were a thousand unselected members which possessed the same advantage, I doubt very much whether the patent could be sustained. The quality must be of a special character. It must not be one which those skilled in the

> art will expect to find in a large number of the members. It would be rash to attempt a closer definition; for the question is ultimately one of appreciation."

97. It is quite clear from an earlier passage in the judgment that Maugham J did not see himself as creating an exception to the law of novelty: see page 321 line 32-34. The question being assessed was whether it is possible to show "subject matter" in respect of a selection patent, i.e. an inventive step. It is significant that Maugham J was of the view that it was no more difficult in such a case than it was in the case of "a mechanical or combination patent" see page 321 1ines 29-40. The compounds in question had, of course, to be novel.

98. Maugham J also added some observations on the drafting of selection patents.

> "I must add a word on the subject of the drafting of the specification of such a patent. It should be obvious, after what I have said as to the essence of the inventive step, that it is necessary for the patentee to define in clear terms the nature of the characteristic which he alleges to be possessed by the selection for which he claims a monopoly. He has in truth disclosed no invention whatever if he merely says that the selected group possesses advantages. Apart altogether from the question of what is called sufficiency, he must disclose an invention; he fails to do this in the case of a selection for special characteristics, if he does not adequately define them."

99. The law of selection under the Patents Act 1949 was considered further by the House of Lords in *E.I. Du Pont de Nemours & Co.'s (Witsiepe's) Application* [1982] FSR 303. A prior specification in the name of ICI described a series of polymers made by polymerising any one of nine glycols with terephthalic acid (TPA). The ICI specification said that the polymers had improved adsorptive capacities whilst maintaining their softening points. It contained a specific suggestion of making such a polymer using 1,4 butane diol as the glycol (one of the nine). However, the worked examples in the specification used ethylene glycol alone.

100. The Du Pont specification was based on the discovery that one of these polyesters, namely that made with 1,4 butane diol and TPA, was useful in injection and high speed extrusion operations, especially for making hosepipes. It was common ground that the claim extended to the result of carrying out the prior ICI specification, provided that one had chosen the 1,4 butane diol. Nevertheless the House of Lords held that Du Pont claim was novel. Lord Wilberforce concluded:

> "It is the absence of the discovery of the special advantages, as well as the fact of non-making, that makes it possible for such persons to make an invention related to a member of the class."

101. This is not an easy passage to understand in the light of their Lordships later decision in *Synthon*. Normally, the fact of non-making, or the discovery of advantages, whether alone or in combination, would not confer novelty on a product or process specifically described in a prior publication. The House of Lords was wrestling with a problem which has re-surfaced in patent law from time to time, namely how to

reward sufficiently the inventor of a new use of a known material where the new use is based on the discovery of some unknown property of the known material. It is clear from the speeches in that case that their Lordships regarded "the invention" as not merely the compound but its advantages as well: see per Lord Wilberforce at 310-312.

102. I would like to think that, nowadays, the problem which *Du Pont* raised would be dealt with by means of limiting the claim to a method of high speed extrusion, or a product claim to an article of manufacture such as a hosepipe, both of which claims would clearly have novelty over the disclosure of that compound for a different purpose.

103. I think that there may also be a difference between the approach of the House of Lords under the 1949 Act to the question of whether the claim in *Du Pont* was novel and the approach of the EPO today under the EPC. If there is, it is not a great one. Application of the EPO approach would mean that one would ask the question whether there was an individualised disclosure of the claimed compound in the ICI specification. The question would be whether the need to choose the 1,4 butane diol from a single list of nine diols, in the absence of any example of its use, would be a sufficiently individualised disclosure. It would appear that Whitford J at first instance thought that there was no *clear* disclosure of the claimed compound: see [1981] FSR 377 at 384-5; and Buckley LJ in the Court of Appeal thought that there was no specific direction in the ICI patent to make the claimed compound: see the paragraph bridging 395 and 396. On either of those approaches, the decision in *Du Pont* is uncontroversial.

104. However, for present purposes it is sufficient to note that *Du Pont* cannot possibly stand for the proposition that the *only* way in which a claim to an individual compound can be new when compared to a prior disclosed class is if the specification satisfies Maugham J's criteria in *IG Farbenindustrie.* It is true that Lord Wilberforce said that

> "in order to leave open a field for selection by a subsequent inventor it does not matter whether the original field is described by formula or enumeration".

I do not read Lord Wilberforce's judgment as deciding that every individual compound within the original field is necessarily to be regarded as disclosed. Obviousness is another matter.

105. I therefore see nothing in *Du Pont* which requires me to hold that the EPO approach to disclosure of an individual compound is wrong as a matter of English law.

106. It would appear that the basic principles of selection inventions as explained in the *IG Farbenindustrie* and *Du Pont* cases have survived the introduction of the 1977 Act. In *Hallen v Brabantia* [1991] RPC 195 at 217-218, the Court of Appeal proceeded on the basis that those cases were still good law when considering a patent granted under the 1977 Act. The Court of Appeal rejected an argument that a patent for a corkscrew which was otherwise obvious could be saved on the selection patent principle. The Court did so on the basis that the drafting of the specification did not meet Maugham J's requirements.

107. Finally in *Ranbaxy v Warner Lambert* [2005] EWHC 2142 (Pat); [2005] FSR 14, Pumfrey J reviewed the authorities and said this about the role of selection:

> "65. I think that the belief that the law of selection is concerned with obviousness to be a misconception. Obviousness only becomes relevant if the later patent is not anticipated, and the obviousness of the selected class will be decided according to the normal principles. It will no doubt help the patentee to repel an allegation of obviousness if he can point to a statement of the advantage possessed by the selected class, but I do not believe it to be essential, as I believe Lord Wilberforce makes clear.
>
> 66. The EPO view is stricter. As expressed in T198/84 *Hoechst/Thiochloroformates* (1985) O.J. EPO 209, it seems to be to the effect that a newly discovered effect can never add novelty to a narrower class if the class is otherwise old. The claim was to a method of making thiochloroformates using a particular catalyst in the range 0.02 to 0.2 mol per cent. The prior art was a disclosure of the process with the same catalyst present in the range 0-100 mol per cent. The Board held that there was no anticipation: in (7) they say this:
>
> > "To prevent misunderstanding, it should be expressly emphasised that when examining so-called selection inventions as to novelty the Board adheres to the principle that the sub-range singled out of a larger range is new not by virtue of a newly discovered effect occurring within it, but must be new *per se (*cf. T12/81 *BAYER/Diastereoisomers* OJ EPO 8/1982 296 303). An effect of this kind is not therefore a prerequisite for novelty; in view of the technical disparity [sc. between the new class and the old] however, it permits the inference that what is involved is not an arbitrarily chosen specimen from the prior art, that is, not a mere embodiment of the prior description, but another invention (purposive selection)".
>
> 67. I read this as saying that so far as the EPO is concerned, there must be no disclosure of the selected class, either as to its individual members or as to the class as a whole if the invention is to be new. To give an example, if the disclosure of the seven inorganic cations was to be construed in context as a disclosure of the class but not of the individual members, the calcium salt would be new. If it were a disclosure of the individual salts made having those cations, the invention would be old. The advantage possessed by the selected class or individual over the prior art class merely confirms the conclusion to be drawn from considering the prior art disclosure as a whole."

108. I agree with Pumfrey J that a newly discovered effect is not an essential requirement to be satisfied before a selected compound or class can be inventive. On the other hand, I doubt whether a principle which allows considerations of advantages obtained by a selected compound or class to trump what is otherwise a novelty destroying disclosure will be able to survive in the light of the EPO jurisprudence. But I have not found it necessary to come to a final conclusion on that question.

109. I conclude that

i) In relation to lack of novelty, it is doubtful in the light of the EPO jurisprudence whether a newly discovered effect complying with Maugham J's principles could overcome a finding that a compound was specifically disclosed in a prior document.

ii) Whether or not that is so, provided there is novelty on conventional grounds, obviousness is to be decided according to ordinary principles.

iii) The existence of an advantage possessed by the selected compound will be relevant to the overall assessment of obviousness, but is not an essential pre-requisite.

iv) Compliance with Maugham J's principles in *IG Farbenindustrie's Patent* is equally not an essential requirement for inventive step to be found.

Obviousness – Law

110. 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.

111. The familiar structured approach first articulated by the Court of Appeal in *Windsurfing v Tabur Marine* [1985] RPC 59 (CA) has recently been explained and restated in the judgment of Jacob LJ in *Pozzoli v BDMO SA*, [2007] EWCA Civ 588; [2007] FSR 37 at [23].

> "In the result I would restate the *Windsurfing* questions thus:
>
> (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?"

112. In *H. Lundbeck A/S v Generics (UK) Limited* [2008] EWCA Civ 311; [2008] RPC 19 at [24] Lord Hoffmann (sitting as a member of the Court of Appeal) approved without qualification a statement of principle by Kitchin J in that case which reads as follows:

> "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."

113. Commercial success can be a relevant secondary indicator of non-obviousness. Like all secondary indications it needs to be kept in its place. Why is it relevant at all? It is said that, when coupled with a long felt want which skilled researchers were attempting to meet, it is evidence that the claimed solution cannot have been obvious. In other words, commercial incentives would have driven those skilled in the art to the claimed solution but for one thing: it was not obvious.

114. Any influence an argument of commercial success might have on the issue of obviousness can be negated by a number of factors. In some cases the prior art over which the invention is said to be obvious was published only shortly before the priority date. So the commercial success just proves that the prior art made a good commercial idea obvious. In other cases there may have been some practical or commercial impediment to embarking on the line of enquiry in question, such as the existence of a prior patent. In yet further cases such commercial success as occurred can be demonstrated to be due to factors other than the invention: such as a newly created need or to marketing or other factors. The net effect of all this has to be included in the exercise described by Kitchin J in *Lundbeck.*

Insufficiency – Law

115. A patent will be insufficient if the specification does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art.

116. In *Lundbeck* the Court of Appeal held at [27] in the judgment of Lord Hoffmann that,

> "In an ordinary product claim, the product is the invention. It is sufficiently enabled if the specification and the common general knowledge enables the skilled person to make it. One method is enough."

117. In that case the trial judge (Kitchin J) had found that the patentee's only contribution to the art had been a way of separating an enantiomeric compound which was known to exist, albeit in admixture with its fellow enantiomers. Accordingly he held, by reference to the decision of the House of Lords in *Biogen v Medeva* [1997] RPC 1, that a claim which extended to all ways of making the claimed enantiomer was too wide and insufficient. The Court of Appeal was of the view that the requirement for

sufficiency of a product claim did not differ according to the nature of the inventive step. Lord Hoffmann said

> "35. In my opinion, therefore, the decision in *Biogen* is limited to the form of claim which the House of Lords was there considering and cannot be extended to an ordinary product claim in which the product is not defined by a class of processes of manufacture. It is true that the House in Biogen indorsed the general principle stated by the Board of Appeal in *T409/91 Fuel Oils/EXXON* (1994) OJ EPO, that-
>
> > "the extent of the patent monopoly, as defined by the claims, should correspond to the technical contribution to the art in order for it to be supported or justified."
>
> 36. The judge said that in holding claim 1 insufficient, he was applying this principle. But then he treated the relevant "technical contribution to the art" as being the inventive step, namely a way of making the enantiomer. That, I respectfully consider, was a mistake. When a product claim satisfies the requirements of section 1 of the 1977 Act, the technical contribution to the art is the product and not the process by which it was made, even if that process was the only inventive step."

118. Mr Waugh QC, who argued this part of the case on behalf of Lilly, said that the effect of this judgment was that even in the case of a compound selection patent which owes its very existence to the special advantage contributed by the disclosure of the specification, the sufficiency requirement is satisfied provided that the person skilled in the art is able to make the compound. This, he said, will remain true even if it is established that the claimed advantages do not in fact exist. If correct, this is a remarkable conclusion. The patentee's only contribution to the art would have been the misrepresentation of the advantages of his invention. I believe that the propostion is incorrect.

119. Lord Hoffmann was careful in both the passages which I have cited to limit his observations to the case of an "ordinary" product claim. In such a case it is possible to say, as Lord Hoffmann did, that the technical contribution is the product, and it is only that product which needs be enabled. But if it is indeed the case that a compound which is already specifically taught in a prior document can be rendered novel by the doctrine of selection, then it seems to me that the position must be, indeed would have to be different. The claim no longer fits the description "ordinary product claim", and Maugham J's requirements for a sufficient disclosure of the advantage ought in principle to hold true.

120. Support for that view is to be found in the judgment of Jacob LJ in *Lundbeck* where, at [62], having considered two examples, he said:

> "Those examples form two extremes - there may be cases in between where the invention may lie in appreciating that a particular combination of desirable properties is of special

> value. The validity of that sort of claim will be particularly sensitive to the context of the teaching of the patent and the prior art."

121. I think that Jacob LJ was leaving open for future consideration special cases, of which selection is an example. Of course, if it is no longer the law that selection considerations can trump what would otherwise be a finding of lack of novelty, the problem does not arise.

Lack of novelty over 235 Provisional

122. I have summarised the disclosure of the 235 provisional above. In order to arrive at olanzapine the skilled reader would have to make numerous choices as to the values he gives to the unspecified substituents. Olanzapine is not one of the over 100 compounds listed in the specification – it is merely an unmentioned member of the class – albeit the preferred class – of compounds encompassed by the formula.

123. I think that the process of distilling the disclosure of 235 to the point where olanzapine emerges from it can be categorised as selecting the relevant components of the molecule from "lists of some length". It follows that there is no individualised disclosure of olanzapine.

124. In my judgment, therefore, claim 3, the claim to the specific compound olanzapine, is not deprived of novelty by the disclosure of the 235 Provisional.

125. Claims 1 and 2 are slightly broader in that they cover salts of olanzapine; but this does not alter my conclusion on lack of novelty. It is true that these claims are no longer claims to single compounds: but the class which they cover is strictly tied to the structure of olanzapine. It would be a bizarre result if a claim to olanzapine was novel, but a claim to its salts was old.

Lack of novelty over Chakrabarti 1980

126. I have summarised the disclosure of Chakrabarti 1980 above. DRL relied on two passages from the disclosure, namely the disclosure of compound 6, ethyl olanzapine and the statement that short alkyl substitution (Me, Et, i-Pr) at position 2 seems to increase activity. Taking these together, DRL submits that olanzapine is disclosed.

127. Lilly submits that olanzapine is not disclosed. To arrive at olanzapine one needs to pick one individualised compound and modify it in a particular way, without modifying anything else. That is to read the document with a view to seeing whether you can get to olanzapine from it, not to ask whether olanzapine is disclosed. Whether the skilled team would get to olanzapine from the document is a question of obviousness.

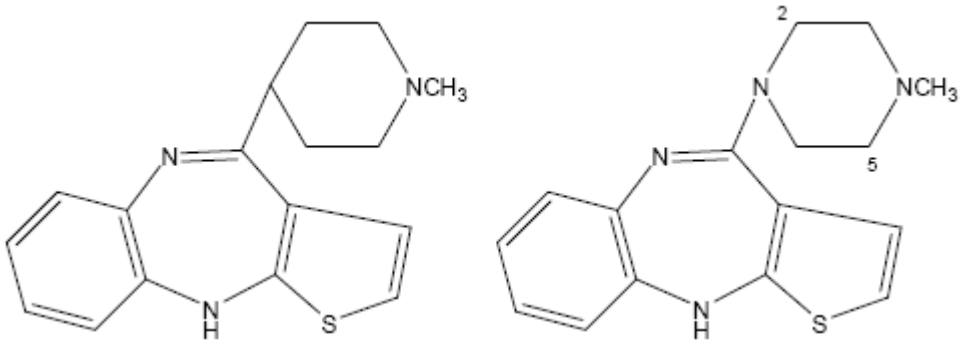
128. I agree with Lilly that there is no disclosure of olanzapine in Chakrabarati 1980, for the reason Lilly gives.

Lack of novelty over Schauzu

129. Schauzu is the only item of prior art that does not stem from Lilly itself. It is entitled "A Free-Wilson Study of 4-**piperazinyl**-10H-thienobenzo diazepine analogues". A

Free-Wilson study is a type of analysis of structure-activity relationships. Its details are not important. Schauzu was published in Pharmazie in 1983.

130. Schauzu reports data on a series of compounds defined by a formula and listed in a table. There is an inconsistency between the title of the paper and the generic formula. In the title the compounds are referred to as having a **piperazinyl** group (right hand formula below), whereas in the formula they are shown as having a piperidinyl group (left hand formula below). The difference is a missing nitrogen atom at the bridge position.



131. Compound 11 in the table discloses a methyl group in the 2-position of the thiophene ring, and no substituents on the phenyl ring. So if the resolution of the inconsistency is that the compounds disclosed are piperazinyl compounds, compound 11 is olanzapine. If the right answer is that the compounds are piperidinyl, then olanzapine is not disclosed.

132. Schauzu contains a cross reference to a Chakrabarti 1982 paper for details of its binding experiment. From that paper it is possible to work out that the data in Schauzu are in fact merely calculated from values given by Chakrabarti. If the skilled person got that far he would observe that the compounds were indeed piperazinyl compounds, in accordance with Schauzu's title. He would also notice another error in Schauzu, namely that the compounds in question had a fluorine substituent on the phenyl ring. Applying both corrections would mean that compound 11 was not olanzapine after all.

133. DRL submits that the skilled reader would resolve the inconsistency in favour of the conclusion that it is the formula and not the title which is wrong. Lilly submits that the directions are unclear: and if the skilled person investigated the matter further he would observe both errors in Schauzu, not just one.

134. Professor Roberts advanced the following reasons why he would read Schauzu as clearly disclosing the piperazinyl and not the piperidinyl compounds:

i) The numbering of the ring in the formula in Schauzu was consistent with the compounds being piperazinyl, as it started from a hetero atom which the piperidinyl compound would not have;

ii) If the bridge atom in the formula was supposed to be carbon, the carbon atom would be chiral and one would expect to see the stereochemistry depicted;

iii) It is easier to make a mistake in a formula than in a title.

135. Professor Roberts accepted that other skilled people might "make a mistake or see it the other way". Professor Nichols believed that the skilled person would focus more on the formula than the title.

136. If the skilled person would have recognised the error in the way for which Professor Roberts contended, there can be lack of novelty: see Decision T412/90 *Kawasaki/Alloy Steel Powder* [1997] EPOR 538 at [4.5] to [4.6]. It is, however, necessary to distinguish between what the document probably means and whether that meaning is clear and unambiguous. A finding that the skilled person would, on balance, conclude that Schauzu was disclosing piperazines is not the same thing as a finding that he would conclude that it was doing so clearly and unambiguously.

137. In my judgment Schauzu does not amount to a clear disclosure of olanzapine. DRL's strongest point is the numbering on the ring. I cannot attach any weight to the other two points made by Professor Roberts: the authors might not have been interested in stereochemistry, and I do not see why an error is more likely to occur in one place rather than another. The numbering certainly weighs in favour of DRL's conclusion, but I cannot accept in the light of Professor Nichols' evidence that the skilled person would necessarily notice this point or regard it as conclusive. The fact is that the disclosure is neither clear nor unambiguous.

138. I have reached this conclusion without needing to consider whether the skilled person would appreciate the second error in Schauzu by an analysis of the cross-referenced Chakrabarti paper. The document fails as an anticipation before one reaches that point.

Conclusion on novelty

139. None of the three citations cited is prejudicial to the novelty of the Patent. I have been able to reach that conclusion without analysing whether the Patent would withstand scrutiny as a selection patent based on *IG Farbenindustrie*. The debate about the advantages disclosed in the patent therefore does not arise. Nevertheless, in case I am wrong as to the legal approach to lack of novelty, I have dealt with the facts in Appendix 2 to this judgment.

Obviousness generally

The skilled addressee

140. There is not much room for debate about the identity of the team to whom the patent is addressed. It is a team of scientists working in the central nervous system area of research with a particular interest in psychotic illnesses and interested in finding a new anti-psychotic agent. The team would be led by a medicinal chemist who would have access to other disciplines such as pharmacology and toxicology as necessary.

The common general knowledge

141. The medicinal chemist would know from his general knowledge that even small modifications to compounds known to have good activity could significantly affect

that activity. He would know that such changes could affect activity *inter alia* by causing steric hindrance (i.e. making it more difficult for the compound to engage with a receptor), by adversely affecting electron density or by adversely affecting hydrophobicity/hydrophilicity.

142. The skilled team would understand that when choosing a lead compound to take forward for clinical testing a structure-activity relationship had to be developed. There were no rigid rules as to how this should be done. A first series of compounds would be synthesised and tested, and then additional analogues might be looked at depending on the results of the first tests. There is a substantial amount of work involved here: Professor Nichols indicated that a dozen compounds might keep a small laboratory going for about a year.

143. The skilled team would know about the currently used typical neuroleptics and their tendency to cause EPS. The team would also be aware of clozapine and its ability to avoid those side effects but with its attendant tendency to cause agranulocytosis. Thus it was understood that antipsychotic activity and EPS were not inevitably linked: clozapine showed this. What was not known was whether this combined result could be produced in other drugs without other side effects such as agranulocytosis.

144. As to agranulocytosis, this might have been an idiosyncratic property of clozapine. The mechanisms responsible for it were unknown.

145. The skilled team would also be aware of the *in vitro* binding assays and *in vivo* animal models used for indicating potential antipsychotic activity.

146. The front-running theory was that dopamine response was implicated in schizophrenia, although other receptors were definitely candidates for investigation. Anti-cholinergic activity was thought to contribute to reduced EPS. Professor Jenner put it very fairly in this way:

> A. Well, I think in terms of saying that schizophrenia is most
> 20 likely a multitransmitter system disease, I think that that is
> 21 very fair comment. I think you have to look at this in the
> 22 context in which it exists. That is that the brain still
> 23 operates largely as a black box. Schizophrenia is a complex
> 24 psychiatric disorder which we still do not fully understand.
> 25 What we did understand in 1990 was that you could influence
> 2 what went on in that black box through dopamine receptors.
> 3 Nobody was saying that schizophrenia was purely due to
> 4 dopaminergic disfunction. I think people were well aware that
> 5 other neurotransmitters could be potentially involved.
> 6 What we knew at that time was a way of accessing the
> 7 black box and controlling that psychotic phenomena was through
> 8 dopamine receptors. That is why there was such a focus on
> 9 dopamine receptors.

147. There was a dispute as to whether the skilled team would consider it essential to have a halogen at the 7-position in the structure. Professor Nichols' evidence in his report was that the "prevailing view" until the introduction of olanzapine was that such a "neuroleptic substituent" was essential.

148. There was certainly no general and immutable belief that all anti-psychotics required such a halogen atom. In the case of tricyclic compounds with two phenyl rings

flanking a central ring, the position was more uniform. In those circumstances the skilled person would understand that an electron withdrawing group of some kind was necessary or at the very least advantageous in order to create an electron imbalance which was linked to activity. In other contexts, the skilled team would view the halogen atom as one tried and tested way of creating such an imbalance. The team would certainly be aware that it was potentially important.

The inventive concept of the Patent

149. The inventive concept of the Patent is olanzapine (or, for what it is worth, olanzapine and its salts).

Obviousness over 235 Provisional

150. Obviousness over this document was not DRL's strongest attack: the later Chakrabarti papers are much closer starting points.

151. The difference between 235 and olanzapine is the lack of any clear direction to make the relevant combination of substitutions in the preferred class of compounds.

152. Professor Nichols' view was that a sensible approach to this document would be to choose substituents as close as possible to clozapine. He would therefore have chosen a selection of compounds with an electron withdrawing group at the 7-position of the phenyl ring.

153. Professor Roberts considered that a more general approach was justified, selecting a strong and weak electron withdrawing, unsubstituted and electron donating groups at the 7 and 8 positions. He based this on the fact that the preferred thiophene group had a different electronic structure from the diphenyl case. So one had to investigate the effect of that.

154. Having listened to the evidence I came to the very clear conclusion that olanzapine was not obvious in the light of the disclosure of 235.

155. Firstly I consider that Professor Roberts' plan is in the nature of a research program. As he fairly recognised, the impact of the thiophene group was not known. In any case, I see no reason why the skilled team would follow up this line of research without first making and testing the compounds actually disclosed. There is no evidence as to where that first step would have led.

156. Secondly I consider that the skilled team would have been predisposed, on the basis of the common general knowledge, towards including an electron withdrawing group on the phenyl ring, rather than leaving it unsubstituted. The team would have no reliable basis for concluding that unsubstituted compounds would work at all. To include such compounds in the research is, in my judgment, not an obvious step to take.

157. Thirdly it is significant that the complete specification, which would be published with the 235 provisional, excludes the case where the phenyl ring is unsubstituted. It is unrealistic in the context of obviousness to consider 235 in isolation. The skilled team would take this as an indication that this arrangement is unfavoured. Moreover

the complete specification gives its own indication of where particularly good activity is to be found: flumezapine. That would strongly confirm the team's belief in the need for an electron withdrawing group. None of this leads in the direction of olanzapine.

158. Fourthly, given that the problem the art was facing was to mimic clozapine, and given the vast area covered by the disclosure of 235, I believe that there is force in Professor Nichols' simpler approach, which accords more closely with the teaching of the document as well as the thinking of the skilled team. Such an approach would not have got near to olanzapine.

159. Fifthly, it is relevant that there is nothing in 235 to suggest that *any* of the compounds would behave like clozapine. The efficacy statement is in very general terms. The document would not give the skilled team any reason to believe that the solution to their problem lay within that class of compounds. That consideration gives more credence to Professor Nichols' somewhat less committed approach, and less to that of Professor Roberts.

Obviousness over Chakrabarti 1980

160. The difference between Chakrabarti 1980 and the inventive concept of the Patent is the absence in Chakrabarti 1980 of an individualised teaching of the structural substituents of olanzapine.

161. DRL advances two ways in which the skilled person would arrive at olanzapine without invention from Chakrabarti 1980:

i) the first, which it called "obvious by SAR optimisation", involves following up Chakrabarti with a program of optimisation directed to finding the best compound;

ii) the second, which it called "obvious in the light of compound 6", is based on the statement about alkyl substitution. Given that compound 6 is ethyl olanzapine, it is obvious to change the ethyl substituent to methyl.

162. Chakrabarti's 1980 paper was essentially concerned with exploring whether the effect which had been observed in clozapine due to the electron withdrawing chlorine substituents on phenyl ring A could be replicated or enhanced by changing ring C into an electron-rich thieno- group. The skilled person would be strongly influenced by the section of the paper dealing with structure activity relationships. In that connection it is important to note that Chakrabarti 1980 teaches that activity of these thiophenes is still enhanced by a halogen substitution on the retained phenyl ring, notwithstanding the electron-donating effect of the thiophene ring.

163. Professor Roberts' evidence was that the skilled team would set about a systematic study to complete the series of compounds which Chakrabarti discloses. The team, he says, would be particularly interested in the five highlighted compounds, 9, 12, 17, 29 and 34. The team would note that not all combinations of the substituents used in these specific compounds had been made and tested. Before picking a compound to proceed with, the skilled team would prepare a matrix to ensure that the series was

complete. Potentially the series so constructed consisted of 18 compounds[1], but seven of these had already been made and tested by Chakrabarti. So the team would go ahead and synthesise the other 11. One of these would be olanzapine.

164. The evidence did support the view that those seeking fully to explore the structure activity relationships of a class of compounds would adopt something approaching the systematic approach described by Professor Roberts. For example Professor Nichols' lecture notes revealed a section on "Lead Optimization – What Everyone Does" in which he taught that drug development went through the following four stages:

i) "Find lead

ii) Synthesis[e], and test exploratory series of analogues

iii) Formulate preliminary QSAR (Statistics); Design further analogs to test and expand QSAR, until

iv) Complete/satisfactory QSAR. Confidence that "best" analog has been found."

165. It is also fair to say that a careful analysis of the data in Chakrabarti would lead the skilled team to conclude that a halogen substituent on the phenyl ring was not absolutely essential for activity. One of the recommended compounds (34) was unsubstituted on the phenyl ring.

166. What the experts could not agree on was the stage of the process that was represented by the data in Chakrabarti's 1980 paper. On the whole, I prefer the view that Chakrabarti had done more than merely test an initial exploratory series. The large number of test compounds reported, together with the robust conclusions on structure-activity relationships would be likely to indicate to the skilled person that a substantial degree of iterative testing had been carried out.

167. It was common ground that the highlighted compounds showed excellent activity. Those compounds had been selected on the basis of the difference between their scores in the CAR and CAT tests. A high score in the CAR test indicates high potency. A low score in the CAT test indicates low side effects. Thus the greater the difference between CAR and CAT at equivalent dosage, the more attractive the compound. The highlighted compounds showed results of 3 or 4 in the CAR test and 1 or 2 (or in one case 3) in the CAT test.

168. Given the scope and extent of the testing revealed by the paper, and the attractive levels of differentiation in the tests, I prefer the view of Professor Nichols that the skilled person would select one or more of the highlighted compounds to take forward into further testing, rather than embarking on a more systematic review by synthesising further compounds. The skilled person would have no basis for believing that any better compound would be uncovered by such a systematic research program.

---

[1] Two possible substituents at the 4-position on the piperazinyl group, and three each on the phenyl and thiophene rings: 2x3x3 = 18

169. That view is supported by Lilly's own history. They took forward flumezapine (compound 9 from Table 1 of Chakrabarti, and one of the highlighted compounds) rather than delay doing so and embark on further systematic syntheses.

170. It is also important to bear in mind that Chakrabarti 1980 contains no hint or suggestion that the compounds it specifically teaches will be a solution to the problem of finding a replacement for clozapine which does not exhibit agranulocytosis. To that extent 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.

171. Viewed without hindsight, the research program advocated by Professor Roberts would have been just that: an exploration of further compounds without any real prospect that any of them would have solved the problem with which the art was concerned. The problem was not to find another compound like clozapine: but finding one which did not have the same impact on white blood cells.

172. I therefore reject the obviousness attack based on SAR optimisation.

173. The alternative attack, based on compound 6 (ethyl olanzapine) also fails. Compound 6 compares unfavourably with the highlighted compounds. It is true that the CAR and CAT tests are carried out at different doses, indicating that a greater differentiation between the two might be achievable. It is also true that the difference between compound 6 and olanzapine is only the changing of an ethyl group to a methyl group, something which the general teaching of the document suggests makes no difference. Nevertheless, I consider that the selection of compound 6 as a starting point for exploring structural variations is one which the skilled person would be unlikely to make. On the basis of a comparison of compounds 6 and 34 he is more likely to conclude that if he is to dispense with the halogen substitution, he will lose activity unless he restores it by doing something else elsewhere in the molecule. That process of thought will lead him away from olanzapine.

174. It is significant (as I have explained in Appendix 1) that the information which led Lilly to use a methyl substituent on the thieno- ring rather than an ethyl substituent was not in the public domain. Absent that information Chakrabarti gives the skilled team no reason to alter compound 6 (or any of the ethyl substituted compounds). Indeed it positively suggests that there is no purpose in making that alteration.

Obviousness over Chakrabarti 1989

175. The step from Chakrabarti 1989 to olanzapine involves rather more than the step from Chakrabarti 1980. First the skilled team has to revert to the core structure of the 1980 article. Then it has to adopt the substitutions appropriate to olanzapine.

176. To use a railway metaphor, Chakrabarti's 1989 paper is something of a branch off the main line of Lilly's research. The purpose of the excursion was to see if alternative ring-structures were any better than those disclosed in the 1980 paper. The answer was that they were not, so the branch line met the buffers: it led nowhere.

177. DRL's obviousness argument involves the skilled team picking out of this paper the preferred substitution pattern which Chakrabarti had carried forward into the testing of these novel compounds, and then re-applying it to the 1980 core structure. There would be reason to do so, DRL argues, because the conclusion of Chakrabarti 1989 is that the 1989 compounds are about ten times less active than "similarly-substituted" thieno- compounds. Rather than start from the structure-activity information in Chakrabarti 1980, one would use the information about substitutions in the later article.

178. Lilly's principal answer to this attack is to say that it disregards the teaching of the document and its own research history. It disregards the teaching of the document because Chakrabarti 1989 explains that flumezapine has been selected as the lead compound. If the skilled team is minded to revert to the 1980 structure, it would be unlikely to choose to repeat the work which drove Lilly to make that selection. Such a conclusion would also tie in with the consistent teaching of both documents that halogen substitution enhanced activity.

179. Professor Nichols' view is that he would see no point in going back to test further thiophenes when told that flumezapine had been selected as the clinical candidate:

> Q. I am not asking you whether you could do it. We all know you could do it. I am suggesting to you that it would be a routine thing to do because Chakrabarti is telling you that similarly substituted thienobenzodiazepines are better than their triazolo equivalents.
>
> A. I guess it is not clear to me what your motivation is for doing that.
>
> Q. Well, to get a better compound.
>
> A. How do we know there is not a better compound? They state that flumezapine is a clinical candidate.
>
> Q. So you don't agree that having read Chakrabarti 1989 this substitution would be a routine thing to do. Is that right or not?
>
> A. They have already published Chakrabarti 1980 where they have done a fairly comprehensive study. They have drawn their structure activity conclusions and now they have come back with the triazolo compounds and said by and large these are not so interesting. I don't understand what the motivation is to translate those substituents back to the thienobenzodiazepines.
>
> Q. So the answer to my question is you don't think that substitution would be a routine thing to do in the light of the teaching of Chakrabarti 1989. Is that right?
>
> A. It would be a chemically feasible transformation ----
>
> Q. That is not what I am asking you.
>
> A. I don't understand the motivation to do that.

180. Later Professor Nichols was pressed on the conclusion from the 1989 paper:

A. Let me just clarify so I can give a good answer. They used what they learned in Chakrabarti 1980 to apply to these compounds.

Q. So they could make a limited number of compounds, for example, in the triazolo series.

A. Exactly, and what they generally found was that the compounds that they made were less active in the triazolo series.

Q. Yes?

A. And I don't think that necessarily leads to the conclusion that one should therefore take compounds from the triazolo series and translate them back into the thiophene series.

Q. I appreciate you don't think one should do that, but what I am putting to you is that since, in the context of your comment, to change from triazolo to a thieno is not a small change, I am putting to you, as we have discussed, that in this paper the authors of Chakrabarti were trying to substitute thieno rings with triazolo rings and their experience of the thienos led them to synthesize only a limited number of triazolos, correct?

A. Correct.

Q. And that clearly suggests that experience of the thieno has guided their choice of triazolos obviously.

A. Yes.

Q. And therefore, assuming that one wishes to look back at thienos, the reverse must be true: experience of the triazolos must guide the choice of thienos.

A. Experience with the triazolos would suggest that the thienos might be more active, yes.

Q. And the thieno analogues that Chakrabarti is referring to in the passage we have just read, "Experience in the SAR of the thienobenzodiazepines", they must have had a good therapeutic index otherwise they would not have been used as the basis for the choice of the triazolos, obviously. They must have had a good, as you put it, relationship between the CAR and the CAT.

A. The specific compounds with the particular substitutions that they used. Is that what you are asking?

Q. Yes, because it guided the choice. A limited number.

A. Yes. They no doubt took the favourite compounds and then applied the substituents on those compounds to the triazolos.

Q. Thank you.

181. I do not think that Professor Nichols ever accepted that Chakrabarti 1989 would provide an incentive to look back at the thieno compounds in the way DRL suggest. I think he is right that the overall view would be that Lilly's examination of the structure-activity relationship had concluded that the flumezapine was the best compound to take forward. Certainly there would be no basis provided by Chakrabrati 1989 for abandoning the halogen substituent on the phenyl ring.

182. Accordingly, I also reject the obviousness attack based on Chakrabarti 1989.

Obviousness over Schauzu

183. DRL's pleaded case that certain subsidiary claims of the Patent were obvious over Schauzu was based on the premise that Schauzu discloses olanzapine. As I have rejected the premise, the attack fails.

184. If I am wrong and Schauzu is a disclosure of olanzapine, then claims 1 and 3 would fall for obviousness, but I am not persuaded that the subsidiary claims would fall as well. Those claims would not be rendered obvious by the mere inclusion of olanzapine in a testing programme: it would be necessary to show that it was obvious to take olanzapine forward to clinical use. I was not satisfied on the evidence that olanzapine would be so selected. Moreover there is force in Mr Thorley's submission that, before spending money on such research, the skilled team would make sure they were working on the right compounds. Professor Roberts agreed:

> Q. And if it were important, I think we are agreed, if you are going to spend money on this, you would do your damnedest to find out exactly what was intended and not merely trust on your judgment. Is that fair?
> A. Yes, that is right.

Commercial Success

185. It is clear that olanzapine has been a commercially and technically successful product. That fact alone does not assist Lilly on obviousness if olanzapine was technically obvious. I have not found the commercial success of olanzapine helpful in deciding the issue of obviousness.

186. As I have indicated, olanzapine was protected within the broad class of compounds protected by the 235 patent. That patent would have prevented the manufacture and sale of olanzapine, or any other compound encompassed by that very broad class. There is therefore a very clear explanation of why, despite the potential for commercial gain, no third party ever launched olanzapine. The commercial success does not show that third parties had not appreciated the advantages of following the course which DRL say is obvious

187. Arguments based on commercial success of products the subject of anterior patent protection are more or less doomed to failure. I am afraid this is another example. For earlier cases, see *Cipla Ltd v Glaxo Group Ltd* [2004] R.P.C. 43 at [115]; *Generics (UK) v Lundbeck* [2007] EWHC 1040 (Pat) at [251].

Insufficiency

188. The pleaded attack on insufficiency is as follows:

(i) In the case of an alleged selection invention, the invention lies in the discovery of a surprising advantage which the selection is said to possess over the previously disclosed class. Unless that advantage is set out in clear terms in the patent, the invention is not disclosed, either at all or with sufficient clarity and completeness.

(ii) The Patent does not contain any disclosure, or alternatively any sufficiently clear or complete disclosure, of any surprising advantage which olanzapine is alleged to possess over the preferred class, alternatively the entire class, of compounds disclosed in the Provisional Specification of GB 1 533 235.

(iii) The Patent does not enable the skilled person to conclude that olanzapine would have any advantages when compared with other members of the preferred class, alternatively the entire class, of compounds disclosed in the Provisional Specification of GB 1 533 235.

(iv) Without prejudice to the generality of the foregoing, insofar as the Court finds that there is any disclosure in the Patent of the advantages of olanzapine over any compounds within the preferred class of the '235 provisional specification, this disclosure is limited to the following:

(a) alleged lower elevation of plasma levels of CPK in patients when compared to flumezapine; and

(b) alleged absence of elevation of cholesterol in dogs compared to a significant rise in cholesterol levels in dogs treated with ethyl olanzapine.

The Patent does not enable the skilled person to conclude that olanzapine would have those alleged advantages when compared with other members of the preferred class, alternatively the entire class, of compounds disclosed in the Provisional Specification of GB 1 533 235.

(v) Claims 11, 14 and 17 (alleged to be independently valid) claim a dosage comprising from about 0.1 to 20 mg of olanzapine or another compound in the class claimed in claim 2 or 3. Doses of olanzapine below 0.5 mg are not clinically effective for the treatment of any psychotic disorder. Accordingly, such doses cannot enjoy any relevant advantage over the previously disclosed class. Further this dosage range overlaps with dosage ranges disclosed in the Provisional Specification of GB 1 533 235, and no advantage is disclosed in the Patent for the dosage range claimed in the said claims.

189. All these insufficiency attacks are based on the premise that the Patent can only be upheld over the disclosure of the 235 Provisional Specification if it is a valid selection patent. As I have endeavoured to explain, I have felt able to hold that olanzapine is both novel and not obvious as a chemical compound without reliance on selection principles. In those circumstances the insufficiency attack does not arise.

190. In case I am wrong about my approach to these issues, I have explained my conclusions of fact and law about the selection case in Appendix 2.

Result

191. The attacks on the validity of the Patent fail. I will hear counsel on the form of order.

APPENDIX 1

Lilly's research leading to olanzapine

1. Lilly's objective from 1974 was to discover an atypical antipsychotic with the positive properties of clozapine but without the side effects. In particular a compound was wanted which (a) had the antipsychotic effects of clozapine (b) shared the lack of EPS and which (c) did not cause agranulocytosis.

2. The research commenced in 1974 when the first compounds within Lilly's class of thienobenzodiazapines were made. Lilly's research was carried out at its Neuroscience Research Centre at Erl Wood Manor in Windlesham, Surrey. Lilly first explored a number of potential candidates, as reported in Chakrabarti 1980, and identified the most promising in the mid '70s.

Ethyl flumezapine

3. Initially, the most promising candidate was known internally as EW 5508 (ethyl flumezapine). The structure of 5508 is:

5508 (ethyl flumezapine)

4. A project team for this compound was formed and toxicity studies were carried out throughout 1976. However, in November 1976 the conclusion was reached that the animal tests did not suggest that 5508 would have any advantage over competing products (which would have included clozapine) so far as toxicity was concerned and that successful approval of the compound would therefore depend on the demonstration of a clear cut advantage as regards efficacy.

5. In April 1977, a six-month toxicological study (started in September 1976) was completed using 5508 in dogs. Part way through this dog toxicology study, animals were found to be undergoing weight loss, anorexia, infection, blood cell

changes and, in some cases, there was also enlargement of the mammary glands. Of particular concern was the fact that, like clozapine, 5508 was found to cause severe blood disorders and human volunteer studies were postponed indefinitely.

Flumezapine

6. In parallel with the development of 5508, the pharmacology department had been continuing the analysis of other compounds from the series, in particular compound 5852 (flumezapine).

(5852) Flumezapine

7. An initial study on 5852 compared dogs treated with high doses of either 5852 or 5508. In this comparison, neutropoenia was not observed in dogs treated with 8 mg/kg of 5852. In contrast, two animals both given 5508 at 8mg/kg group experienced severe granulocytopoenic episodes. In each case a drastic fall in the number of neutrophils was observed. 5508 was accordingly dropped as a candidate for development and the 5508 Project Team disbanded.

8. Following the discovery that compound 5852 did not cause granulocytopoenia in dogs dosed at 8mg/kg/day for 40 days, in September 1978, it was decided to initiate six month studies in rats and dogs, a pilot rat production study, a pilot rabbit teratology study and acute toxicity studies in rats, mice, dogs and monkeys. Preclinical data were collected over the next two years.

9. In January 1981 an IND for 5852 was filed and from January to October 1981 Phase I safety trials were conducted in healthy human volunteers. In addition, further longer-term toxicity studies in animals were continuing throughout 1981. The conclusion reached from these tests was that 5852 had a sufficiently safe profile to enable it to be administered to patients suffering from schizophrenia. Phase II clinical trials were then initiated.

10. In early April 1982, studies in 13 schizophrenic patients showed that 5852 caused increases in the muscle enzyme creatine phosphokinase (“CPK”) and the liver enzymes SGOT and SGPT. Less frequently, LDH and alkaline phosphatase were elevated. As a result, Lilly decided not to add any new patients to the clinical trials and immediately reported the fact of these raised liver enzymes to the FDA on 2 April

1982. The same day the FDA advised that patients be withdrawn from the drug as soon as possible.

11. During the very short period of clinical exposure before the hepatotoxicity was observed, 5852 was found to be an effective anti-psychotic with a rapid onset of action and very few reported acute side effects.

12. DRL suggested that Lilly was not as persistent as it could have been in seeking to persuade the FDA to allow it to continue with the human trials on flumezapine. It is clear that the decision not to progress flumezapine was Lilly's alone. The evidence surrounding the decision not to take flumezapine further is unsatisfactory. For example there are no minutes of the meeting at which the decision was taken, and Dr Pullar was not present at it. All one can say is that the human clinical trials of flumezapine encountered an initial adverse toxicological indication which Lilly chose not to investigate further.

The decision to proceed with olanzapine

13. Despite research on 5508 and 5852 spanning the period 1974 to 1983, Lilly had failed to discover a compound with the potential to develop into a drug for human use. Dr Bill Dawson, the Manager of Biology at Erl Wood, was anxious to try to salvage something from the project given that, despite the significant resources provided to Erl Wood, Erl Wood had thus far not produced a successful marketed compound. The Erl Wood scientists were thus given a final chance and a small sub-group was formed in August 1982 charged with the specific task of finding one, or possibly two replacements for 5852.

14. Seven new compounds were synthesised, all of which were methyl-substituted on the thiophene ring and one of which was olanzapine, the des-fluoro analogue (i.e. not fluorine-substituted) of 5852 which was first synthesised on or around 29th April 1982.

15. Dr Pullar explained the reason for the preference of the methyl as opposed to the ethyl group. Lilly made a connection between the agranulocytosis seen with ethyl flumezapine and the presence of the ethyl group which could be metabolised quite easily. Lilly therefore had a preference for methyl in the 2-position. Lilly submitted, and I accept that this is not information which was in the public domain. No common general knowledge reason was suggested for this preference.

16. Initial data showed that olanzapine was much less potent than 5852 which carried with it the expectation that there would be more side effects which were not related to the mechanism of action of the drug.

17. Nevertheless Lilly decided to progress olanzapine. Over the next seven years, Lilly carried out tests on olanzapine to determine its pharmacological profile. Overall, Lilly found olanzapine to be sufficiently safe to progress to human studies.

18. Thereafter, Phase I human clinical trials were carried out in 1986 and 1987 in healthy volunteers, and further clinical trials were carried out in 1989 in

schizophrenic patients. Olanzapine appeared to be a safe and effective new antipsychotic product with less propensity to induce extrapyramidal symptoms and cause side effects connected with elevation of prolactin levels than conventional treatments. It was also found to be active at lower doses than were expected given the preclinical test results.

APPENDIX 2

The selection case

1. Only two claimed advantages versus compounds described or claimed in 235 appear in the Patent:
    a. alleged lower elevation of plasma levels of the enzyme CPK when compared to flumezapine
    b. alleged absence of elevation of cholesterol in dogs as compared to a significant rise in dogs treated with ethyl olanzapine.
2. The first problem to be met by a classical selection case is that the Patent does not even assert any quality for olanzapine which is of a special character not shared by the whole class. The advantages alleged are only over individual members of the disclosed class. There is no disclosure of whether olanzapine is special in this regard, or whether this is a property shared by a large part of the class. I accept DRL's submission that this is not enough for a valid selection patent. In this connection, the advantages over "currently used neuroleptics" are not relevant (although of course the absence of any influence on white blood cell count is relevant to the general obviousness case). The currently used neuroleptics are not part of the class of 235.
3. That is sufficient to dispose of the selection case. Lilly submitted that a broader view of the advantages of olanzapine was appropriate. I disagree, but record my findings of fact in case they are important:
    a. *The fact that olanzapine is a clinically approved, safe and effective treatment*. This is not in dispute.
    b. *The absence of the tendency to cause agranulocytosis*. As compared with clozapine it is clearly the case that olanzapine does not cause white blood cell disorders. I have taken this fact into account in my consideration of obviousness generally.

       Lilly relied at trial on their own experience with ethyl flumezapine in support of a submission that olanzapine has this advantage over flumezapine (albeit not one mentioned in the Patent). There was no real challenge to Lilly's evidence that this tendency to affect white blood cells was Lilly's reason for abandoning ethyl flumezapine; but issue was not really joined on whether the data were robust enough to have supported this conclusion as it was not part of Lilly's pleaded case.

c. *Olanzapine has a reduced tendency to cause EPS (in particular tardive dyskinesia) as compared with FGAs.* Overall this was established, although of course olanzapine has its own side effect profile including a tendency to cause weight gain. DRL's argument was that this advantage was not sufficiently established, for example the Summary of Product Characteristics says this cannot be concluded as a basis for clinical action as against haloperidol. Nevertheless, on balance, the advantage exists.

d. *Olanzapine causes lower prolactin levels.* There is a relationship between dopamine agonists and prolactin levels: prolactin release was a known effect of anti-psychotic drugs. Lilly's case was that olanzapine had an advantage in this respect as compared with ethyl olanzapine and either flumezapine or ethyl flumezapine.

   The evidence focussed on *ethyl olanzapine.* Another pharmaceutical company, Ivax, commissioned a dog study for the purposes of United States proceedings in the course of which prolactin levels were measured. An indication of elevation of prolactin levels in the animals treated with ethyl olanzapine was observed at 13 weeks, but not in those treated with olanzapine. Lilly rely on this study, although they were not in a position to offer a repetition.

   There are a number of problems with this evidence. The study was not set up to measure prolactin, so no baseline measurements were taken. No measurements of prolactin level were taken after the thirteen week reading which showed the difference.

   Despite these reservations, in the absence of any conflicting evidence, I consider that olanzapine did show an advantage over its ethyl analogue in terms of elevation of prolactin levels in dogs.

   There was no real basis for a direct comparison in relation to prolactin levels between olanzapine and either flumezapine analogue.

e. *Raised enzyme levels.* Raised enzyme levels are a potentially serious concern with any drug, if encountered at or below therapeutic doses. Lilly relies on its own experience with flumezapine which I have described in Appendix 1. As I have said, the most one can say from this history is that the human clinical trials of flumezapine encountered an initial adverse toxicological indication which Lilly chose not to investigate further. In later trials with olanzapine some raised enzyme levels were also observed, but only at higher doses than was the case with flumezapine. This enabled Dr James to say that the decision to proceed further with olanzapine in preference to flumezapine was justified from a toxicological standpoint. Neverthless Dr James accepted that a head to head comparison between the two drugs in relation to enzyme levels was not possible. Nevertheless I think Lilly is right that, on the balance of probabilities, olanzapine had an advantage over flumezapine in that olanzapine's regulatory pathway was likely to be easier than flumezapine.

f. *Lower cholesterol levels in dogs.* Lilly contends that the evidence established that olanzapine has a lower tendency to raise cholesterol levels in dogs than ethyl olanzapine. In my judgment it was established that olanzapine does show such an advantage in female dogs. It was not established that this advantage would be replicated clinically. In fact it is now known that olanzapine does raise cholesterol levels in humans, to the extent that Lilly has warned doctors of this fact.