Neutral Citation Number: [2015] EWHC 2548 (Pat)

Case Nos: HP-2014-000035, HP-2014-000021, HC-2014-001795

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Rolls Building
Fetter Lane, London, EC4A 1NLL

Date: 10 September 2015

Before :

THE HON MR JUSTICE ARNOLD

- -

Between :

GENERICS (UK) LIMITED trading as MYLAN	**Claimant**
- and -	
WARNER-LAMBERT COMPANY LLC	**Defendant**
And between :	
ACTAVIS GROUP PTC EHF	**Claimant**
- and -	
WARNER-LAMBERT COMPANY LLC	**Defendant**
And between :	
WARNER-LAMBERT COMPANY LLC	**Claimant**
- and -	
(1) ACTAVIS GROUP PTC EHF	**Defendants/**
(2) ACTAVIS UK LIMITED	**Part 20**
(3) CADUCEUS PHARMA LIMITED	**Claimants**
- and -	
PFIZER LIMITED	**Part 20 Defendant**
- and -	
SECRETARY OF STATE FOR HEALTH	**Intervener**

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Piers Acland QC and **Kathryn Pickard** (instructed by **Taylor Wessing LLP**) for **Mylan** (validity)

Richard Meade QC and **Isabel Jamal** (instructed by **Powell Gilbert LLP**) for **Actavis** (validity)
Tom Mitcheson QC, Miles Copeland and **Katherine Moggridge** (instructed by **Allen & Overy LLP**) for **Warner-Lambert** (validity)
Charlotte May QC and **Tim Austen** (instructed by **Allen & Overy LLP**) for **Warner-Lambert** and **Pfizer** (infringement and threats)
Adrian Speck QC (instructed by **Powell Gilbert LLP**) for **Actavis** (infringement and threats)
Michael Silverleaf QC, Philip Moser QC and **Richard Davis** (instructed by the **Government Legal Department**) for the **Secretary of State** (infringement)

Hearing dates: 29-30 June, 1-3, 6, 8 July 2015 (validity),
9-10, 13-15, 17 July 2015 (infringement and threats)
Further written submissions 29 July and 18 August 2015 (infringement)

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Approved Judgment

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

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THE HON MR JUSTICE ARNOLD

MR JUSTICE ARNOLD :

Contents

Introduction

1. These claims all concern European Patent (UK) No. 0 934 061 entitled "Isobuytlgaba and its derivatives for the treatment of pain" ("the Patent"), which is owned by Warner-Lambert Company LLC ("Warner-Lambert"). The Patent is a second medical use patent with claims in Swiss form (see paragraphs 88-92 below for an explanation of what this means). The claims are directed to the use of pregabalin for treating pain. There is no challenge to the claimed priority date of 24 July 1996. The application was filed on 16 July 1997. The Patent was granted on 28 May 2003. The claims of the Patent were centrally limited on 21 January 2015 pursuant to an application made by Warner-Lambert to the European Patent Office on 23 September 2014.

2. Warner-Lambert markets pregabalin under the trade mark Lyrica for the treatment of epilepsy, generalised anxiety disorder ("GAD") and neuropathic pain through Pfizer Ltd ("Pfizer"), which holds the relevant marketing authorisation. Patent protection for pregabalin itself (under European Patent No. 0 641 330, "the Basic Patent") expired

on 17 May 2013. Warner-Lambert obtained a supplementary protection certificate (SPC/GB04/034, "the SPC") based on the Basic Patent which extended protection for pregabalin to 17 May 2018, but allowed the SPC to lapse for non-payment of fees. This was first noted on the Register of Patents on 14 October 2013. Warner-Lambert's data exclusivity in respect of the data used to obtain the marketing authorisation for Lyrica expired on 8 July 2014.

3. Generics (UK) Ltd trading as Mylan ("Mylan") commenced a claim for revocation of the Patent on 24 June 2014. Actavis Group PTC EHF ("Actavis PTC") commenced a claim for revocation of the Patent on 12 September 2014. On 16 September 2014 Birss J ordered an expedited trial of Mylan's claim, to commence on 29 June 2015. On 3 November 2014 Birss J ordered Actavis PTC's claim to be tried together with Mylan's claim. I shall refer to Mylan and Actavis PTC collectively as "Mylan and Actavis". At trial Mylan and Actavis presented a common case with respect to the validity of the Patent, although counsel for Mylan and counsel for Actavis PTC divided the work between them. Mylan and Actavis challenge the validity of the Patent on the grounds of obviousness over a number of items of prior art and insufficiency.

4. On 8 December 2014 Warner-Lambert commenced a claim for infringement of the Patent against Actavis PTC, Actavis UK Ltd ("Actavis UK") and Caduceus Pharma Ltd ("Caduceus") (collectively "Actavis"), and applied for an interim injunction, in respect of Actavis' intended launch of a generic pregabalin product for the treatment of epilepsy and GAD under the trade mark Lecaent. I heard the application for an interim injunction on 13-15 January 2015. On the first day of the hearing I directed that the trial of the infringement claim should be expedited so as to be heard immediately after the trial of the claims for revocation.

5. I dismissed the application for an interim injunction for the reasons given in my judgment dated 21 January 2015 [2015] EWHC 72 (Pat) ("*Warner-Lambert I*"). Subsequently I dismissed an application by Actavis to strike out, alternatively for summary judgment dismissing, Warner-Lambert's claim for infringement under section 60(1)(c) of the Patents Act 1977 for the reasons given in my first judgment dated 6 February 2015 [2015] EWHC 223 (Pat) ("*Warner-Lambert II*"), but acceded to Actavis' application to strike out the claim for infringement under section 60(2) for the reasons given in my second judgment dated 6 February 2015 [2015] EWHC 249 (Pat) ("*Warner-Lambert III*"). On 26 February 2015 I made an order, largely by consent, requiring the National Health Service Commissioning Board ("NHS England") to issue guidance to Clinical Commissioning Groups ("CCGs") in England and to the NHS Business Services Authority ("BSA") for transmission to NHS pharmacy contractors for the reasons given in my judgment dated 2 March 2015 [2015] EWHC 485 (Pat) ("*Warner-Lambert IV*"). On 28 May 2015 the Court of Appeal dismissed an appeal by Warner-Lambert against *Warner-Lambert I* and allowed an appeal by Warner-Lambert against *Warner-Lambert III* for the reasons given in the judgment of Floyd LJ delivered on that date [2015] EWCA Civ 556 ("*Warner-Lambert CA*").

6. Since 26 February 2015, there have been a number of case management hearings of the infringement claim. At a pre-trial review on 14 May 2015, the Secretary of State for Health applied for permission to intervene in the infringement claim. That application was not opposed by either party and I granted it. At trial both Warner-

Lambert and Actavis instructed separate teams of counsel and called different witnesses for the infringement case to those instructed and called for the validity cases. As well as defending the infringement claim, Actavis counterclaim in respect of threats allegedly made by Pfizer. Two issues have been reserved for consideration later if necessary: a defence to the infringement claim raised by Actavis that the grant of any relief would be contrary to competition law, and a defence to the threats claim raised by Pfizer under section 70(2A)(b) of the Patents Act 1977.

The parties

7. Warner-Lambert and Pfizer are both subsidiaries of Pfizer Inc and part of the Pfizer Group. The Pfizer Group is one of the world's largest groups of pharmaceutical companies, and it develops and markets a range of branded pharmaceutical products. The invention claimed in the Patent and some of the prior art relied upon by Mylan and Actavis emanate from Warner-Lambert's Parke-Davis subsidiary. (Parke-Davis was acquired by Warner-Lambert in 1970 and Warner-Lambert was acquired by Pfizer in 2000.)

8. Actavis PTC and Actavis UK are both subsidiaries of Actavis plc and part of the Actavis Group. Since March 2015, the Actavis Group has been one of the world's top 10 pharmaceutical company groups by sales revenue. It markets a range of branded and generic pharmaceutical products. It is currently the largest supplier of generic pharmaceutical products in the UK. The UK is the Actavis Group's second largest market after the USA. Actavis PTC holds the majority of the marketing authorisations for Actavis' products in Europe and is responsible for pan-European regulatory strategy, as well as a number of other functions. Actavis UK is responsible for Actavis' commercial activities in the UK, including the marketing of new generic products.

9. Caduceus is an independent company that is not a member of the Actavis Group. It holds the marketing authorisation for a number of Actavis' products in the UK, including Lecaent. Lecaent is packaged in Caduceus' livery, which bears the name "Caduceus". Caduceus is also the marketing authorisation holder for a generic pregabalin product marketed by Dr Reddy's Laboratories Ltd ("Dr Reddy's") (as to which, see further below) and a defendant to a claim for infringement brought by Warner-Lambert against Dr Reddy's.

10. The Secretary of State for Health has ultimate responsibility for the healthcare system in England, although, as described in more detail below, NHS England has a substantial degree of operational independence and the system is quite a decentralised one. In Wales, Scotland and Northern Ireland, healthcare is a devolved matter. The Secretary of State has intervened in these proceedings because, while he is strongly supportive of upholding the right of patent holders, including holders of second medical use patents, to the protection conferred by such patents, he is concerned that such protection should not extend beyond its proper bounds, so as to prevent generic manufacturers from supplying drugs for non-patented indications. This is for both clinical and financial reasons.

The witnesses: validity

11. Mylan and Actavis and Warner-Lambert both called two expert witnesses in relation to validity, namely a neuroscientist and a clinician. Both of Warner-Lambert's experts had previously given evidence in proceedings concerning the US equivalent of the Patent. The parties also adduced some factual evidence in relation to validity.

Neuroscientists

12. Mylan and Actavis called Professor John Wood, who is Professor of Molecular Neurobiology and Head of the Molecular Nociception Group at University College London ("UCL"). He obtained a BSc in Biochemistry from Leeds in 1971, an MSc in Molecular Enzymology from Warwick University in 1972 and a PhD in Virology from Warwick in 1976. After post-doctoral studies at the Institut du Radium and the Institut Pasteur, in 1979 he took up a research post in the Immunology Department at St George's Hospital London. From 1981 to 1984 he was a Senior Scientist in the field of Neuroimmunology employed by Wellcome Foundation Research Laboratories. From 1984 to 1994 he was Head of Neuroimmunology at the Sandoz Institute for Medical Research. Whilst at Sandoz, he was primarily involved in identifying new molecules with analgesic properties. As part of this drug development work, candidate molecules were regularly tested in animal models of pain. In 1994 he joined the Department of Biology at UCL as a Senior Lecturer, becoming Professor in 1998. In 2001 he co-founded a start-up company to develop analgesic drugs directed at novel molecular targets. In 2009 he was elected a Fellow of the Royal Society and a Fellow of the Academy of Medical Sciences. He is the author of three books and over 150 scientific publications. He also has a number of patents to his name. His current role is primarily as a pain geneticist, but his work has covered a range of disciplines within the field of pain research.

13. Counsel for Warner-Lambert suggested that Prof Wood had specialised in the peripheral nervous system, and specifically ion channels. It was put to Prof Wood, and he accepted, that his work before the priority date had focussed on peripheral mechanisms. It was also put to him, and he appeared to accept, that he was an expert in ion channels, but it was not put to him that he had specialised in ion channels. Counsel accepted that Prof Wood had tried to assist the court, but nevertheless criticised certain aspects of his evidence. Counsel's main point, which related to Prof Wood's reliance in oral evidence upon papers as evidence of common general knowledge which he had not mentioned in his reports, applies equally to Prof Woolf, however. In my view Prof Wood was a well qualified and very fair witness.

14. Warner-Lambert called Professor Clifford Woolf, who is Director of the Program in Neurobiology at Children's Hospital Boston and Professor of Neurology and Neurobiology at Harvard Medical School. He obtained a BSc in Physiology from the University of the Witwatersrand in 1972, an MB, BCh from the same university in 1977 and a PhD in Physiology from the same university in 1979. From 1979 to 1981 he was a Lecturer in the Department of Physiology at Middlesex Hospital Medical School. Between 1981 and 1997 he was successively Lecturer, Senior Lecturer, Reader and Professor of Neurobiology at UCL. During this period, he discovered the phenomenon of the central sensitisation of neurons in the dorsal horn to peripheral painful stimuli, which was published in a much-cited paper (C.J. Woolf, "Evidence for a central component of post-injury pain hypersensitivity", *Nature*, 306, 686-688

(1983)), and much of his subsequent research has been in this area. In the 1980s he attended a weekly pain clinic at the Royal National Orthopaedic Hospital. In 1995 he was appointed as an Honorary Consultant at University College Hospital where in 1996 he served on a committee that reviewed the needs and treatment options for pain patients, including opportunities for new therapies. In 1997 he was appointed as Director of the Neural Plasticity Research Group at Massachusetts General Hospital and Professor of Anaesthesiology Research at Harvard Medical School. He took up his present position at Children's Hospital Boston in 2010. He has acted as a consultant to many pharmaceutical and biotech companies. He has received a number of awards. He has published over 350 scientific papers in the field of pain research. He is also a named inventor on 16 patents.

15. Counsel for Mylan and Actavis made three criticisms of Prof Woolf's evidence. First, he submitted that, as the originator and principal proponent of the central sensitisation theory, it was difficult for Prof Woolf to put himself into the position of the ordinary skilled neuroscientist at the priority date. This is not, of course, a criticism of Prof Woolf himself. When this point was put to Prof Woolf, he disputed it on the basis that he had had extensive discussions about the theory with others in the field between 1983 and 1996 (and subsequently). I accept that evidence, and I also accept that Prof Woolf did his best to put himself into the position of the ordinary skilled neuroscientist. Nevertheless, it was clear from his evidence that, particularly during the period up to the priority date, he had a strong focus on central sensitisation which would not necessarily have been shared by the ordinary skilled neuroscientist.

16. Secondly, counsel submitted that Prof Woolf's views were significantly influenced by post-priority information or materials that were not part of the common general knowledge at the priority date. Counsel gave a number of examples of this. It is, of course, always very difficult for expert witnesses in patent cases entirely to avoid hindsight. I am sure that Prof Woolf did his best to do so, but nevertheless I consider that there is some force in this submission.

17. Thirdly, counsel submitted that Prof Woolf had tended to argue Warner-Lambert's case rather than provide impartial evidence. Again, counsel gave a number of examples of this. This is a more serious criticism than either of the previous two, and I have considered it with care. I am sure that Prof Woolf was trying to be independent and impartial, and I have no doubt that much of the time he succeeded in this. Nevertheless, I have to say that his evidence did give me the strong impression that some of the time, and no doubt unconsciously, he was supporting Warner-Lambert's case. I suspect that this may be explained by his prior participation in the US proceedings.

18. For all three reasons, I have concluded that Prof Woolf's evidence must be approached with a degree of caution. Nevertheless, as will appear, much of his evidence was supported by other evidence, and thus I have accepted many of the points he made.

Clinicians

19. Mylan and Actavis called Dr John Scadding OBE, who is Emeritus Honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, part of University College London Hospitals Foundation NHS Trust, and Emeritus

Academic Dean at the Royal Society of Medicine. He obtained a BSc in Anatomy from UCL in 1969 and an MB BS from UCL in 1972. He trained in general medicine and then in neurology at University College Hospital, the Royal Free Hospital and the National Hospital for Nervous Diseases (as it was then called). During this period he undertook research into peripheral nerve injury in mice which led to a clinical trial of propanolol for post-traumatic neuralgia, for which he was awarded an MD. He was appointed as Consultant Neurologist at the National Hospital and Whittington Hospital in 1982. From 1982 to 2008 he was Honorary Senior Lecturer at the Institute of Neurology. He has also held various clinical consultant/adviser positions to St Luke's Hospital for the Clergy (1983 to 2002), the Ministry of Defence (1983 to present), King Edward VII Hospital for Officers (1993 to 1995), the Royal Navy (1983 to 2003), the Royal Society of Musicians (1996 to 2006) and the Royal Air Force (1997 to present). He was elected a Fellow of the Royal College of Physicians in 1988. In 1994 he was a member of the International Association for the Study of Pain's ("IASP's") Task Force on Taxonomy (as to which, see below). He has published 115 scientific papers. He was awarded an OBE earlier this year.

20. Counsel for Warner-Lambert pointed out that Dr Scadding had no experience of drug development, and I have taken this into account in his assessing his evidence. Counsel rightly accepted, however, that Dr Scadding's evidence was clear and fair.

21. Warner-Lambert called Professor Daniel Clauw, who is Professor of Anesthesiology, Medicine (Rheumatology) and Psychiatry at the University of Michigan Medical School and Director of the University of Michigan's Chronic Pain and Fatigue Research Center. After undergraduate education at the University of Michigan, he obtained an MD from the University of Michigan Medical School in 1985. From 1985 to 1988 he undertook an Internal Medicine Residency, and from 1988 to 1990 a Rheumatology Fellowship, at Georgetown University Medical Center. From 1990 to 1991 he was an Instructor, from 1991 to 1997 he was Assistant Professor of Medicine and from 1997 to 2002 he was Associate Professor of Medicine and Orthopedics and Director of the Rheumatology Fellowship Program at Georgetown. In 1999 he founded the Chronic Pain and Fatigue Research Center at Georgetown, which he subsequently moved to Michigan. He has held his current positions since 2002, although the title of his chair has changed in that time. He has edited several books about pain, written about 35 book chapters and published more than 200 articles. He has consulted for numerous pharmaceutical companies and has received a number of awards.

22. As counsel for Mylan and Actavis pointed out, although Prof Clauw had experience of treating patients with a wide range of painful conditions, he generally treated patients with musculoskeletal conditions, and his particular speciality at around the priority date was the treatment of fibromyalgia and related conditions (such as eosinophilia myalgia syndrome, interstitial cystitis, vulvodynia, chronic fatigue syndrome and Gulf War syndrome). Counsel rightly accepted that Prof Clauw was a fair witness who tried to assist the court. Indeed, counsel relied on the fact that some of Prof Clauw's evidence contradicted that of Prof Woolf.

Factual witnesses

23. Mylan and Actavis adduced evidence from two witnesses of fact, neither of whom were cross-examined by Warner-Lambert:

i) Professor Howard Fields. Since 1972 he has been at the University of California, San Francisco, where he is now a Professor in Residence at the Department of Neurology. From 1973 to 2009 he was a Staff Neurologist at the University of California, Hospitals and Clinic. His clinical work has always focused on the treatment of pain, particularly neuropathic pain. By the mid 1990s his greatest interest was in the treatment of post-herpetic neuralgia ("PHN") and reflex sympathetic dystrophy ("RSD"). His evidence addressed the treatment options for neuropathic pain in the USA in the 1990s, his knowledge of the use of gabapentin for treating pain in the USA in 1996 and his own use of gabapentin to treat pain in the USA in 1996.

ii) Professor Gary Bennett. From 1978 to 1996 he was a researcher at National Institute of Dental Research in Bethesda, Maryland. Subsequently he spent five years at Allegheny University of Health Sciences before moving to McGill University as Professor and Canada Senior Research Chair. He now divides his time between McGill and a role as Adjunct Professor at the Department of Anethesiology at the University of California San Diego. His evidence addressed experiments he undertook in 1994 and 1995 involving the use of gabapentin in the chronic constriction injury model of pain in rats in the light of being informed of the data in Mellick, and his subsequent involvement in the Parke-Davis Gabapentin Advisory Board.

24. Warner-Lambert adduced factual evidence from Dr Berkeley Phillips, the Medical Director of Pfizer and the UK Medical Lead for Pfizer Group's Global Innovative Pharma business. His witness statement presented IMS prescribing data for gabapentin for 1996 and 1997. Dr Phillips was not cross-examined by Mylan and Actavis on this evidence.

The witnesses: infringement and threats

Factual witnesses

25. Warner-Lambert and Pfizer called three factual witnesses in relation to infringement and threats. First, Paula Tully, Head of the Pfizer Group's Global Established Pharma business in the UK. She gave evidence about the market for pregabalin in the UK, about sales of Lyrica, about the steps taken by Pfizer to address Lyrica's loss of exclusivity and about the alleged threats made by Pfizer. I regret to say that Ms Tully was an unimpressive witness. She appeared more concerned to articulate Pfizer's corporate position than to answer the questions put to her. Furthermore, she had not taken adequate care over the preparation of her evidence. In particular, the cross-examination on the section of her second witness statement on the purchasing practices of Pfizer's pharmacy customers showed that it made no sense and Ms Tully was unable to explain it. It was evident that she had just adopted material prepared by others without understanding it. I was left wondering how much of the rest of her evidence was also prepared by others.

26. Secondly, Dr Phillips. Dr Phillips mainly presented IMS data about sales of pregabalin in 2014 and 2015. He also gave a little evidence about the steps taken by Pfizer to address Lyrica's loss of exclusivity.

27. Thirdly, Nicola Dagg, a partner at Allen & Overy, who has conduct of this matter on behalf of Warner-Lambert. She gave evidence which was partly first-hand and partly hearsay about instances of the dispensing of generic pregabalin for pain. She was not cross-examined on this evidence.

28. Actavis called two factual witnesses in relation to infringement and threats. First, Jonathan Wilson, Managing Director of Actavis UK. He was a straightforward and fair witness, and I accept his evidence without reservation.

29. Secondly, Claire Wright, Operations Manager of John Preddy Co Ltd, a group of ten pharmacies in the South East and South West of England, and superintendent pharmacist of six of the ten. She was an impressively clear and direct witness. Again, I accept her evidence without reservation.

30. The Secretary of State called one witness, namely Jeanette Howe, who has been Head of Pharmacy in the Medicines, Pharmacy and Industry Division of the Department of Health since 2002. She is a registered pharmacist. She has been a senior civil servant at the Department of Health, working in the area of pharmacy, for 14 years. She gave evidence about a number of aspects of the healthcare system in England. Neither of the other parties cross-examined her on this evidence.

Expert witnesses

31. Warner-Lambert and Pfizer called three expert witnesses in relation to infringement. First, Dr Alastair Bint. He obtained an MB ChB from the University of Edinburgh in 1998. Between 1998 and 2003 he worked in hospitals and obtained a number of Diplomas. He has been a qualified general practitioner and member of the Royal Colleges of General Practitioners (RCGP) since 2003 and a Fellow of the RCGP since 2009. Between 2003 and 2005 he was a locum GP in a number of different practices. From 2006 to 2014 he was a partner in a GP practice in Guildford. Since then he has worked as an occasional freelance GP in several practices in the South-East, averaging about a day a week. For the past six years he has practised primarily as an expert witness, having prepared over 2000 reports in clinical negligence cases and having a particular speciality in coroner's cases. He has also undertaken various administrative and training roles. As counsel for Actavis submitted, Dr Bint's immersion in expert witness work meant that he was not ideally placed to assist the court with regard to the current prescribing practices of GPs.

32. Secondly, Jon Merrills. He obtained a degree in Pharmacy from Nottingham University in 1968. He then worked as a pharmacist until 1976. From 1976 to 1983 he was the managing director if a small group of community pharmacies based in Nottingham. From 1983 to 1995 he was successively Principal Pharmaceutical Officer, Superintendent Pharmaceutical Officer and Deputy Chief Pharmacist at the Department of Health. Since 1995 he has run his own consultancy business providing advice to pharmaceutical companies, community pharmacies and health authorities. He also spends half a day a week as a pharmacist consultant at an independent community pharmacy in Nottinghamshire, but he frankly acknowledged that the purpose of this was to obtain material for the next edition of his book. He is the author of *Pharmacy Law and Practice* (5^{th} ed) and has contributed to other textbooks. As counsel for Actavis submitted, Mr Merrills was a fair witness, but he was not best placed to assist the court with regard to the current practices of pharmacists.

33. Thirdly, Dr Phillips. He qualified as a doctor in 1993 after studying at the University of Cambridge and training at St Mary's Medical School in London. He then specialised in cardiology. He joined Pfizer's Medical Department in 2001 and became Medical Director in 2009. As Medical Director, he is responsible for the medical aspects of all of Pfizer's products in the UK, including both clinical and regulatory issues. Using his clinical knowledge, Dr Philips reinterpreted the IMS data relating to sales of pregabalin as discussed below. Dr Phillips was placed in a difficult position for two reasons. The first is that he was a senior employee of Pfizer who had originally prepared the evidence contained in his second witness statement on the basis that it was all factual evidence. After I had ruled that some of it was expert evidence, but given Warner-Lambert and Pfizer permission to adduce that expert evidence, Dr Phillips made a third witness statement in which he confirmed that, subject to certain minor clarifications, the views he had expressed were consistent with the duties of an expert. Secondly, it became clear in cross-examination that the exercise reported by Dr Phillips had been mainly carried out by others, although he had gone through it and satisfied himself as to its correctness. Furthermore, the two individuals who had done most of the work had doctorates in unspecified scientific disciplines, and were not medically qualified. I have no doubt that Dr Phillips did his best to discharge his duties as an expert, but for these reasons I consider that his evidence must be approached with a degree of caution.

34. Actavis called two expert witnesses in relation to infringement. First, Dr Brian Curwain. He obtained a degree in Pharmacy from Brighton School of Pharmacy in 1968 and a PhD in Pharmacology from St Mary's Medical School in 1972. From 1973 to 1988 he was a lecturer in Physiology at St Mary's Hospital Medical School and also (from 1985) Senior Pre-Clinical Tutor. For much of this time he continued to practice as a locum community pharmacist. From 1988 to 1999 he worked full-time as a community pharamacist. From 1999 to 2001 he was a Prescribing Advisor to New Forest Primary Care Group. From 2002 to 2007 he was Chief Pharmacist for New Forest Primary Care Trust and also (from 2004 to 2006) Head of Primary Care. Since 2007 he has worked as a pharmacist, freelance pharmacy consultant and clinical scientist in a variety of roles. He is the author of more than 50 scientific articles. Dr Curwain was knowledgeable, measured and fair in his evidence.

35. Secondly, Dr Neill Jones. He received an MB BS from Newcastle University Medical School in 1981. From 1986 to 1998 he practised as a general practitioner. During this period he was responsible for the introduction of an IT system into the practice. Between 1984 and 1988 he was involved in a number of projects at the Centre for Coding and Classification in Loughborough. In particular, he was involved in the development of the Read Codes, Clinical Terms Version 3. From 1994 to 2004 he was Head of Informatics at the Sowerby Centre for Health Informatics at Newcastle University. From 2004 to 2006 he was Clinical Lead at Accenture, from 2006 to 2009 he was Clinical Lead at BT and from 2009 to 2012 he was Clinical Director at First Databank Europe. In all of these roles he was heavily involved in health information systems. He is currently Clinical Lead for the GP Systems of Choice program at the Health and Social Care Information Centre ("HSCIC"). In addition he consults as a health informatics expert for a large NHS organisation. Since 1998 he has continued to practice part-time as a GP. Dr Jones was outstandingly well-qualified to give expert evidence in this case, since he had both extensive experience as a GP, including personal experience of prescribing pregabalin, and 30 years' experience

with medical coding systems. He was also scrupulously objective and fair. I have no hesitation in placing great weight on his evidence, and in preferring it to that of Dr Bint and Dr Phillips where they are in conflict.

Technical background

36. The parties did not provide the court with a technical primer in this case. Even though there are substantial disputes as to common general knowledge, it would have been preferable to have agreed a technical primer dealing with the uncontentious technical background. This is particularly so because the expertise of the neuroscientist and that of the clinician is closely related, and thus there was inevitable overlap between the experts' reports on each side.

The nervous system

37. The nervous system comprises two main parts: the central nervous system ("CNS") and the peripheral nervous system ("PNS"). The CNS comprises the brain and spinal cord and the PNS comprises the nerves outside those structures.

38. The PNS is divided into the somatic nervous system and the autonomic nervous system. It is the somatic nervous system that is involved in the detection of noxious stimuli. The somatic system consists of afferent (sensory) neurons, which transmit impulses from the PNS to the CNS and efferent (motor) neurons, which transmit impulses from the CNS to the PNS.

39. The nervous system comprises two types of cells: neurons, which transmit information through electrical and chemical signals; and glial cells, which support and protect neurons.

40. Nerve endings have specific protein receptors which bind neurotransmitters or other chemical activators and cause the membrane to depolarise. This, in turn, leads to the opening of voltage-gated sodium channels, allowing the influx of Na^+ ions into the cell, which causes an action potential to be set up. The action potential is transmitted along the length of the axon (nerve fibre) to the axon terminal where it depolarises the membrane, leading to the opening of voltage-gated calcium channels. Ca^{2+} ions flood into the terminal through these channels and, in turn, trigger the release of neurotransmitters into the synaptic cleft between neurons. The neurotransmitters bind to receptors in the membrane of the adjacent neuron, either exciting or inhibiting it.

41. Various types of neurons are responsible for transmitting information about different types of stimuli from the PNS to the CNS. These include Aα, Aβ, Aδ and C fibres:

    i) Aα and Aβ fibres transmit information about low intensity innocuous stimuli such as touch, pressure and vibration;

    ii) Aδ fibres transmit information about non-painful cold, painful mechanical and heat stimuli; and

    iii) C fibres transmit information about noxious heat and mechanical or chemical stimuli.

42. Aα, Aβ, Aδ and C fibres are known as primary sensory neurons. Their cell bodies are situated in the dorsal root ganglion, in close proximity to the spinal cord and their centrally-directed axon processes terminate in the dorsal horn of the spinal cord. The dorsal horn is a complex, multi-layered structure of neurons in which different fibres terminate at different layers.

43. So-called projection cells in the upper layer of the dorsal horn are innervated directly and indirectly by Aδ and C fibres. Deeper within the dorsal horn are "wide dynamic range" neurons which receive inputs from Aα and Aβ fibres as well as both direct and indirect inputs from Aδ and C fibres. By this anatomical arrangement, the wide dynamic range neurons receive sensory information concerning both painless and painful events for onward transmission to the brain.

44. Within the laminated structure of the dorsal horn, signals from Aδ and C fibres may be inhibited by painless inputs from Aα and Aβ fibres, a process known as "segmental inhibition". Aδ and C fibre outputs can also be inhibited by descending pathways from the brainstem, a process known as "descending inhibition".

Pain

45. In 1994 the IASP published the second edition of its *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*, prepared by a Task Force on Taxonomy of which Dr Scadding was a member. The second edition defined "pain" as follows:

> "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".

Types of pain

46. In 1996 pain was classified into a number of different types, but the distinctions between these categories were neither absolute nor consistently understood. In particular, neuroscientists and clinicians would not necessarily categorise pain types in precisely the same way. With those caveats, the following types of pain were generally recognised.

47. *Nociceptive pain*. In the normally functioning human body, pain plays an important bioprotective role: it alerts the brain to the presence of a noxious stimulus so that appropriate avoidance measures may be taken. Noxious stimuli such as heat, extreme cold, intense mechanical pressure and chemicals stimulate the Aδ and C fibres, which are also known as nociceptors. Those fibres then transmit impulses via the spinal cord to the brain where they are perceived as pain. This is referred to as nociceptive pain.

48. *Inflammatory pain*. Inflammatory pain is a type of nociceptive pain. The inflammatory response to an injury involves the release of various chemical mediators which increase the sensitivity of nociceptors, causing pain both at the site of injury and in the surrounding area. Inflammatory pain also plays a bio-protective role in that it promotes healing by causing the body to rest or isolate the injured part so as to minimise contact with it.

49. One of the features of nociceptive/inflammatory pain is that it resolves with treatment of the underlying cause. For example a swollen finger will no longer hurt once the inflammation has died down; gout pain will be resolved by treating the gout; post-operative pain will usually resolve once the surgical wound has healed; and the pain associated with sunburn will subside once the burn has subsided.

50. *Neuropathic pain*. In contrast to nociceptive/inflammatory pain, another type of pain known as neuropathic pain exists which is pathological and serves no bio-protective function. Neuropathic pain is caused by damage to the somatic nervous system itself. The second edition of the *Classification of Chronic Pain* defined "neuropathic pain" as:

> "pain initiated or caused by a primary lesion or dysfunction of the peripheral or central nervous system".

51. The lesion or dysfunction can occur either in the PNS (referred to as peripheral neuropathic pain) or in the CNS (referred to as central neuropathic pain or simply central pain). This lesion or dysfunction causes changes both at the site of damage and centrally. Such changes typically involve the development of neuronal hyperexcitability.

52. The symptoms of neuropathic pain are quite different to those associated with nociceptive/inflammatory pain. Patients report a different quality of pain - they use terms such as "raw", "gnawing", "burning' and "deep aching" to describe their pain – and also report shooting or electric-shock like pains. Unlike nociceptive/inflammatory pain, there is frequently a delay in the onset of neuropathic pain after the initiating injury (although this is not always the case). Furthermore, whereas nociceptive/inflammatory pain subsides either when the noxious stimulus is removed or when the originating injury heals, neuropathic pain often persists for many years and sometimes for life. Finally, the symptoms of neuropathic pain can vary from patient to patient even within a single diagnostic category.

53. Neuropathic pain is severe and debilitating. Co-morbidities such as depression, anxiety, sleep disturbance, social isolation, reduced employment prospects and drug misuse are common. In 1996 there was a significant need for further and better treatments for neuropathic pain.

Causes of neuropathic pain

54. A wide range of diseases affecting the nervous system may cause neuropathic pain. These include diabetic (peripheral) neuropathy ("DPN"), PHN, trigeminal neuralgia and phantom limb pain. In 1996 the prevailing view was that RSD should be included as a cause of neuropathic pain, although not everyone agreed with this.

DPN and PHN

55. DPN and PHN are two of the most common causes of neuropathic pain. DPN results from damage to peripheral nerves caused by diabetes. PHN is a complication of shingles.

Trigeminal neuralgia

56. Trigeminal neuralgia is a specific type of neuropathic pain characterised by a stabbing or electric-shock like pain. The pain can be triggered by everyday activities and is believed to be caused by hyperexcitability of the trigeminal nerve.

Fibromyalgia

57. Fibromyalgia is a rheumatic condition characterized by muscular or musculoskeletal pain with stiffness and localized tenderness at specific points on the body.

Idiopathic pain

58. Idiopathic pain is pain of unknown origin.

Hyperalgesia and allodynia

59. The term "hyperalgesia" is used to describe the increased response to a stimulus that is normally painful. Primary hyperalgesia occurs at the site of injury, whereas secondary hyperalgesia is pain experienced in areas surrounding the injured site. Hyperalgesia may be experienced in relation to thermal or mechanical stimuli, and hence referred to as thermal hyperalgesia or mechanical hyperalgesia. The term "allodynia" is used to describe pain that is experienced in response to stimuli that would not normally be expected to cause pain (e.g. light touch). Again, one can distinguish between thermal and mechanical allodynia. In addition, there is a distinction between dynamic and static allodynia, depending on whether the stimulus moves across the area in question or not.

Sensitisation

60. Neurons can become sensitised i.e. they display increased activity with a lower threshold to stimulation. In 1996, it was known that such sensitisation could occur both at the periphery and centrally in the dorsal horn.

Central sensitisation

61. A large part of the expert evidence relating to the validity of the Patent was devoted to the topic of central sensitisation. It is important to appreciate that, at the priority date, the term "central sensitisation" might be used by a neuroscientist or clinician in one of two ways. (The term was not defined in the IASP *Classification of Chronic Pain* in 1994.) The first (and probably more common) way was to use it narrowly and specifically to denote the theory devised by Prof Woolf (referred to for convenience in much of the evidence as *central sensitisation* or "central sensitisation in the italicised sense"). The second way was to use it more broadly and loosely to denote not only central sensitisation in the narrow sense, but also other central amplification and augmentation mechanisms. In this judgment I shall endeavour to confine use of the term "central sensitisation" to the first sense. The following account of central sensitisation in that sense is taken almost verbatim from paragraphs 58-61 of Prof Woolf's first report.

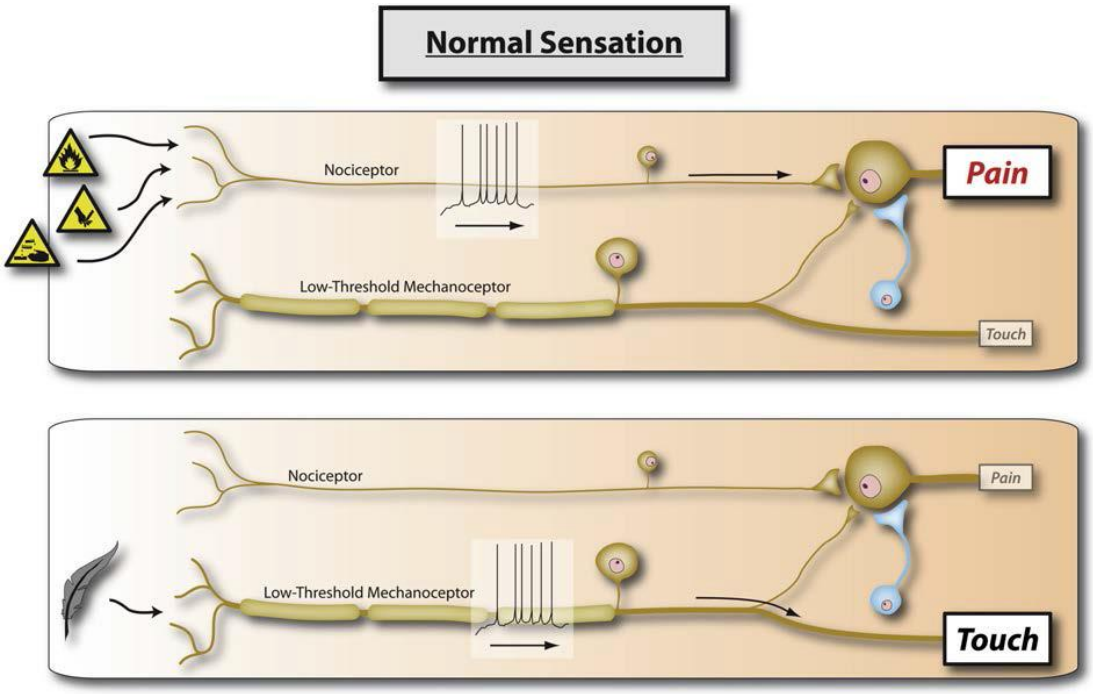
62. Central sensitisation was first discovered as a response in the spinal cord to a barrage of activity in C fiber nociceptors that detect noxious stimuli and connect the

peripheral nervous system to the central nervous system. This form of central sensitisation is now known as "activity-dependent central sensitisation" and can be induced by producing trains of action potentials in nociceptors by diverse means; for example, repeated noxious heat stimuli, tissue injury, tissue inflammation, injury to a nerve or ectopic activity in an injured nerve, chemical irritants that activate nociceptors, and electrical stimulation of nociceptors. This activity in nociceptor sensory fibers triggers an increase in synaptic strength in neurons in the dorsal horn of the spinal cord; changes called "synaptic potentiation".

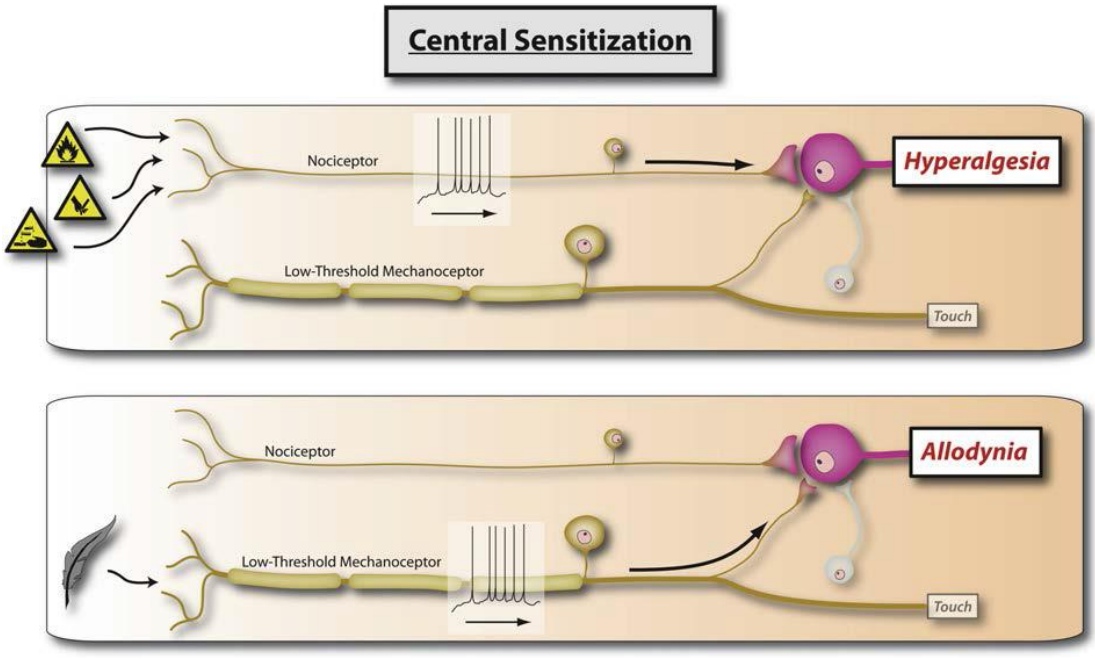
63. A critical component of activity-dependent synaptic potentiation is mediated by N-methyl-D-aspartate ("NMDA") receptors. The NMDA receptor is a glutamate receptor and is an ion channel protein expressed by neurons. The pore of the NMDA ion channel receptor is normally blocked by a magnesium ion in a voltage-dependent way. When the membrane potential of a neuron is reduced (becomes more depolarised), the magnesium block of the NMDA receptor is relieved and the ion channel receptor now responds to synaptic release of glutamate, and this augments, facilitates, amplifies or sensitises the response of the neuron. In addition, the NMDA receptor allows calcium to enter the neuron, which then acts as a second messenger producing further changes in the neuron and its excitability that persist after the initiating barrage of activity. NMDA receptor antagonists are often used to validate preclinical models of central sensitisation due to the crucial role of NMDA receptors.

64. The result of activity-dependent central sensitisation includes (a) dynamic mechanical allodynia, (b) mechanical secondary hyperalgesia, and (c) temporal summation, such that repeated stimuli produces a progressive increase in pain, and a spread of pain sensitivity away from the site of injury. This phenomenon has been described or characterised as an increase in "gain" in the dorsal horn, where pharmacological treatment to reduce the "gain" may treat the underlying pain symptoms. Such treatment typically does not reduce or block nociceptive pain, but normalises pain hypersensitivity.

65. In normal sensation, the somatosensory system is organised such that the highly specialised primary sensory neurons that encode low intensity stimuli only activate those central pathways that lead to innocuous sensations, while high intensity stimuli that activate nociceptors only activate the central pathways that lead to pain and the two parallel pathways do not functionally intersect. This is mediated by the strong synaptic inputs between the particular sensory inputs and pathways and inhibitory neurons that focus activity to these dedicated circuits.



66. With the induction of central sensitisation in somatosensory pathways which increases in synaptic efficacy and reductions in inhibition, a central amplification occurs enhancing the pain response to noxious stimuli in amplitude, duration and spatial extent, while the strengthening of normally ineffective synapses recruits subliminal inputs such that inputs in low threshold sensory inputs can now activate the pain circuit. The two parallel sensory pathways converge.



67. It should be noted that, as Prof Woolf explained later in his first report, thermal hyperalgesia in the carrageenin test described below was understood to be primary hyperalgesia. Accordingly, it was not regarded as an indicator of central sensitisation, but rather of peripheral sensitisation.

Animal models

68. A number of pre-clinical animal models were available in 1996 which were used to test new drugs for the treatment of pain. These tests involved observing the response of rats to stimuli. The efficacy of new drugs would be examined in a group of rats (usually six) and compared with a control group to identify alterations in behaviour.

69. One group of models involved injecting a noxious agent into the rat's paw. This group included the following tests. (Note that I have included for completeness descriptions of two tests which I shall not refer to again.)

70. *Rat paw formalin test*: formalin (a solution of formaldehyde in isotonic saline) is injected into a rat's paw. The rat's behaviour is then monitored over the next hour and the amount of time that the rat spends licking or biting the injected paw is recorded. There are two phases in the test: the early (or first) phase of licking and biting, which lasts around 10 minutes, followed by a late (or second or tonic) phase of licking and biting which starts at around 10 minutes and lasts for about 45 minutes.

71. *Carrageenin test*: carrageenin, an inflammatory agent, is injected into the sole of the paw of a rat and tests are carried out to determine the extent of thermal and/or mechanical hyperalgesia.

72. *Complete Freund's Adjuvant ("CFA") test*: CFA, another inflammatory agent, is injected into a rat's paw and tests are carried out to determine the extent of thermal and mechanical hyperalgesia.

73. A second group of models involved nerves in the rat being damaged (either constricted, crushed or ligated). This group included the following tests.

74. *Chronic constriction injury ("CCI") model*: a sciatic nerve is ligated and the animal tested for pain threshold using thermal and mechanical tests. This model is also referred to as the "Bennett" model, since it was devised by Prof Bennett. It was a well-recognised model of neuropathic pain.

75. *Spinal nerve ligation model:* this model requires a tight ligature around the L5 and L6 spinal segmental nerve as it exits the dorsal root ganglion, which damages all the axons leaving a dorsal root ganglion. This is also called the "Kim and Chung" model.

76. *Neuroma model*: a peripheral nerve in the paw is transected and ligated to prevent regeneration, leading to encapsulation of the nerve and formation of a neuroma. The animal is observed for autotomy (self-mutilation of the paw), which it was believed correlates with the neuropathic pain sensation of nerve injury.

77. A third type of model is where the rat's paw is incised, but the nerve is not damaged. This included the *postoperative pain model*: under anaesthetic the rat paw's plantaris muscle is incised and the wound closed by suture. After 24 hours the rat is assessed for mechanical hyperalgesia and tactile allodynia.

Treatments for pain

78. A number of different drugs can be used effectively to treat nociceptive/inflammatory pain including simple analgesics (e.g. paracetamol), non-steroidal anti-inflammatory

drugs or NSAIDs (e.g. aspirin, ibuprofen), weak opioids (e.g. dihydrocodeine), mid-strength opioids (e.g. tramadol) and strong opioids (e.g. oxycodone and morphine).

79. Unlike nociceptive/inflammatory pain, for which well-known and efficacious treatments were available in 1996, neuropathic pain was (and still is) notoriously difficult to treat. In 1996 an exception was a type of neuropathic pain called trigeminal neuralgia, which responded well to carbamazepine (an anti-convulsant). The main types of drugs used to treat neuropathic pain at the priority date were:

    i) tricyclic anti-depressants, notably amitriptyline, and other anti-depressants;

    ii) local anaesthetics such as lidocaine and membrane-stabilising drugs such as mexiletine;

    iii) clonidine, which acted in the CNS;

    iv) opioids; and

    v) certain anti-convulsants (as to which, see further below).

80. As explained in more detail below, NSAIDs were not considered to be effective for the treatment of neuropathic pain.

Gabapentin

81. Gabapentin is a derivative of the natural inhibitory neurotransmitter γ-aminobutyric acid (GABA). In 1996 gabapentin was known to be an effective anti-convulsant and had been licensed for such use in the UK in February and the USA in December 1993. It was marketed by Parke-Davis under the trade mark Neurontin. The mechanism of action of gabapentin was not understood.

Pregabalin

82. Pregabalin is another derivative of GABA. Pregabalin is the (S) or (+) enantiomer of 3-isobutyl GABA (sometimes referred to as 3-isobutylgaba). It is also referred to by its chemical name (S)-3-(aminomethyl)-5-methylhexanoic acid. The racemate (i.e. the mixture of the (S) and (R) enantiomers) is variously referred to as isobutyl GABA, 3-isobutyl GABA and (RS)-3-isobutyl GABA. In July 1996 pregabalin had not yet received a marketing authorisation.

"Off-label" prescribing

83. Pharmaceuticals must receive a marketing authorisation (or licence) from a competent authority before they can be marketed. The competent authority will require evidence that the substance in question is both efficacious and safe. Marketing authorisations are granted for one or more specific indications. Generally speaking, a prescribing doctor is entitled to rely upon the fact that a drug has a marketing authorisation for a particular indication when prescribing that drug for that indication. In addition, however, prescribing doctors can, in the exercise of their own clinical judgment and at their own risk, prescribe an authorised drug for an unauthorised indication. Because it has been authorised, it should be generally safe (although care will need to be taken in relation to known side effects). Even if it has not been authorised for the indication in

question, the prescribing doctor may have a reason for believing that the drug will be effective in treating that indication. This is commonly referred to as "off-label" prescribing.

IMS data, Read codes and ICD 10 codes

84. IMS Health ("IMS") is a global information and technology services company that provides information to subscribers with respect to the prescribing and sales of pharmaceutical products in the UK. In particular, it provides sales data obtained from approximately 10,900 retail pharmacies. In addition, it provides data based on returns from approximately 500 GPs (about 0.77% of the current total GP population of 65,000 GPs) which is used to estimate the number of prescriptions of drugs that are used to treat different indications by recording the diagnoses given by the GPs when prescribing. As I shall explain in more detail later, the diagnoses are recorded by the GPs using prescription software and by means of Read codes. Currently, but not in the past, the Read codes are "translated" by IMS into ICD 10 classifications, and the ICD 10 classifications are then analysed by IMS to its produce estimates.

85. Read codes (so called because they were initially devised by Dr James Read) are a thesaurus of clinical terms, various versions of which have been used by the NHS since about 1985. They provide a standard vocabulary by which clinicians can record findings in patients' records. Each Read code is a unique alpha-numeric code that identifies a clinical term that can be used to described, for example, a patient's symptoms or the details of a blood test. Read codes are organised in a number of chapters. Chapters 1-9 are used most frequently by GPs and cover history, examination, procedures and administration. GPs can allocate the reason for a medication to any of these categories. As there is often more than one way of describing the same clinical concept, a number of synonymous terms are available. This is managed by having a Preferred Term that clinicians should use and Synonyms; but as the system has developed it is not always the case that Synonyms are actually precisely synonymous with the Preferred Term. Although Read codes are a very useful way of recording clinical information, seeing a Read code in isolation gives no great insight into what was in the mind of a clinician when they prescribe a particular medication, not least because of the time pressure and heavy workload that GPs are under.

86. International Classification of Diseases version 10 (ICD 10) is a diagnostic classification that is used to classify diseases and other health problems. ICD 10 does not cover clinical concepts beyond the patient diagnosis level. As a result, many Read codes have no corresponding ICD 10 classification or correspond with varying degrees of accuracy. For this reason, mapping Read codes accurately to ICD 10 classifications is a difficult exercise. Furthermore, ICD 10 is not well suited to analysing conditions based on symptoms with few objective criteria. Thus the mapping problem is compounded when dealing with pain.

87. It is convenient to note at this point that the manner in which IMS maps Read codes to ICD 10 classifications is proprietary to IMS and is not in evidence before this court. Dr Jones was content to assume that it was as robust as it could be within the constraints described above.

Introduction to second medical use patents with claims in Swiss form

88. It has increasingly been recognised over the past 30 years or so that it is important to find new uses for existing medicines. Existing medicines have the advantage that they are known compounds which have been shown to have acceptable safety profiles, and therefore need much less testing from that perspective. Experience shows that a compound which has therapeutic benefit in one application not infrequently turns out to have therapeutic benefit in another application (sometimes more than one other application) which may be quite different to the first application. Thus there is significant potential and value in finding such second (and third, etc.) medical uses. Discovering such second medical uses requires difficult and expensive research, however. How is such research to be funded? The answer which has been provided by the European patent system is to grant patents for second (and subsequent) medical uses of known compounds. The monopoly thus conferred on the inventor who finds the second medical use provides the return on the investment required to fund the research.

89. There are two significant obstacles to the grant of patents for second medical uses under the European patent system: first, the compounds themselves are not new, which is a fundamental requirement for patentability of a product; and secondly, methods of treatment of the human (or animal) body by therapy are not patentable, in order to protect doctors from claims for patent infringement. The European patent system has attempted to overcome these obstacles in two ways.

90. The first way was through a piece of judicial lawmaking which fudged some of the difficult issues. This involved the use of claims in Swiss form i.e. "use of substance X for the preparation of a medicament (or pharmaceutical composition) for treating indication Y" (a purpose-limited process claim): see G 05/83 *Eisai/Second medical indication* [1985] OJ EPO 64. The history of, and rationale for, granting patents with claims in this form was explained in detail by Jacob LJ giving the judgment of the Court of Appeal in *Actavis UK Ltd v Merck & Co Inc* [2008] EWCA Civ 444, [2009] 1 WLR 1186 at [7]-[49] and by Kitchin J (as he then was) in *Ranbaxy (UK) Ltd v AstraZeneca AB* [2011] EWHC 1831 (Pat), [2011] FSR 45 at [42]-[56].

91. The second way was through legislation, namely Article 54(5) of the European Patent Convention 2000, which enables the grant of claims in the form "product X for treating indication Y" (a purpose-limited product claim). These have now superseded claims in Swiss form, although patents with claims in Swiss form will continue to subsist for some time to come. This is a more satisfactory solution to the problems, although difficulties remain.

92. It is important to note that this case is exclusively concerned with claims in Swiss form. As the Technical Board of Appeal of the European Patent Office explained in Case T 1780/12 *University of Texas Board of Regents/Cancer treatment* [2014] EPOR 28 at [19]-[24], claims in EPC 2000 form have a different scope of protection to claims in Swiss form. It should not be assumed that anything I say in this judgment about Swiss form claims necessarily applies to EPC 2000 claims.

The Patent

93. The specification begins at [0001] with the following statement:

> "The present invention is the use of an analog of gamma-aminobutyric acid (GABA) in pain therapy, as the compound exhibits analgesic/antihyperalgesic action. Advantages of the use of the compound includes the finding that repeated use does not lead to tolerance nor is there a cross-tolerance between morphine and the compound."

94. The specification explains at [0002] that the compound of the invention is known to be useful in antiseizure therapy and that it has been suggested that the compound can be used as an antidepressant, anxiolytic and antipsychotic.

95. The invention is then summarised in the following terms (emphasis added):

> "[0003] The instant invention is a method of using a compound identified below in the treatment of pain, especially for treatment of chronic pain disorders. Such disorders *include, but are not limited to,* inflammatory pain, postoperative pain, osteoarthritis, pain associated with metastatic cancer, trigeminal neuralgia, acute herpetic and postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, burn pain, and other forms of neuralgic, neuropathic, and idiopathic pain syndromes.
>
> [0004] The compound is (S)-3-(aminomethyl)-5-methylhexanoic acid or a pharmaceutically acceptable salt thereof."

96. The detailed description of the invention begins as follows:

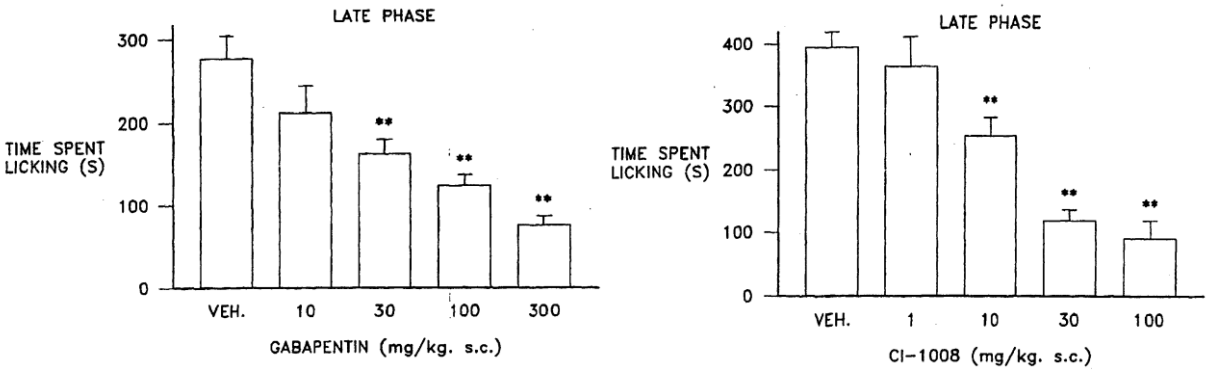
> "[0006] The instant invention is a method of using (S)-3-(aminomethyl)-5-methylhexanoic acid or a pharmaceutically acceptable salt thereof as an analgesic in the treatment of pain as listed above. Pain such as inflammatory pain, neuropathic pain, cancer pain, postoperative pain, and idiopathic pain which is pain of unknown origin, for example, phantom limb pain are included especially. Neuropathic pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain diabetics suffer from.
>
> [0007] The conditions listed above are known to be poorly treated by currently marketed analgesics such as narcotics or nonsteroidal anti-inflammatory drugs (NSAID) due to insufficient efficacy or limiting side effects."

97. The specification then discusses the synthesis of pregabalin (at [0008]-[0012]), formulation (at [0013]-[0014]) and dosage (at [0015]). In the course of doing so, it states (at [0013]):

> "The pharmaceutical can be used in a method for treating such disorders in mammals, including human, suffering therefrom by administering to such mammals an effective amount of the compound as described above in unit dosage form."

98. The remainder of the specification describes the results obtained from four animal pain models used to assess the efficacy of pregabalin (also referred to as CI-1008) compared with the racemate comprising pregabalin and the corresponding R-enantiomer (also referred to as PD 144550), gabapentin and/or morphine. The animal models are as follows.

99. *Rat paw formalin test*. This is discussed at [0005], [0016] and [0017]. The results for gabapentin, pregabalin and racemic 3-isobutyl GABA in the early and late phases are shown in Figs. 1a-1f. I reproduce the late phase results for gabapentin and pregabalin below.



The double asterisk indicates that the results were statistically significant at the $P<0.01$ level.

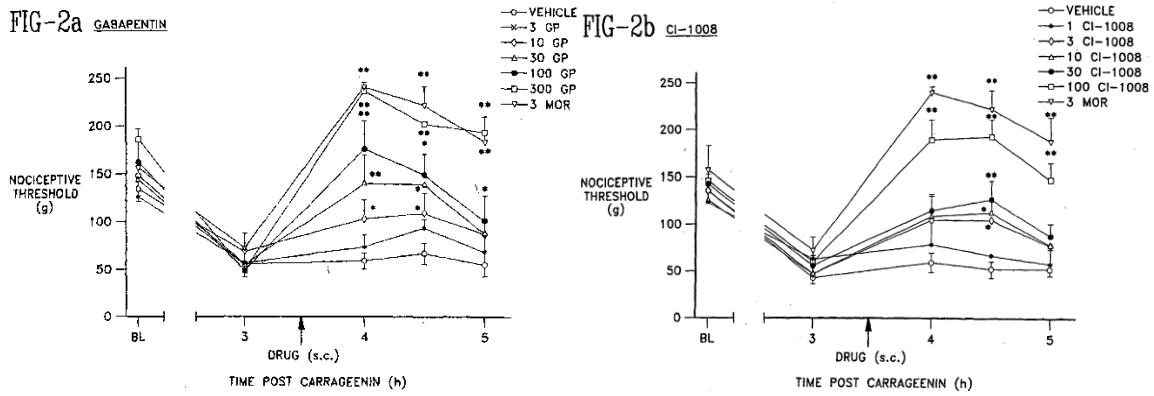
100. The specification states at [0017]:

> "The s.c. administration of gabapentin (10-300 mg/kg) or CI-1008 (1-100 mg/kg) 1 hour before formalin dose-dependently blocked the licking/biting behaviour during the late phase of the formalin response with respective minimum effective doses (MED) of 30 and 10 mg/kg (Figure 1). However, neither of the compounds affected the early phase at any of the doses tested. Similar administration of 3-aminomethyl-5-methyl-hexanoic acid [i.e. the racemate] produced only a modest blockade of the late phase at 100 mg/kg."

101. *Carrageenin-induced mechanical hyperalgesia*. This is discussed at [0005], [0018] and [0019]. The specification states that measurements were obtained using an Ugo Basile analgesiometer. As Prof Woolf explained, the experiment measured the responsiveness of the entire paw, and so included both the inflamed and non-inflamed

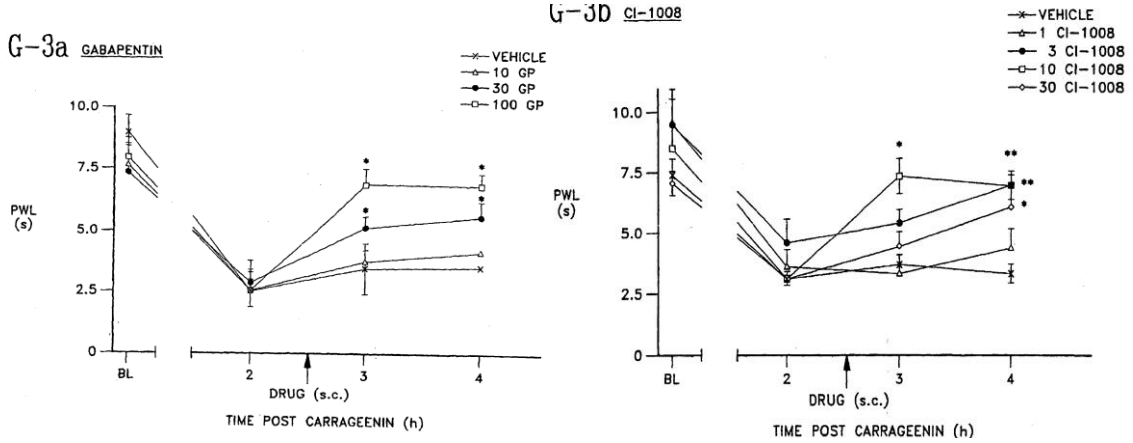
areas. It therefore does not distinguish secondary hyperalgesia from primary hyperalgesia for the reasons explained below.

102. The results are shown in Figs. 2a and 2b, which I reproduce below.



103. The specification concludes at [0019] that gabapentin and pregabalin both dose-dependently antagonised the hyperalgesia, with respective MED of 10 and 3 mg/kg.

104. *Carrageenin-induced thermal hyperalgesia*. This is discussed at [0005], [0018] and [0020]. The results are shown in Figs. 3a and 3b, which I reproduce below.



105. The specification concludes at [0020] that gabapentin and pregabalin both dose-dependently antagonised the hyperalgesia with an MED of 30 and 3 mg/kg respectively.

106. The specification goes on at [0021]:

> "These data show that gabapentin and CI-1008 are effective in the treatment of inflammatory pain."

The reference to "these data" is ambiguous: it is not clear whether this refers solely to the carrageenin model data or to the combination of the formalin test and the carrageenin model data. Neither side suggested this question is crucial, but Mylan and Actavis contend, and I agree, that the latter reading makes more sense.

107. *Post-operative pain model*. This is discussed at [0005] and [0024]-[0035]. The results are shown in Figs. 4a-4c, 5a-5b and 6a-6b. It is common ground that there are some

obvious typographical errors in the figure references in the text: [0031] should refer to Fig. 4, not Fig. 1; [0032] to Fig. 5, not Fig. 2; and [0033]-[0035] to Fig. 6, not Fig. 3. In this model morphine, gabapentin and pregabalin were compared in their effect on thermal hyperalgesia and tactile allodynia, which are both referred to several times as "nociceptive responses" (at [0030], [0032] and [0033]). The tactile allodynia study was conducted using von Frey hairs held in place for six seconds i.e. a static rather than a dynamic stimulus.

108. The specification concludes at [0031] that both gabapentin and pregabalin administered an hour *before* surgery dose-dependently blocked the development of thermal hyperalgesia, with an MED of 30 mg/kg and 3 mg/kg respectively, while morphine administered half an hour before surgery dose-dependently blocked the development of thermal hyperalgesia, with an MED of 1 mg/kg. It concludes at [0032] that both gabapentin and pregabalin dose-dependently prevented development of tactile allodynia, with an MED of 10 mg/kg in both cases, and that pregabalin maintained this effect for three days at a dose of 30 mg/kg, while morphine only prevented the development of tactile allodynia for three hours post-surgery at the highest dose tested of 6 mg/kg. It concludes at [0033] that the administration of 30 mg/kg pregabalin one hour *after* surgery blocked the maintenance of tactile allodynia and thermal hyperalgesia for 3-4 hours.

109. The specification goes on at [0035]:

> "The results presented here show that incision of the rat plantaris muscle induces thermal hyperalgesia and tactile allodynia lasting at least 3 days. The major findings of the present study are that gabapentin and S(+)-3-isobutylgaba are equally effective at blocking both nociceptive responses. In contrast, morphine was found to be more effective against thermal hyperalgesia than tactile allodynia. Furthermore, S-(+)-3-isobutylgaba completely blocked induction and maintenance of allodynia and hyperalgesia.

110. It should be noted that, rather curiously, the specification makes express reference to the Bennett and Kim and Chung models, but neither is used to assess pregabalin (or anything else):

> "[0022] The assay of Bennett G.J. provides an animal model of a peripheral mononeuropathy in rat that produces disorder of pain sensation like those seen in man (Pain, 1988;33:87-107).
>
> [0023] The assay of Kim S.H., et al., provides one experimental model for peripheral neuropathy produced by segmented spinal nerve ligation in the rat (Pain, 1990;50:355-363)."

The claims

111. Claims 1, 2 and 3 are as follows:

> "1. Use of [pregabalin] or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for treating pain.

> 2. Use according to Claim 1 wherein the pain is inflammatory pain,
>
> 3. Use according to Claim 1 wherein the pain is neuropathic pain."

112. Claims 4-14 are limited to various specific types of pain. Thus claim 4 is limited to "cancer pain", claim 5 to "post-operative pain" and so on. Of particular note are claim 6 to "phantom limb pain", claim 13 to "idiopathic pain" and claim 14 to "fibromyalgia pain".

The skilled team

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

114. In the present case it is common ground that the Patent is directed to a team consisting of a neuroscientist and a clinician. I shall refer to the members of the skilled team simply as "the neuroscientist" and "the clinician".

115. It is also common ground that the neuroscientist would be a pre-clinical researcher with an interest in developing new analgesics and knowledge of various animal models of pain. Such a person would typically have a master's degree or PhD in neuroscience, pharmacology or neurophysiology or a related biological field and would be familiar with the molecular physiology of pain and analgesia.

116. It is also common ground that the clinician would specialise in the treatment of pain. Mylan and Actavis contend that the Patent would be of particular interest to neurologists and anaesthetists, while Warner-Lambert contends that it would also be of interest to rheumatologists. In my view the evidence shows that both parties are right: the Patent is addressed to a range of clinicians, including rheumatologists, but it would be of particular interest to neurologists and anaesthetists. This gives rise to an issue as to whose common general knowledge is to be taken into account, which I will consider below.

117. There is no dispute that the neuroscientist and the clinician would work together. Warner-Lambert contends that, in the context of obviousness, the team would be led by the neuroscientist, but that, in the context of sufficiency, the team would be led by the clinician. Mylan and Actavis dispute this.

118. Counsel for Mylan and Actavis submitted that, as a matter of law, a skilled team could not be led by one member. I do not accept this. Counsel relied on the following statement by Jacob LJ in *Halliburton Energy Services Inc v Smith International (North Sea) Ltd* [2006] EWCA Civ 1715 at [14]:

> "Mr Burkill, in his skeleton argument, advanced an argument to the effect that where the skilled addressee was taken to be a team (because more than one skill was involved) then the law requires one member of the team to be the 'head' directing the others. Here the suggestion was that the head of the team would be a rock bit engineer who would be directing a computer model designer as some kind of assistant. That position was not pursued during the oral argument. And rightly so. If the addressee of a patent is a notional team of persons with differing skills, then it is a team with no boss. Each member of the team is assumed to play his/her own part."

I do not understand Jacob LJ to have meant that, as a matter of law, a skilled team can never be led by one member. As he said, each member of the team is assumed to play his (or her) own part. Depending on the facts of the case, that may involve one member taking the lead. Taking the lead is not the same thing as directing the other member as if the other member were a subordinate.

119. In the present case, counsel for Warner-Lambert relied on the evidence of Prof Wood and Dr Scadding that the team would be led by the neuroscientist. This is consistent with what appears from the documentary evidence, and it makes sense. Prof Wood and Dr Scadding did not differentiate between the two contexts, however, nor was it put to either of them that the position would differ. It is true that, as counsel for Warner-Lambert submitted, there is a difference in that, for the purposes of considering obviousness, the skilled team has not read the Patent, whereas for the purpose of considering sufficiency, the skilled team has read the Patent (see *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819, [2010] RPC 33 at [31]-[32] and [64] (Jacob LJ)). In the present case, however, the issue on sufficiency is, as explained in more detail below, one of plausibility in the light of the animal model results reported in the Patent. That is a matter on which the neuroscientist would inevitably take the lead.

Common general knowledge

The law

120. I reviewed the law as to common general knowledge in *KCI Licensing Inc v Smith & Nephew plc* [2010] EWHC 1487 (Pat), [2010] FSR 31 at [105]-[115]. That statement of the law was approved by the Court of Appeal [2010] EWCA Civ 1260, [2011] FSR 8 at [6]. I would add the following points.

121. First, in some cases the party attacking the patent seeks to build up the common general knowledge in order to bolster its case on its obviousness. In other cases the patentee seeks to build up the common general knowledge in order to bolster its case on sufficiency. In the present case both sides sought to build up different aspects of the common general knowledge for their respective purposes. As is common ground, whichever party seeks to establish that something is common general knowledge and whatever that party's purpose in doing so, the burden lies on the party seeking to establish the common general knowledge and the test to be applied is the same.

122. Secondly, in some cases the breadth of the claims is such that they cover two (or more) different fields and hence are addressed to persons skilled in both those fields. The fields may be different aspects of the same art or, in an extreme case, different arts altogether. In such circumstances it is legitimate to consider the question of obviousness from the perspective of each addressee, and hence in the light of that addressee's common general knowledge, although this does not mean that there cannot be invention in marrying two different arts: see *Inhale Therapeutic Systems Inc v Quadrant Healthcare plc* [2002] RPC 21 at [35]-[42] (Laddie J). Counsel for Mylan and Actavis accepted that, at least on the facts of the present case, the same approach should be applied to sufficiency i.e. it is enough if the invention can be performed by one of the addressees using that addressee's common general knowledge.

123. Thirdly, an issue arises in this case as to whether common general knowledge has a territorial dimension. What if a matter was known to persons skilled in the art in the USA, but not to persons skilled in the art in the UK? In *Teva UK Ltd v Merck & Co Inc* [2009] EWHC 2952 (Pat), [2010] FSR 17 Floyd J (as he then was) said:

> "101. A question arises as to whether it is sufficient to establish that a particular fact was known in the United Kingdom, or whether it is necessary to establish, where the art is an international one, that it was known more widely.
>
> 102. Mr Thorley maintained that the relevant common general knowledge was that in this country. Mr Birss was content to accept that proposition, whilst pointing out that where the art was an international one, it is relevant on the facts to take account of evidence that individuals abroad had not heard of it. Neither side showed any enthusiasm for arguing that common general knowledge had to be more extensive than the United Kingdom.
>
> 103. I am content to proceed on this legal basis, as I did not hear detailed argument on the point. It would seem to me to be an odd result if a patent for the United Kingdom could survive if it was obvious in the light of the common general knowledge in this country. A more difficult question may arise if a fact is only common general knowledge abroad. But that does not arise here."

124. The question does arise here. Counsel for Warner-Lambert submitted that matter relied on as being common general knowledge must be shown to be common general knowledge in the UK, but counsel for Mylan and Actavis disputed that this was necessary. Although I only received limited argument on the point, it seems to me that, at minimum, it must be shown that the matter in question was common general knowledge in the UK. The reason for this is that, whether one is concerned with the validity of a European Patent (UK), or a UK patent, one is concerned with a right in respect of the UK. It is true that the prior art may have been published anywhere in the world, but I do not think that alters the need for the skilled team to consider that art as if they were located in the UK. I do not think it matters that a fact was common general knowledge in (say) China, if it was not common general knowledge here. The position may be different if all the persons skilled in a particular art in the UK are

acquainted with the position in China, but no point of that kind arises here. I do not consider that this approach is contrary to Article 27(1) of TRIPS, which provides that "patents shall be available and patent rights enjoyable with discrimination as to the place of invention", as counsel for Mylan and Actavis submitted.

125. Fourthly, as is established by the authorities discussed in *KCI*, in order to acquire the status of common general knowledge, a matter must be generally known and generally regarded as a good basis for further action by the bulk of those engaged in the art in question. What amounts to being "generally regarded as a good basis for further action" is a context-dependent question. Thus a scientific theory does not have to have been generally accepted as correct if it is regarded as a reasonable working hypothesis by the bulk of those skilled in art. Furthermore, a theory may be regarded as a good basis for some forms of action (such as experiments *in vitro* or in animal models) even if not for others (such as administration to humans). See *Intervet UK Ltd v Merial* [2010] EWHC 294 (Pat) at [145] and *Novartis AG v Focus Pharmaceuticals Ltd* [2015] EWHC 1068 (Pat) at [91]-[92]

This case: general observations

126. Perhaps partly as a result of the fact that both parties were seeking to establish that certain matters were common general knowledge, a large part of the written and oral expert evidence was devoted to this topic. By way of example, Prof Wood prepared five reports and was cross-examined for nearly two days. While his evidence also addressed other topics, much of it was devoted to common general knowledge. Furthermore, as I shall explain in a little more detail below, a large quantity of scientific papers were referred to by him in his reports and/or put to him in cross-examination. Unsurprisingly in those circumstances, and helpfully, both parties prepared lengthy and detailed written closing submissions on this topic as well as addressing me orally. I cannot possibly discuss all of the evidence and submissions in detail in this judgment, but I have taken it all into account.

127. It is common ground that the primary source of common general knowledge is the main textbook in the field, namely the *Textbook of Pain* (3rd ed, Churchill Livingstone, 1994) edited by Patrick Wall and Ronald Melzack. The introduction, eight chapters and part of a ninth of the *Textbook of Pain* are in evidence, including chapters contributed by Prof Woolf, Prof Bennett and Prof Fields. It is not common ground that everything in the *Textbook of Pain* was common general knowledge, however. It would be surprising if every word in it was common general knowledge given that it runs to 81 chapters and 1468 pages (excluding the index).

128. In addition to the *Textbook of Pain*, however, a prodigious number of scientific papers was referred to in the evidence: there are no less than 131 papers (including a few abstracts) in the trial bundles, most of which were referred to in written and/or oral evidence (although a few date from after the priority date). In my view some caution has to be exercised in these circumstances in determining what matters formed part of the common general knowledge of the neuroscientist and/or clinician. By way of example, both Prof Wood and Prof Woolf referred in their oral evidence to papers as being part of the common general knowledge which they had not referred to in their reports (in the case of Prof Woolf, he prepared three reports). I am very sceptical that papers which neither expert thought to mention in the course of multiple lengthy and detailed reports can have been common general knowledge.

129. I would add that, as explained above, it is important to take a consistent approach. As will appear, it is Warner-Lambert's case that matter which is clearly set out in the *Textbook of Pain* was not common general knowledge, but matter which is not to be found in the *Textbook of Pain* (or at least, not clearly) was common general knowledge. This is possible, but improbable.

130. There is no dispute that everything I have set out in this judgment under the heading "technical background" was part of the common general knowledge, except that it is not agreed that every part of Prof Woolf's explanation of central sensitisation was common general knowledge.

Whose knowledge?

131. Although there is a considerable degree of overlap between the knowledge of the neuroscientist and that of the clinician, the disputed issues of common general knowledge for the purposes of obviousness are more within the province of the clinician while the disputed issues of common general knowledge for the purposes of sufficiency are more within the province of the neuroscientist.

132. For the reasons given above, I consider that, in the case of the clinician, it is sufficient if a matter would have been common general knowledge to a neurologist or anaesthetist, even if it would not have been common general knowledge to a rheumatologist.

Use of gabapentin for the treatment of pain

133. There are three main issues on common general knowledge which are relevant to the assessment of obviousness. The first concerns the use of gabapentin for the treatment of pain. Mylan and Actavis contend that it was part of the common general knowledge that gabapentin was (i) being used off-label by clinicians for the treatment of pain and (ii) regarded as having therapeutic promise for that indication, although no controlled trials had been carried out. Warner-Lambert disputes both propositions, and in particular proposition (ii).

134. *Literature references*. Mylan and Actavis rely upon the following publications (in approximately chronological order):

i) G.A. Mellick and M.L. Seng, "The use of gabapentin in the treatment of reflex sympathetic dystrophy and a phobic disorder", *American J. of Pain Management*, 5, 7-9 (January 1995) ("Mellick and Seng"). This is a case report by two authors from Ohio concerning a single patient with RSD and phobic disorder. Both conditions were rapidly relieved by daily administration of gabapentin, and this therapeutic effect was sustained for five months. The report concludes:

> "Although the initial clinical experience with gabapentin in the management of reflex sympathetic dystrophy pain and a phobic disorder in this patient is encouraging, the authors recognise the need to subject this new drug therapy to randomized, blinded, prospective scrutiny."

ii) The Mellick prior art relied on by Mylan and Actavis. This is described in more detail below. For present purposes, it is sufficient to note that it is a letter to the editor published in *The American Journal of Emergency Medicine* in January 1995 describing the successful treatment of five patients with RSD (including the one described in Mellick and Seng) with gabapentin.

iii) G.A. Mellick and L.B. Mellick, "Gabapentin in the management of reflex sympathetic dystrophy", *J. Pain and Symptom Management*, 10, 265-266 (4 May 1995) ("Mellick and Mellick"). This is another letter to the editor, which is essentially an update of Mellick, reporting the treatment of nine patients with RSD (including the five previously reported) with gabapentin. The conclusion is expressed in very similar terms to that in Mellick and Seng quoted above.

iv) B.S. Galer, "Neuropathic pain of peripheral origin: Advances in pharmacological treatment", *Neurology*, 45 (Suppl 9), S17-S25 (December 1995). This is a review article by a respected author from the University of Washington in Seattle in a supplement to *Neurology* entitled "Chronic pain mechanisms and management". A section of the article headed "Potentially useful new drugs" begins:

> "Several recently released antidepressant and anticonvulsant agents may prove useful for the treatment of neuropathic pain. Anecdotal evidence exists supporting use of several of these agents as pain relievers. None of these drugs has yet been established as a therapy for neuropathic pain (or for any other painful condition) through published double-blind placebo-controlled studies."

One of the agents discussed is gabapentin. The article states that "Case reports have described pain relief in patients with neuropathic pain treated with gabapentin, but controlled studies have yet to be published". No reference is given for this statement. Gabapentin is also included in an algorithm for the treatment of neuropathic pain, but only as the 13th option.

v) M.C. Rowbotham, "Chronic pain: From theory to practical management", *Neurology*, 45 (Suppl 9), S5-S10 (December 1995). This is another review article by a respected author from the University of California at San Francisco published in the same supplement as Galer. Gabapentin is listed as one of a number of pharmacologic agents for neuropathic pain in Table 5 without further explanation or comment and without any supporting reference.

vi) H. Rosner *et al*, "Gabapentin adjunctive therapy in neuropathic pain states", *Clinical Journal of Pain*, 12, 56-58 (March 1996). This is another case report by three authors from Cornell Medical Center in New York describing the treatment of four patients with neuropathic pain. Daily administration of gabapentin gave good relief of pain over the period of observation, ranging from two to six months. The introduction notes that gabapentin "has yet to be demonstrated clinically effective in management of neuropathic pain", but nevertheless the authors "felt that wider clinical use of gabapentin was warranted for management of … difficult neuropathic pain states that have

been resistant to treatment". The authors conclude that "Further study is warranted to determine the optimal dosing and overall effectiveness". Seven references are cited, including Mellick.

vii) A.Z. Segal and G. Rordorf, "Gabapentin as a novel treatment for postherpetic neuralgia", *Neurology*, 46, 1175-1176 (1996). This is a case report from two authors at Massachusetts General Hospital concerning a patient with PHN who obtained pain relief with daily gabapentin for one month (she was lost to follow up after this period). In their conclusion the authors state that "Use of gabapentin is expanding … Gabapentin should be considered as a treatment for pain …". Seven references are cited, including Mellick.

viii) B.R. Stacey *et al*, "Gabapentin and neuropathic pain states: a case series report", *Regional Anesthesia and Pain Medicine*, 21, 65 (1996). This is another case report in the form of a poster presentation by a team of five authors from the University of Pittsburgh Medical Center. Ten patients suffering from neuropathic pain with a variety of causes were treated with daily gabapentin. At intervals from one to six months, the patients reported substantial pain relief, although it was noted that at follow up pain had returned in four patients who remained on treatment, and in another patient who stopped the treatment when she became pregnant. The authors conclude that "… these initial results appear promising. Detailed, comparative, placebo controlled trials are needed to clarify its appropriate use". Three references are cited, including Mellick and Seng and Mellick and Mellick,

ix) R.H. de Jong, "Neurontin: Pie in the sky or pie on the plate?", *Pain Digest*, 6, 143-144 (June 1996). This is a guest editorial by an author from the University of South Carolina School of Medicine which begins:

> "We haven't seen such anticipation since spinal opiods were introduced. The field is awash with anecdotal accounts of the wonders of gapapentin (Neurontin) in treating both central and perhiperal neuropathic pain syndromes. It began with [Mellick and Mellick] reporting that a patient with refractory reflex sympathetic dystrophy responded nearly instantly to gabapentin, and it has avalanched ever since. Now the time has come to learn whether the claims 'hold water' …"

The article continues:

> "There seems little doubt – including gratifying outcomes in our institution – that gabapentin is highly effective in managing neuropathic pain of central origin. Starting with the original report there have been numerous, albeit still anecdotal, testimonials of gabapentin efficacy, even in carbamazepine-resistant subjects (see table). Several clinical trials are under way, or 'tooling up', to determine whether gabapentin is as powerful a neuropathic pain suppressant as we hope it to be. In fact, as this editorial goes to press, abstracts and posters addressing the issue should be flooding national pain medicine and neurology meetings."

> The table reports the use of gabapentin for the treatment of neuropathic pain arising from a variety of conditions, said to be "all anecdotal at this writing (2/96)". The conditions are divided into two groups, for which the results are described as "remarkably consistent" and "encouraging". The article concludes:
>
> "At present, soft evidence that gabapentin looks promising is tantalizing, if not compelling. Let us hope that the reality of clinical trials matches our high expectations."
>
> Five references are given, including Mellick and Mellick.

x) J.J. Zapp. "Postpoliomyelitis pain treated with gabapentin", *American Family Physician*, 53, 2442-2445 (1996). This is a case report from an author in Oklahoma concerning the successful treatment of a patient with postpoliomyelitis pain with daily gabapentin. Three references are given, but they do not include any of the publications listed above.

135. All of these publications were written by authors located in the USA. Furthermore, all of them were published in US jounals. Still further, a number of these publications are not ones which would regularly have been read by the clinician, whether his background was in anaesthetics, neurology or rheumatology. On the other hand, *Neurology* is a leading journal that the neurologist would have read regularly, and Dr Scadding's evidence was that he would have read the supplement in question and would expect the neurologist to have done so. The skilled reader would be aware, however, that supplements were sponsored and contained articles which were not peer-reviewed. In addition, *Clinical Journal of Pain* is a leading journal that the anaesthetist would have read regularly. Apart from the reports in those two journals, Dr Scadding accepted that he would not have read the other publications, nor would he expect the neurologist to do so (although he thought that the anaesthetist might have seen some). Furthermore, Dr Scadding accepted that the contents of the other publications would not have been common general knowledge.

136. Apart from the review articles, all of these publications are case reports, that is to say, reports of the apparently successful treatment of small numbers of patients by off-label administration of gabapentin. The experts were all agreed that case reports would be treated with caution, because the well-known phenomena of the placebo effect and regression to the mean are particular problems with trials of new treatments for pain.

137. By contrast with the publications mentioned above, Warner-Lambert relies on H.P. Rang and L. Urban, "New molecules in analgesia", *British J. of Anaesthesia*, 75, 145-156 (1995). This is a review article discussing new treatments for pain. Table 1 lists current uses of sodium channel blocking drugs as systemic analgesics, including the anti-convulsants carbamazepine and phenytoin. Table 2 lists quite a number of potential new drug types for use in analgesia. Dr Scadding agreed that the article was quite a good summary of the common general knowledge at least of anaesthetists regarding new drugs in August 1995. There is no mention of gabapentin. Dr Scadding agreed that, if the use of gapapentin to treat pain had been common general

knowledge at that date, one would expect it to have been mentioned in the article. On the other hand, that is a year before the priority date.

138. *USA.* In addition to the literature, Mylan and Actavis rely upon a number of other strands of evidence with regard to the position in the USA. First, there is Prof Fields' unchallenged evidence that he first prescribed gabapentin for pain in 1995 and that by July 1996 he had used gabapentin for pain in "a significant percentage of my patients". He thought that it was likely that he had read several of the publications listed in paragraph 134 above. Furthermore, in an editorial Prof Fields wrote for the *New England Journal of Medicine*, which was published on 25 April 1996, he postulated that gabapentin would prove effective in treating trigeminal neuralgia, due to his positive experiences of using it to treat other neuropathic pain conditions.

139. Secondly, there is documentary and other evidence that Dr Gary Mellick of American Pain Specialists Inc, one of the authors of Mellick and Seng, Mellick and Mellick and Mellick, was an enthusiastic promoter of gabapentin:

i) As he reported to Parke-Davis on 8 August 1994, between 5 and 7 August 1994 Dr Mellick sent a fax addressed to "All Pain Practitioners":

> "Gabapentin (Neurontin®) is a recently released anticonvulsant which appears to provide medical maintenance relief of the symptoms of reflex sympathetic dystrophy (RSD) and many forms of neuropathic pain including peripheral neuropathy. … I hope this new antiepileptic drug proves to be as useful in your pain practice as mine."

He went on to summarise the information reported in Mellick and Mellick. According to a subsequent newspaper report, Dr Mellick faxed his findings to "nearly every anesthesiologist in the country". We know from Prof Bennett's evidence that one of the people Dr Mellick contacted at around this time was Prof Bennett.

ii) On 12 September 1994 Dr Mellick reported to Parke-Davis that he had spoken about the use of gabapentin to treat RSD at an RSD conference in Washington, DC the day before. He also said:

> "In speaking with other neurologists on the telephone conference tonight, I realise the excitement generated when they discover the off label uses of gabapentin. I feel that the most important thing that I could do is to continue to publish so that there is precedence allowing other doctors to feel risk free."

iii) In mid November 1994 Dr Mellick presented his findings in a poster entitled "Successful treatment of reflex sympathetic dystrophy" at the American Pain Society annual conference in Florida.

iv) In February 1995 *Anesthesiology News* published a special supplement entitled "Anesthesia & Pain" which included an article about gabapentin and RSD, quoting Dr Mellick as saying:

> "Not only does gabapentin effectively treat RSD, it also appears to control many forms of deafferentiation pain including peripheral neuropathies. … Although our initial clinical experiences with gabapentin in the management of reflex sympathetic dystrophy are encouraging, we recognise the need to subject this new drug therapy to randomized, blinded, prospective studies."

v) Whether as a result of Dr Mellick's efforts or otherwise, in July, August and September 1995, Parke-Davis received 150-200 letters per month regarding the use of gabapentin for pain, a sharp increase compared to earlier months.

140. Thirdly, there is documentary and other evidence that Parke-Davis promoted the off-label use of gabapentin to treat pain:

i) In about September 1995 Prof Bennett was invited by Parke-Davis to join its Gabapentin Advisory Board. He attended a meeting on 28 September 1995 to discuss gabapentin's use for the treatment of chronic pain conditions, which was attended by a number of pain clinicians. It was reported to the meeting that about 25% of prescriptions of gabapentin were off-label use, including chronic pain conditions. Several of the clinicians present acknowledged that they were using gabapentin in their own patients.

ii) On 6 November 1995 Parke-Davis met with a number of clinicians, one of the objectives being:

> "To discuss the mechanisms by which we can disseminate the information which we currently have regarding the treatment of pain with gabapentin."

iii) A Parke-Davis memo dated 12 December 1995 on the subject "Neurontin Pain Opportunity" includes among the "action steps" with regard to Neurontin:

> "A CME [Continuing Medical Education] Home Study Program on the use of Anticonvulsants for the treatment of neuropathic pain and migraine headaches will be developed. The program will be mailed to neurologists 1st QTR 1996. The mailing will be followed by a series of dinner meetings to be conducted 2nd QTR 1996."

iv) In July 1996 the US Food and Drug Administration complained about Parke-Davis's actions in promoting the off-label use of gabapentin to treat pain as a result of information supplied by a whistleblower called Dr David Franklin, and in August 1996 it brought proceedings against Parke-Davis. (This subsequently resulted in Parke-Davis agreeing to pay $430 million to resolve all civil and criminal liability in May 2004.)

141. Prof Woolf's evidence was that he first became aware of the use of gabapentin for pain as a result of Parke-Davis' campaign. His recollection was that this was in July 1997, when he moved to the USA. Counsel for Mylan and Actavis submitted that it was more likely that Prof Woolf would have heard about the campaign before the

priority date. I do not accept this. In July 1996 Prof Woolf was based in the UK, and there is no evidence that Parke-Davis undertook a similar campaign in the UK. Although Prof Woolf travelled occasionally to the USA for conferences, there is nothing to suggest that he would have learnt about the campaign on those occasions.

142. Fourthly, there are other documentary references to the off-label use of gabapentin to treat pain:

i) On 22 February 1996 Dr Charles Taylor of Parke-Davis (the author of the Taylor I and Taylor II prior art relied on by Mylan and Actavis) wrote to Dr Thomas Feuerstein in Freiburg, Germany saying that gabapentin "is being used increasingly in the clinic for neuropathic pain (diabetic neuropathy, reflex sympathetic dystrophy, neuroma pain etc)". The next day Dr Taylor wrote to Prof Marshall Devor in Jerusalem saying "You are probably aware that gabapentin is being used clinically for analgesia, particularly for neuropathic pain from diabetic neuropathy, sympathetic dystrophy, post-herpetic neuralgia and neuroma pain."

ii) On 29 April Dr Tony Yaksh of the University of California at San Diego, a respected author in the field, wrote to a representative of Parke-Davis referring to "the almost unbelievable interest shown clinically in [gabapentin] where it has been systemically implemented in the treatment of human neuropathic syndromes".

143. Fifthly, Parke-Davis recorded the percentage of Neurontin used to treat neuropathic pain as follows:

1995							1996				
Jun	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May
3.6	5.1	13.9	19.4	6.3	14.0			11			14.8

The last percentage quoted (for May 1996) is of a moving annual total of 802,000 units of Neurontin (it is not clear whether these are tablets or packs).

144. Parke-Davis also recorded the percentage of new patients taking Neurontin who used it for pain as follows:

1996			
Jan	Feb	Mar	Apr
17.2	20.4	19.4	17.0

145. Warner-Lambert point out, however, that Parke-Davis also estimated that Neurontin drug use was less than 1% of total drug uses for neuropathic pain in March 1996.

146. Against these strands of evidence, Warner-Lambert rely in particular on the evidence of Prof Clauw that he was not aware of use of gabapentin to treat pain before the priority date and that his recollection was that he first started to use it for this purpose in 1998. Mylan and Actavis contend that this simply reflects the fact that he was a rheumatologist and that he did not move in the same circles as the anaesthetists and neurologists. Prof Clauw also gave evidence that, although the case reports did not provide proper evidence of efficacy, nevertheless they suggested that gabapentin was worth trying, at least in patients for whom other treatments had failed.

147. Considering the evidence as a whole, my conclusions are as follows. First, it was part of the common general knowledge of anaesthetists and neurologists in the USA at the priority date that gabapentin was being used off-label by clinicians for the treatment of neuropathic pain. Secondly, such anaesthetists and neurologists would have been aware that there was only anecdotal evidence that gabapentin *appeared* to be effective for the treatment of neuropathic pain, and therefore was worth trying, particularly in patients for whom other treatments had been ineffective. It was not known that gabapentin was effective for the treatment of neuropathic pain, nor was there any proper scientific evidence for such a hypothesis (so far as the common general knowledge was concerned, although there was evidence in the Radulovic prior art discussed below).

148. *UK*. Dr Scadding's evidence was that he had prescribed gabapentin off-label for the treatment of neuropathic pain well before the priority date. He had become aware of gabapentin no later than January 1994 when it was profiled in an article in *The Lancet*. His belief was that he had prescribed gabapentin for neuropathic pain before reading the Galer and Rawbotham articles. His opinion was that the use of gabapentin for treating pain was common general knowledge. In support of this, he said that his approach was the same as other clinicians that he knew and that he recalled discussing the use of gabapentin for pain with other people at the time, although he could not pinpoint this knowledge to before July 1996. Dr Scadding accepted, however, that if a drug was being used off-label generally, one would expect to see that represented in case reports from the UK; but there were no case reports from the UK concerning the use of gabapentin to treat pain before the priority date. He also accepted that it takes a considerable time from the very first prescription of a drug for a new condition for that use to become common general knowledge. In addition, he accepted that there was no basis to suggest that it was common general knowledge that gabapentin was effective to treat pain in 1996. Although there had been some enthusiastic case reports, one could have no expectation that it would work, not least because the mechanism of action was unknown. Furthermore, he himself had not achieved the degree of success that some had reported.

149. Prof Wood's evidence was that he recalled excitement about the use of gabapentin for the treatment of neuropathic pain at around this time, but he was not sure that this was before the priority date.

150. Prof Woolf's evidence was that he was not aware of the use of gabapentin for the treatment of neuropathic pain in July 1996, and that he was in a good position to know about it if it was common general knowledge because of his role on the UCH committee.

151. In addition to the evidence of the experts, Warner-Lambert relies on the IMS data presented by Dr Phillips. This shows the prescriptions of gabapentin made by the IMS GP panel in 1996. There were a total of 336 prescriptions in 1996. The three most frequent Read codes are ones clearly associated with epilepsy. There is only one prescription (and that only in the fourth quarter of 1996) that appears to relate to a condition marked by neuropathic pain. On the other hand, the fourth and fifth most common Read codes are "unknown" and "unspecified", which together amount to 18.6% of the prescriptions. Thus this evidence is rather inconclusive.

152. Considering the evidence as a whole, I am not satisfied that it was common general knowledge among anaesthetists or neurologists (let alone rheumatologists) in the UK that gabapentin was being used off-label to treat neuropathic pain (or any kind of pain).

153. *Overall*. Given that it was not common general knowledge in the UK, I find that it was not common general knowledge among anaesthetists or neurologists (let alone rheumatologists) that gabapentin was being used off-label to treat neuropathic pain (or any kind of pain).

Anticonvulsants

154. The second issue as to common general knowledge relevant to the assessment of obviousness concerns anticonvulsants. It is common ground that certain anticonvulsants, in particular carbamazepine and phenytoin, were known to be useful for the treatment of certain types of neuropathic pain, and in particular trigeminal neuralgia. It is also common ground that the mere fact that a new drug was an anticonvulsant would not give the skilled team an expectation that the drug would be useful for the treatment of neuropathic pain. Mylan and Actavis contend, however, that the skilled team's perception was that there was sufficient commonality between epilepsy and neuropathic pain, in that both could be characterised by neuronal hyperexcitability, that there was a reasonable basis for thinking that such a drug might be effective in treating neuropathic pain. Warner-Lambert disputes this.

155. Again, Mylan and Actavis rely upon a number of publications as supporting their position (in approximately chronological order):

i) M. Swerdlow, "Anti-convulsant drugs and chronic pain", *Clinical Neuropharmacology*, 7, 51-82 (1984). In this review article the author concludes:

> "It would appear from the clinical reports analyzed herein that anticonvulsant drugs can provide relief of the paroxysmal lancinating pain that occurs in a number of clinical conditions. The explanation for this is not yet complete, but the clinical value is clear".

ii) R.K. Portenoy, "Pharmacologic management of chronic pain" in *Pain Syndromes in Neurology*, ed. H.L. Fields (Butterworths, 1990). In this chapter the author states (references omitted):

> "Despite the paucity of controlled clinical trials, anticonvulsant medications (Table 11.2) have become widely accepted in the management of chronic neuropathic pain, particularly those characterised as lancinating pains. Their mode of analgesic action in these syndromes is not known, but presumably relates to the variety of mechanisms underlying their anticonvulsant effects such suppression of paroxysmal discharges, neuronal hyperexcitability or spread of abnormal discharges."

iii) Chapter 46, "Central pain", in the *Textbook of Pain*, contributed by J. Boivie. This states (references omitted):

> "The commonly used AEDs [anti-epileptic drugs] are listed in Table 46.9. Carbamazepine is probably the most widely used drug, but in recent years clonazepam has gained popularity. The rationale underlying the use of AEDs for central pain is their ability to suppress discharge in pathologically altered neurones, an effect that is also the basis for their use in epilepsy. Carbamazepine and phenytoin probably exert their effect by inactivation of sodium channels."

iv) H. McQuay *et al*, "Anticonvulsant drugs for management of pain: a systematic review", *B.M.J.*, 311, 1047-52 (21 October 1995). The authors stated in the introduction (footnote omitted):

> "Anticonvulsant drugs have been used in pain management since the 1960s, soon after they were first used to revolutionise the management of epilepsy. The clinical impression is that they are useful for neuropathic pain, especially when the pain is lancinating or burning".
>
> A box headed "Key messages" states:
>
> "Anticonvulsants are used widely to control trigeminal neuralgia and other neuropathic pains".

v) de Jong (cited above). The author states:

> "The excitable-membrane stabilizing properties of anticonvulsants probably account for their ability to diminish intrinsic neuronal hyperactivity/hyperexcitability in epileptic foci. As neuropathic pain arises, in part, from local neural hyperexcitability and self-sustaining ectopic discharges, membrane stabilizers such as anticonvulsants and local anaesthetics can be effective suppressants, with reduced pain the result."

vi) Rosner *et al* (cited above). The authors state:

> "Medications that reduce pathologically altered neurons from excessive discharge would seem to be good choices for management of [neuropathic pain] syndromes. Anticonvulsants have therefore been advocated in management of refractory neuropathic pain, by virtue of their pharmacological properties."

vii) Stacey *et al* (cited above). The authors state:

> "As the other anticonvulsants have been useful for a variety of neuropathic pain conditions, we utilized gabapentin in a series

> of patients with neuropathic pain who had failed previous treatment."

156. Against this, Warner-Lambert relies on three other publications:

i) C.P.N. Watson, "Postherpetic neuralgia: clinical features and treatment" in Fields (cited above). In this chapter the author states (references omitted):

> "Studies utilizing the anticonvulsants carbamazepine, phenytoin and valproic acid for PHN have been either unimpressive or difficult to interpret because of the concomitant use of antidepressants. Although carbamazepine is a popular agent for the paroxysmal lancinating pain that commonly occurs, there is no conclusive evidence to justify its use in this fashion.
>
> …
>
> Although widely used, there is no good evidence of [sic – probably "for"] the use of anticonvulsants alone in this disorder."

ii) J.W. Scadding, "Neuralgia, post-herpetic" in *Handbook of Current Diagnosis & Treatment*, ed. R. Rounder and M. Hamilton (Current Medicine, 1995), in which Dr Scadding stated:

> "Anticonvulsants, e.g. phenytoin, carbamazepine, sodium valproate, and clonazepam, have not been shown to relieve postherpetic neuralgia; any effect will probably be short-lived and consistent with a placebo response".

iii) J.W. Scadding, "Pain management" in *Concise Oxford Textbook of Medicine*, ed. J.G.G. Ledingham and D.A. Warrell (OUP, 2000), based on an edition of the *Oxford Textbook of Medicine* from 1996, in which Dr Scadding stated:

> "Antiepileptic drugs have no effect on nociceptive pain. With the exception of the specific effect of carbamazepine in trigeminal neuralgia, antiepileptic drugs are also disappointingly ineffective in neuropathic pains. Although claims have been made for carbamazepine, phenytoin, valproate, and clonazepam in a variety of neuropathic pain, positive results have only emerged from poorly controlled short-term trials."

157. Dr Scadding agreed that the statements from his publications quoted above were representative of the common general knowledge. More generally, Dr Scadding explained that, as a clinician, the only anticonvulsants that he would be interested in were those that had already been approved. He would wait until they were in clinical practice and he was able to prescribe them for pain (i.e. off-label). He agreed that, even amongst those anticonvulsants, there was a huge drop out rate. Only a handful had been shown to have any effect as analgesics, and the vast majority failed. There

was no general class effect of anticonvulsants given that they had different mechanisms of action. There was only one mechanistic category of anticonvulsants where more than one drug had been shown to have any effect, namely sodium channel modulators. Even within this category, there were drugs which were not effective as analgesics, despite having similar mechanisms to those drugs which did have some effect. It was not possible to have even a general expectation that a particular sodium channel modulator would be effective in pain, let alone anticonvulsants in general.

158. Prof Clauw was adamant that, in general, there was no clinical rationale for using anticonvulsants for the treatment of neuropathic pain.

159. Prof Wood agreed that it was an oversimplification to say that pain and epilepsy are diseases of neuronal hyperexcitability. He explained that there was not an important mechanistic link between epilepsy and pain, just a relationship. The commonalities between epilepsy and pain were really limited to the single subset of neuropathic pain, trigeminal neuralgia, and to use of one or two sodium channel blockers which were first developed as anticonvulsants. Prof Wood explained that only one of the sodium channel blockers was really useful in pain and this was the anticonvulsant carbamazepine. He agreed that the vast majority of anticonvulsants as a class were not useful.

160. Prof Woolf's evidence was that anticonvulsants were not generally known to be effective for the treatment of pain.

161. Considering the evidence as a whole, my conclusion is that the skilled team would not have considered that there was a reasonable basis for thinking that a new anticonvulsant might be effective in treating neuropathic pain simply because of the relationship between epilepsy and neuropathic pain.

Calcium channels

162. The third issue as to common general knowledge relevant to the assessment of obviousness concerns calcium channels. Mylan and Actavis contend that it was common general knowledge that work on drugs which targeted calcium channels was an area that was of interest at the priority date. Warner-Lambert disputes this. I can deal with this topic shortly. Prof Wood agreed that the sodium channel was the main focus of work in the field of ion channels in the context of research for potential analgesics. Both Prof Wood and Prof Woolf said that there was some interest in calcium channel blockers, but only the N- channel type. Thus there was no particular focus on calcium channels, still less any particular reason for thinking that calcium channel blockers would be effective.

Central sensitisation

163. The single biggest issue in the validity case concerns the common general knowledge with regard to central sensitisation, and in particular its role in neuropathic pain. This is relevant to sufficiency, because Warner-Lambert relies heavily on this aspect of the common general knowledge to answer Mylan and Actavis' allegation of insufficiency. As indicated above, there was a lot of evidence on this topic.

164. In broad outline, Warner-Lambert contends as follows:

i) central sensitisation was recognised to be a common mechanism in many pain states;

ii) it was known that central sensitisation was a component in both neuropathic pain and inflammatory pain; and

iii) it was recognised that there was a causal link between central sensitisation and hyperalgesia and allodynia.

165. Mylan and Actavis dispute these propositions, at least to some extent. In broad outline, Mylan and Actavis contend that:

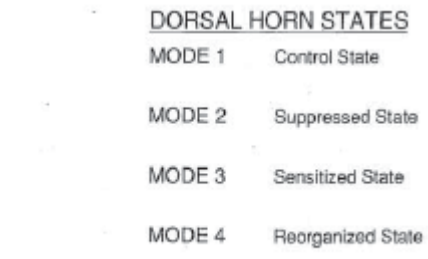
i) it was known that a number of different mechanisms were at play in neuropathic pain, of which central sensitisation was (at best) only one, whose relative importance compared with the other potential mechanisms was unknown;

ii) it was not known to what extent central sensitisation actually occurred in patients suffering from neuropathic pain; and

iii) it was known that there were significant numbers of patients suffering from neuropathic pain who did not demonstrate signs of allodynia or secondary hyperalgesia.

166. *The Textbook of Pain*. In considering these contentions, it is convenient to begin with what is said about central sensitisation in the *Textbook of Pain*, and in particular in Chapter 5, "The dorsal horn: state-dependent sensory processing and the generation of pain", which was contributed by Prof Woolf ("Woolf").

167. After introducing the dorsal horn, Woolf states (at page 102):

> "Key to understanding the role of the dorsal horn in pain mechanisms has been the appreciation that the sensory response generated by the somatosensory system to a defined input is not fixed or static. A stimulus that generates an innocuous sensation may produce pain on another. Essentially what this means is that the somatosensory system operates in a number of different states or modes (Fig. 5.1).
>
> 
>
> **Fig. 5.1** The four modes of the dorsal horn. "

It goes to say that a "highly simplified" analysis of the different states of the somatosensory system is presented in Figures 5.1-5.10. Modes 1 and 2 are unimportant for present purposes.

168. Woolf describes Mode 3 (the sensitised state) as follows (at page 103):

> "Mode 3 is that state of the dorsal horn where its excitability is increased, and its response to sensory inputs is augmented or facilitated, where it has become hypersensitive or sensitized. A low-intensity stimulus in this mode can, acting via low-threshold afferents, generate pain, the phenomenon of allodynia (Fig 5.5). This needs to be differentiated from the situation which operates when the transduction properties of high-threshold afferents are changed so that their threshold falls (peripheral sensitization) (Fig. 5.6 and see Ch. 1). The sensitization of the dorsal horn can occur following peripheral tissue injury, peripheral inflammation and damage to the peripheral and central nervous systems. In addition to the reduction in the threshold of stimuli required to elicit pain in Mode 3, the response to suprathreshold high-intensity stimuli is exaggerated (Fig. 5.7). Mode 3 essentially represents an increase in gain in the system …"

169. I reproduce Figures 5.5 and 5.7 below:

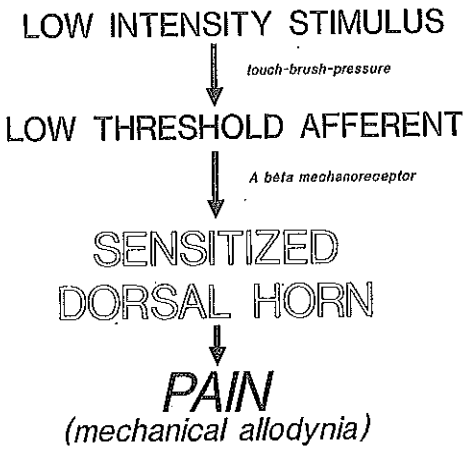


Fig. 5.5 Sensitization of the dorsal horn (Mode 3) results in low-threshold afferents gaining the capacity to evoke the sensation of pain, the phenomenon of mechanical allodynia.

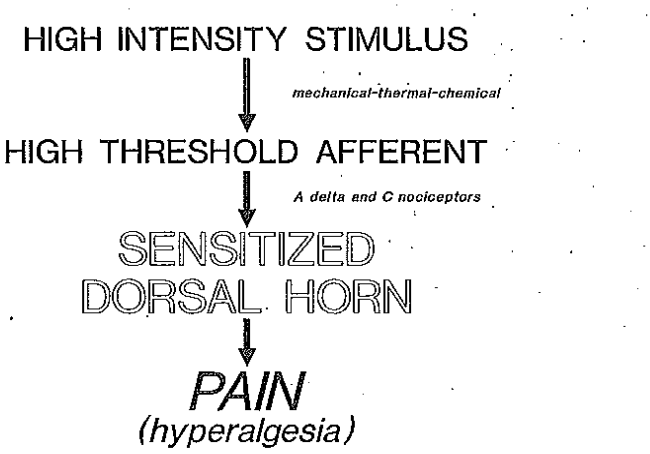
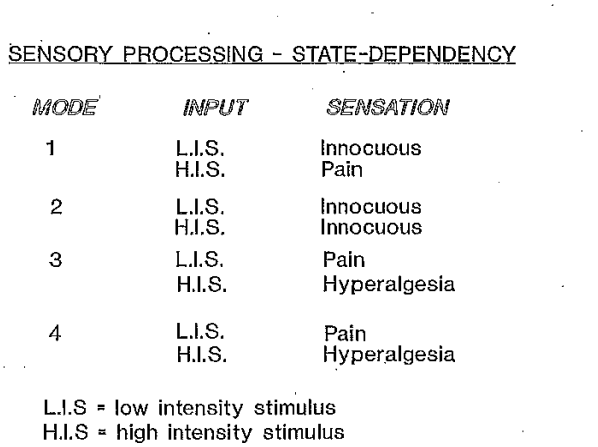


Fig. 5.7 Sensitization of the dorsal horn (Mode 3) results both in mechanical allodynia (Fig. 5.5) and an exaggeration in the response to activation of high-threshold afferents, the phenomenon of hyperalgesia.

170. Woolf describes Mode 4 (the reorganised state) as follows (at pages 103-104):

> "The last mode of the dorsal horn, Mode 4, differs from the first three in that it represents a potentially irreversible, or at the least prolonged, reorganization of the synaptic circuitry of the system. The first three modes reflect a system operating in a range of states of excitability, from suppressed to hypersensitive, determining the sensation produced by defined stimuli. Mode 4, in contrast, is that state which occurs when there is degeneration of elements of the system, or the formation of novel inputs. Such changes have been documented after injury to the nervous system, both peripheral and central, leading to a range of sensory abnormalities including neuropathic pain."

171. Woolf goes on to say that Figure 5.9 presents a summary of the state-dependent processing of low- and high-intensity sensory stimuli according to the different modes of the dorsal horn. I reproduce Figure 5.9 below:



SENSORY PROCESSING - STATE-DEPENDENCY

MODE	INPUT	SENSATION
1	L.I.S. H.I.S.	Innocuous Pain
2	L.I.S. H.I.S.	Innocuous Innocuous
3	L.I.S. H.I.S.	Pain Hyperalgesia
4	L.I.S. H.I.S.	Pain Hyperalgesia

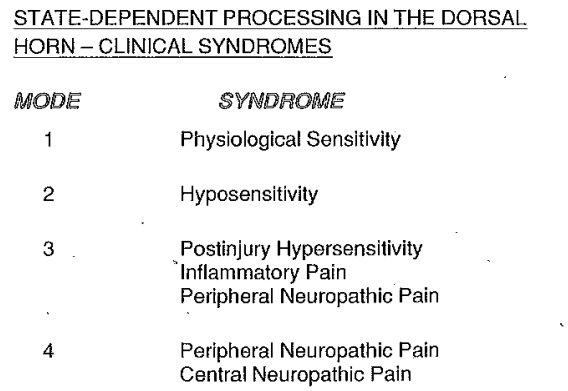
L.I.S = low intensity stimulus
H.I.S = high intensity stimulus

Fig. 5.9 A summary of state-dependence of sensory processing in the spinal cord illustrating the different sensory responses evoked by low or high intensity stimuli in the different modes (see Fig. 5.1) of the dorsal horn.

172. It explains (at page 104):

> ".. if a stimulus of an intensity sufficient to threaten damage to the system is applied to a body part, this initiates a protective withdrawal response together with a feeling of discomfort or pain (Fig. 5.10). This system operates, therefore, as an early warning device protecting from or eliminating contact with potentially damaging stimuli."

173. I reproduce Figure 5.10 below:



STATE-DEPENDENT PROCESSING IN THE DORSAL HORN – CLINICAL SYNDROMES

MODE	SYNDROME
1	Physiological Sensitivity
2	Hyposensitivity
3	Postinjury Hypersensitivity Inflammatory Pain Peripheral Neuropathic Pain
4	Peripheral Neuropathic Pain Central Neuropathic Pain

Fig. 5.10 A summary of the different clinical sensory disturbances that can manifest in the different modes or states of the dorsal horn.

174. After further discussion of Mode 2, Woolf returns to Mode 3 (at page 105):

> "Mode 3, representing a state of hypersensitivity also has survival value in some circumstances. The state of central sensitization is triggered by certain types of nociceptor afferent input which will occur with tissue damage, peripheral inflammation and following nerve injury where injury discharge and spontaneous activity occur (Fig. 5.11). A state of

> excessive sensitivity, such that low-intensity stimuli begin to initiate pain, can help to protect injured body parts from further injury while recuperation or healing occurs. …. Sensitization is not always adaptive, however, and when it is produced in situations where the initial damage has healed or following nerve injury, it can result in pain with no apparent benefit to the sufferer."

175. I reproduce Figure 5.11 below:

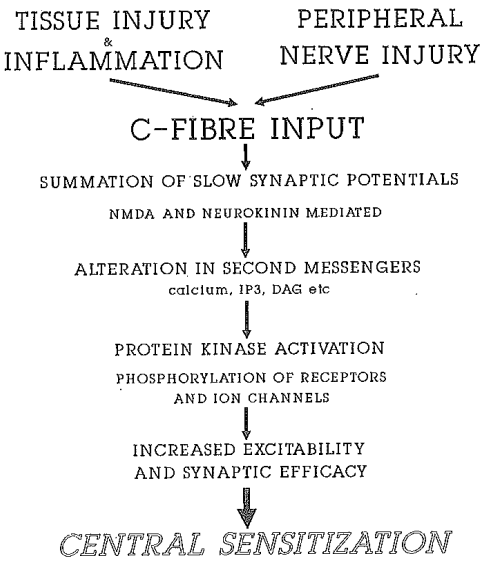


Fig. 5.11 A simple model of the pathogenesis of central sensitization by C-fibre input generated by tissue injury/inflammation or following peripheral nerve injury.

176. Woolf then moves on to Mode 4 (at page 105):

> "Modes 1, 2 and 3 reflect the capacity of the nervous system for functional plasticity, the dynamic alteration in the performance of the system in response to changing situations. Mode 4 is qualitatively quite different. In this situation cells die, axon terminals degenerate or atrophy, new axon terminals may appear, and the structural contact between cells at the synapses may be considerably modified (Fig. 5.12). This mode represents true pathology and its contribution to neuropathic and central pain disorders is only just beginning to become apparent."

177. I reproduce Figure 5.12 below:

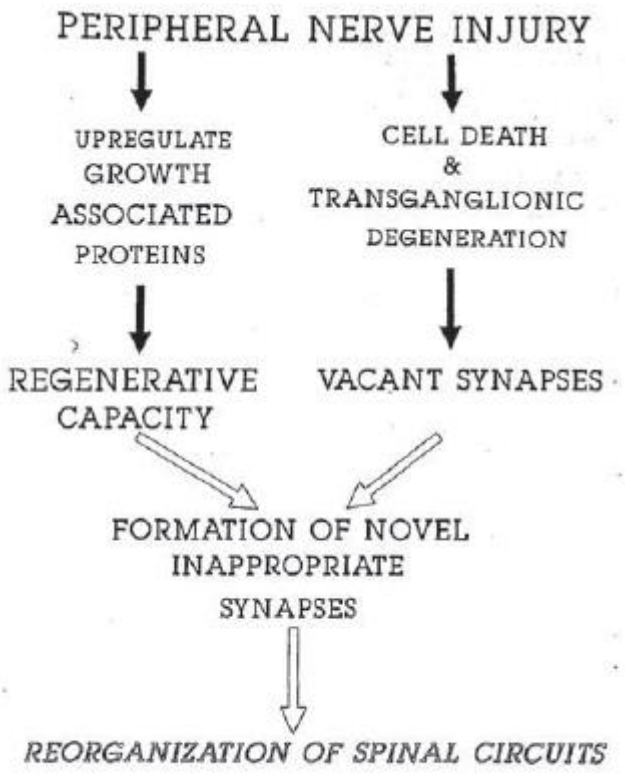


Fig. 5.12 A model of the sequence of events that can lead to a reorganization of spinal circuits following peripheral nerve injury.

178. In the rest of the chapter, Woolf considers each of the four Modes in more detail. In relation to Mode 3, it states (at page 109):

> "While it is now clear that during and immediately following inputs in nociceptors the excitability of a sizeable fraction of dorsal horn neuron increases and that this is almost certainly responsible for mechanical allodynia and secondary hyperalgesia (Torebjörk et al 1992), what is less certain is the extent to which such sensitization plays a role in the sensory abnormalities accompanying chronic pain states. Acute tissue damage and inflammatory states will directly and indirectly lead to the activation of nociceptors which will induce central sensitization. On recovery from the damage or inflammation, the source of the input during the central changes is removed and the hyperalgesia and allodynia commonly disappear within several hours or days. Neuropathic pain, in contrast, is typically persistent and intractable (Ch.10). One explanation may be that a constant drive of input from axotomized nociceptors is present (Devor 1991), which maintains the central sensitization. Another is that associated with peripheral nerve damage is the decrease in segmental inhibitory mechanisms (Wall & Devor 1981; Woolf & Wall 1982) which exaggerates the synaptic response to afferent input."

179. In relation to Mode 4, it states (at pages 109-110):

> "… Of particular interest is the finding that large myelinated afferent fibres which normally terminate in the deeper laminae of the dorsal horn, grow into lamina II, the site of C-fibre terminals (Woolf et al 1992). This may result in the formation of novel and inappropriate synapses which could dramatically alter the central processing of signals generated in the low-threshold mechanoreceptors. Peripheral neuropathic pain may be an expression, therefore, of an alteration in the circuitry of the spinal cord as well as of changes due to the maintenance of central sensitization by a nociceptor drive (Ch.10)
>
> Central neuropathic pain resulting from spinal cord injury and a number of central lesions may also alter the spinal cord by removing some of the descending influences originating from the brainstem that control the gain of the system. If such changes resulted in a removal of a descending inhibitory input, the consequence might be a form of sustained central sensitization due to disinhibition."

The last paragraph quoted needs to be treated with some care, because, as Prof Woolf explained, he was not using "central sensitisation" in the narrow, NMDA-receptor mediated sense here.

180. *The concept of central sensitisation*. There was no disagreement between the experts that, as these passages suggest, central sensitisation was a well-known concept. Indeed, as noted above, Prof Woolf's 1983 *Nature* paper had been widely cited. Furthermore, as can be seen from the papers considered below, there had been a substantial body of other work on the subject by July 1996.

181. *Central sensitisation as a contributor to peripheral neuropathic pain*. Nor was there any real disagreement between the experts that it was generally understood that central sensitisation *contributed* to peripheral neuropathic pain. Rather, the difference between them, and in particular between Prof Wood and Prof Woolf, was as to the extent to which central sensitisation was considered to be *causative* of peripheral neuropathic pain. Both Dr Scadding and Prof Wood gave evidence that it was thought that other mechanisms were likely to be involved in neuropathic pain. Moreover, in Prof Wood's view, central sensitisation was regarded as an amplification mechanism in the central nervous system that occurred in response to a variety of painful stimuli, and it was not the fundamental mechanism that drove neuropathic pain. Warner-Lambert does not contend, however, that it was common general knowledge that central sensitisation was causative of peripheral neuropathic pain, nor that it was not thought that other mechanisms could be involved.

182. In these circumstances I shall only refer relatively briefly to a number of other publications which are relied upon by Warner-Lambert in support of the proposition that it was common general knowledge that central sensitisation contributed to peripheral neuropathic pain, nor shall I discuss the witnesses' evidence about these papers:

i) P.D. Wall, "Neuropathic pain and injured nerve: Central mechanisms", *B. M. Bull.*, 47, 631-646 (1991). One of the central mechanisms discussed in this

paper (at page 636) is central sensitisation, with reference to the work of Prof Woolf and his collaborators.

ii) J.D. Kristensen *et al*, "The NMDA-receptor antagonist CPP abolishes neurogenic 'wind-up pain' after intrathecal administration in humans", *Pain*, 51, 249-253 (1992). This paper in a leading journal concludes that the NMDA-receptor system plays an important role in "neurogenic" (i.e. neuropathic) pain. I shall discuss this paper further below.

iii) T.J. Coderre *et al*, "Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence", *Pain*, 52, 259-283 (1993). This review article explains (at page 260) that "evidence suggests that although nociceptive and neuropathic pain depend on separate peripheral mechanisms, they are both significantly influenced by changes in CNS function". It continues that "recent evidence supports the view that hyperalgesia depends in part on central sensitization" and that "for hyperalgesia to develop it is critical that initial inputs from the injury reach the CNS. However once hyperalgesia is established, it does not need to be maintained by inputs from the peripheral tissue." Under the heading "Central sensitisation" the article states that "recent experimental studies suggest that sensitisation within the CNS also contributes significantly to this phenomenon [hyperalgesia]" (page 261). Again, I shall return to this paper below.

iv) S.B. McMahon *et al*, "Central hyperexcitability triggered by noxious inputs", *Current Opinion in Neurobiology*, 3, 602-610 (1993). This is another review article, which begins with an introduction to the phenomenon and physiology of central sensitisation. This states that, following Prof Woolf's 1983 paper in *Nature* and other papers by Prof Woolf and his collaborators (page 602):

> "There followed an intensive development of various animal models of this central sensitization to peripheral stimuli induced by various chemical stimulations of peripheral tissue and by lesions of soft tissue and peripheral nerves (see Table 1 and [8]). Interest was further stimulated by the demonstration that the widespread hyperalgesia in man that follows local intense cutaneous stimulation has to be attributed to central sensitization [9]. By analogy it is presumed that many of the pathological hyperpathic states in humans include central sensitization."

The article continues (at 603-604):

> "There are now many other experimental models of central sensitization associated with activation of peripheral C-fibres (see Table 1). Where central plasticity is triggered by irritant chemicals, soft tissue injury or nerve stimulation, the effects develop over minutes. The effects associated with tissue inflammation, however, have a slower onset, typically measured in hours, while nerve injury-associated central change may take days to develop. A striking feature of all these

> manifestation of central sensitization is that, where tested, they are blocked by NMDA receptor antagonists."

v) In the Introduction to the *Textbook of Pain* Patrick Wall states (at page 4):

> "... we are now beginning to realise, as described in the first ten chapters of this book, that a peripheral event may trigger long lasting changes in the spinal cord and brain by way of nerve impulses and transported substances. This means that overt peripheral pathology is capable of initiating a cascade of changes which may persist in the central nervous system long after peripheral pathology has disappeared."

vi) Chapter 1 of the *Textbook of Pain*, "Peripheral neural mechanisms of nociception", contributed by R.A. Mayer *et al*. This states under the heading "Central mechanism of secondary hyperalgesia" (at page 24, emphasis in the original):

> "Substantial evidence favours this important tenet: *the peripheral signal for pain does not reside exclusively with nociceptors. Under pathological circumstances, other receptor types, which are normally associated with the sensation of touch, acquire the capacity to evoke pain*. This principle applies not only to secondary hyperalgesia but also to neuropathic pain states in general. This condition arises through augmentation of responsiveness of central pain-signalling neurons to input from low-threshold mechanoreceptors, a phenomenon often termed *central sensitization*."

vii) S.W.N. Thompson *et al*, "Injury-induced plasticity of spinal reflex activity: NK1 neurokinin receptor activation and enhanced A- and C-fiber mediated responses in the rat spinal cord in vitro", *J. Neuroscience*, 14, 3672-3687 (1994). Towards the end of the summary the authors conclude (at 3672):

> "The enhanced ventral root responses and changes in receptor sensitivity may contribute to the phenomenon of central sensitization and may be directly relevant to the behavioural hyperalgesia observed. Moreover these findings may be relevant to the mechanisms of enhanced excitability that occur in clinical conditions of inflammatory hyperalgesia and neuropathic pain."

viii) M. Koltzenburg *et al*, "Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain", *Brain*, 117, 579-591 (1994). The title speaks for itself and clearly connects central sensitisation and neuropathic pain.

ix) K.M. Park *et al*, "Effects of intravenous ketamine, alfentanil, or placebo on pain, pinprick hyperalgesia, and allodynia produced by intradermal capsaicin

in human subjects", *Pain*, 63, 163-172 (1995). The introduction states (at pages 163-164):

> "The phenomenon of sensitization of central nervous system (CNS) neurons is well established in animal models of acute and chronic pain (Woolf 1983; Dubner 1991; Woolf and Thompson 1991; Bennett 1994) and has been inferred from sensory studies in some patients with chronic neuropathic pain and post-traumatic pain syndromes (Campbell et al 1988; Price et al 1989, 1992; Gracely et al 1992; Koltzenburg et al 1994). Animal studies in many laboratories have shown that N-methyl-D-aspartate (NMDA) receptor-mediated processes play a role in central sensitization. For example, spinal administration of NMDA receptor antagonists blocks central sensitization caused by the repeated electrical stimulation of C-fiber nociceptors (Davis and Lodge 1987; Dickenson and Sullivan 1990) and by the peripheral injection of capsaicin (Ault and Hildebrand 1988; Nagy et al 1993) and diminishes hyperalgesia and allodynia in animal models of neuropathic pain (Yamamoto and Yaksh 1992; Mao et al 1993; Tal and Bennett 1993)."

x) C.J. Woolf, "Somatic pain – pathogenesis and prevention", *B. J. Anaesthesia*, 75, 1691-76 (1995). This is a short review article by Prof Woolf. Under the heading "Central sensitization", Prof Woolf states (at page 171, references omitted):

> "Central sensitization has been documented in a large number of laboratories in a wide variety of species, including humans and is now accepted as a major contributor to post-injury pain hypersensitivity."

Under the heading "Neuropathic pain", Prof Woolf states (at page 172, references omitted):

> "Neuropathic pain, the pain produced by damage to the central nervous system, is also characterised by central changes in sensitivity including A-mediated pain. This may be the consequence of three different kinds of pathological change produced by nerve lesions. First, a maintained state of central sensitization in response to ongoing ectopic C-fibre input either from the site of injury or the DRG (the generator model). Second, decreased inhibition due to impaired inhibitory transmission, as a result of either a decrease in GABA levels or an excitotoxic loss of inhibitory neurones (the disinhibition model). We have recently shown that disinhibition results in a central hypersensitivity phenomenon. Finally, A-mediated pain might be the consequence of a reorganization of synaptic connections in the spinal cord (the structural model)."

Prof Woolf goes on:

> "It is likely that neuropathic pain in humans involves various combinations of these and other maladaptive changes that occur in response to nerve damage some of which may resemble inflammatory changes and others which will be quite different What will be critical now, is to establish what initiates which change and when, and to determine if the changes are reversible. It is particularly encouraging that neuropathic pain in laboratory animals can be prevented by some manipulations such as preventing an injury discharge with local anaesthetic block, NMDA-receptor antagonists or morphine and that this is also true for patients with intercostal neuralgia and phantom limb pain."
>
> He concludes:
>
> "Although inflammatory and neuropathic pain are generally different in their presentation and natural history, related general pathophysiological mechanisms may be involved. These include alterations in chemical expression or phenotype and growth status of primary sensory neurons and increases in excitability or disinhibition of dorsal horn neurons. There are important differences though …"

183. *The reorganised state.* Going back to Woolf, Mylan and Actavis rely upon what is said in it about Mode 4, the reorganised state. Mylan and Actavis contend that this was also part of the common general knowledge. Warner-Lambert disputes this.

184. Prof Woolf's opinion was that, even though he had discussed the reorganised state in Woolf, it was not common general knowledge. He drew a distinction between central sensitisation and the reorganised state on the basis that, whereas central sensitisation had been the subject of a large body of work going back to his widely-cited 1983 paper and was generally accepted by July 1996, the reorganised state was a relatively new theory mainly supported by just two papers (one by Prof Bennett and one by himself) which had been very little cited, and thus was not generally accepted. Counsel for Mylan and Actavis suggested that Prof Woolf had been influenced by the knowledge that, as he explained, the theory advanced in his own paper had been shown after the priority date to be incorrect. This suggestion does not address the points that that there were just two papers (or three, if one includes the one referred to in the next paragraph) and that they had been very little cited, however.

185. In addition to Woolf, Mylan and Actavis rely upon C.J. Woolf and T.P. Doubell, "The pathophysiology of chronic pain – increased sensitivity to low threshold Aβ-fibre inputs", *Current Opinion in Neurobiology*, 4, 525-534 (1994). This is a short review article by Prof Woolf which Prof Woolf exhibited to his first report as part of his discussion of the common general knowledge (I mention this because counsel for Mylan and Actavis criticised Prof Woolf for not referring to the reorganised state in this report). It was probably written not long after Woolf, and was published at around the same time. Unsurprisingly, it presents the reorganised state in similar terms, although it contains more detail and it cites a 1993 paper by R. Baron and M. Sauger as "clinical evidence in support of structural reorganization" (at page 531). I do not consider that this advances Mylan and Actavis's case much beyond Woolf,

particularly given that there is no evidence that this was a widely-read journal. (I would add that the Baron and Sauger paper is not itself in evidence, although an apparently similar paper by the same authors dating from 1995 is.)

186. Prof Clauw's evidence was supportive of Prof Woolf's opinion: he said that he personally was not familiar with the reorganised state in 1996, and he did not think the clinician would be.

187. Dr Scadding's opinion was that what was said in Woolf about the reorganised state was common general knowledge, not least because Woolf's description of the four modes aligned closely with clinical experience, and in particular the description of Mode 4 corresponded well with the clinical features of neuropathic pain. He did not agree that work on the reorganised state was in its infancy.

188. Prof Wood's evidence was that the reorganised state was a topic of great interest at the time and he believed that it was the critical element in neuropathic pain. He accepted, however, that it was a new interpretation of cutting-edge research.

189. Considering the evidence as a whole, I am not satisfied that it has been shown that the reorganised state was part of the common general knowledge of the neuroscientist or the clinician.

190. *Central sensitisation as a contributor to inflammatory pain*. It can be seen from the passages quoted from Woolf above that central sensitisation is described as contributing to inflammatory pain (see in particular Figures 5.10 and 5.11). Both Dr Scadding and Prof Wood accepted that this was common general knowledge.

191. *Central sensitisation as a common mechanism in peripheral neuropathic pain and inflammatory pain*. It can also be seen from the passages quoted from Woolf above that central sensitisation is presented as a mechanism which is common to peripheral neuropathic pain and inflammatory pain (again, see in particular Figures 5.10 and 5.11). Dr Scadding agreed that central sensitisation contributed to both neuropathic pain and inflammatory pain. Prof Wood accepted that it was recognised that there were mechanisms in common between neuropathic pain and inflammatory pain, that central sensitisation was one such mechanism, and that it was the mechanism on which most interest was focused.

192. On the other hand, Prof Wood emphasised that the pharmacology of these pain states was very different: drugs that were very effective in treating inflammatory pain did not affect neuropathic pain at all. Thus, as noted in paragraph 80 above, it was common ground between the experts that NSAIDs were ineffective for the treatment of neuropathic pain.

193. *No involvement of central sensitisation in central neuropathic pain*. As can be seen from the IASP definition quoted in paragraph 50 above, neuropathic pain is not limited to pain caused by damage to or dysfunction of the peripheral nervous system, but also includes pain caused by damage or dysfunction of the central nervous system. Unsurprisingly, Prof Clauw agreed with this. As noted in paragraph 54 above, a wide variety of diseases that affect the nervous system may cause neuropathic pain. Some of these have nothing to do with damage to peripheral nerves. Accordingly, central sensitisation cannot be a contributor to these types of pain, as there is no damaged

nerve to provide the repetitive C-fibre barrage required. Prof Woolf accepted that, with some possible exceptions, there was no evidence that central sensitisation contributed to central pain states. This is consistent with Woolf, which states that central neuropathic pain may be due to disinhibition (see paragraph 179 above).

194. The main exception referred to by Prof Woolf was phantom limb pain. Dr Scadding gave unchallenged evidence that phantom limb pain was classified as a form of central neuropathic pain. Prof Woolf said in cross-examination that phantom limb pain "almost certainly would have" a central sensitisation component. It was not put to Prof Wood that this was common general knowledge, however. (Indeed, all that was put to Prof Wood on the subject of phantom limb pain was a very short extract from a passage in Coderre *et al* (1993) discussing the role of central plasticity in neuropathic pain, which comes after the authors' discussion of central sensitisation. The authors may be referring to central augmentation more generally, and the question put to Prof Wood did not distinguish between the two.) Nor was Dr Scadding asked about this at all. Accordingly, I am not satisfied that it has been established that this was common general knowledge.

195. It is also necessary to consider the position with respect to fibromyalgia. Dr Scadding's evidence was that he would defer to Prof Clauw when it came to fibromyalgia, since Dr Scadding was not a rheumatologist and Prof Clauw was not only a rheumatologist, but also an expert in fibromyalgia. Prof Clauw stated in his second report that "the … IASP definition of neuropathic pain …. encompassed conditions such as fibromyalgia". He also explained in cross-examination that the same drugs were used to treat fibromyalgia as other forms of neuropathic pain. Despite this, counsel for Warner-Lambert relied in his closing submissions on evidence given by Dr Scadding that fibromyalgia was not considered to be a form of neuropathic pain in 1996. Given Prof Clauw's clear evidence on the point, I do not accept this.

196. Prof Clauw distinguished fibromyalgia (and related conditions) from classic rheumatic diseases (such as osteoarthritis and lupus) on the basis of the lack of any nociceptive input or damage in the periphery. His evidence was that the prevailing view at the priority date (and indeed today) was that in fibromyalgia there was no peripheral damage or inflammation that was playing a causative role in the pain being experienced. He agreed that the clinician would have thought it unlikely that central sensitisation was a component of fibromyalgia. Dr Scadding did not accept that fibromyalgia had a central sensitisation component, although as noted above he made it clear that this was not his specialist field.

197. *The link between central sensitisation, neuropathic pain and secondary hyperalgesia and allodynia*. It can be seen from the passages quoted above that Woolf describes central sensitisation as resulting in (secondary) hyperalgesia and allodynia (see in particular Figures 5.5 and 5.7). Warner-Lambert contends that this was common general knowledge. Mylan and Actavis contend, however, that it was known that significant numbers of patients suffering from neuropathic pain did *not* exhibit signs of secondary hyperalgesia or allodynia.

198. In addition to Woolf, Warner-Lambert relies on a number of other publications:

i) R.-D.Treede *et al*, "Peripheral and central mechanisms of cutaneous hyperalgesia", *Progess in Neurobiology*, 38, 397-421 (1992). This is a review article which states (at 400):

> "In summary, the most prominent feature in neuropathic pain patients is hyperalgesia to mechanical stimuli. Hyperalgesia to cold stimuli is often also observed. In contrast to primary hyperalgesia after tissue injury, hyperalgesia to heat stimuli is not prominent in neuropathic pain. The hyperalgesia in neuropathic pain bears a marked resemblance to secondary hyperalgesia, and may represent a form of chronic secondary hyperalgesia."

The article goes on (at page 412):

> "Substantial evidence points to central sensitisation as the principal mechanism in secondary hyperalgesia. ... Dorsal horn neurons exhibit both changes in stimulus-response functions and in receptive field size due to remote injury. In the case of mechanical stimuli, central sensitisation may be such that the response to a given nociceptor input is enhanced. On the other hand there is mounting evidence that the response to central pain-signalling neurons to input from low threshold mechanoreceptors is enhanced."

It also states (at page 413):

> "Based on the psychophysical characteristics, neuropathic pain may arise from neural mechanisms similar to those of secondary hyperalgesia … In neuropathic pain, as in secondary hyperalgesia, mechanical hyperalgesia is the hallmark sign. …
>
> Several lines of evidence have shown that mechanical hyperalgesia in neuropathic pain is mediated by low-threshold mechanoreceptors rather than nociceptors. …
>
> Since excitation of low-threshold mechanoreceptors does not normally cause pain, the responsiveness of central neurons must have changed in neuropathic pain, such that the hyperalgesia is mediated by these afferents …"

ii) E. Torebjörk, "Human microneurography and intraneural microstimulation in the study of neuropathic pain", *Muscle & Nerve*, 16, 1063-1065 (1993). This states (at page 1064):

> "Evidence is accumulating to support the notion that an ongoing discharge from hyperexcitable nociceptive afferents can change the impulse processing at central levels of the nervous system in such a way that normally nonpainful stimuli are now perceived as painful. This is termed central sensitization. The phenomenon has long been recognized

clinically and can also be observed in normal subjects treated with chemical irritants to produce experimental pain.

…

It is concluded that the primary cause for neuropathic pain seems to be an abnormal excitability of primary nociceptive afferents. Sensitization of nociceptive afferents may express itself as mechanical hyperalgesia to pressure and hyperalgesia to heat. Secondary central changes in signal processing can aggravate these symptoms. The dynamic mechanical hyperalgesia to gentle stroking or vibration is regarded as a physiologic central consequence of ongoing activation of nociceptive fibers, regardless of the underlying pathophysiologic mechanism."

iii) Chapter 1 of the *Textbook of Pain* states (at page 13) that:

"Once tissue is damaged, a cascade of events results in enhanced pain to natural stimuli termed hyperalgesia. A corresponding increase in the responsiveness of nociceptors called sensitisation occurs."

As Dr Scadding accepted, this paragraph does not distinguish between neuropathic and inflammatory pain. The chapter continues (at page 19):

"Hyperalgesia is a consistent feature of tissue injury and inflammation. … Hyperalgesia may be prominent in neuropathic conditions such as post-herpetic neuralgia, certain cases of diabetic neuropathy and certain cases of traumatic nerve injury."

It also states (at page 23):

"As noted above, and as will be clarified further in this section, the distinction between primary and secondary hyperalgesia is to some extent artificial. The mechanisms that account for hyperalgesia to mechanical stimuli in the secondary zone may very well account for mechanical hyperalgesia in the primary zone."

iv) Chapter 10 in the *Textbook of Pain*, "Neuropathic pain", contributed by Prof Bennett ("Bennett") explains (at page 203):

"Allodynia and hyperalgesia are very common symptoms. They may occur, singly or in various combinations, in any of the peripheral neuropathies and in patients with central pain. [...] The conceptual difference between allodynia and hyperalgesia is straightforward, but it must be admitted that in

> practice it is often difficult or impossible to differentiate the two."

v) Koltzenburg *et al* (cited above). The summary begins by saying that "Brush-evoked pain (mechanical allodynia, dynamic mechanical hyperalgesia) is a hallmark of neuropathic and inflammatory pain states". The principal finding of the paper is that the severity of the brush evoked pain correlates both with the intensity of background pain in patients suffering from chronic painful neuropathies and also in normal subjects with acute chemogenic pain. The authors conclude that "in normal volunteers, brush-evoked pain can be induced by short periods of nociceptor C-fibre excitation which induces a state of central nervous sensitisation as the basis of Aβ fibre-mediated mechanical hyperalgesia".

199. Prof Wood agreed that several of these passages reflected the common general knowledge. More specifically, he agreed that there was very good evidence that secondary mechanical hyperalgesia involved central sensitisation, and he agreed that mechanical hyperalgesia and cold allodynia often occurred in neuropathic pain.

200. Dr Scadding's evidence was that, in his clinical experience, significant numbers of patients with neuropathic pain did not exhibit hyperalgesia or allodynia. He also relied on two papers as supporting this. The first in time is C.P. Watson *et al*, "Post-herpetic neuralgia: 208 cases", *Pain*, 35, 289-297 (1988). As the title suggests, the authors examined 208 patients with PHN. Those examinations were carried out at the start of a prospective, longitudinal study that was designed, amongst other things, to examine long-term responses to pain treatment. The results were recorded in two tables. Table IV indicates that in a sample of 158 patients with PHN, hyperesthesia (a term used to cover both hyperalgesia and allodynia) was confirmed in 65% and absent in 28%. Table V reports on a more detailed examination of 50 patients, and indicates that 58% had allodynia and only 14% had hyperalgesia. Thus about 30% of the patients did not have either hyperalgesia or allodynia. But about 70% did.

201. The second is R. Baron *et al*, "A cross-sectional cohort survey in 21000 patients with painful diabetic neuropathy and postherpetic neuralgia: Differences in demographic data and sensory symptoms", *Pain*, 46, 34-40 (2009). This study found that only 47% of patients with PHN and only 18% with DPN reported dynamic mechanical allodynia ("DMA"). This is well after the priority date, however. Moreover, as counsel for Warner-Lambert pointed out, the authors state (at page 37):

> "The frequency of DMA in PHN is intriguing since in most of the clinical descriptions DMA is mentioned in at least 90% of patients [11,18]."

Reference 11 is a paper published in 2008 and reference 18 is a paper by Rowbotham and Fields published in 1996.

202. Moreover, Dr Scadding agreed that neuropathic pain was characterised by hyperalgesia and allodynia, in the sense that these features were frequently present, albeit not in every patient.

203. Prof Clauw said in his first report that hyperalgesia and allodynia were hallmarks of central sensitisation. In the report, he appeared to be talking about central sensitisation in the narrow sense defined above. In cross-examination, however, he clarified that he meant central sensitisation in the broader sense of central amplification or augmentation, which includes central sensitisation in the narrow sense within it. Furthermore, he said that he believed the broader sense was clinically more important. He explained why this was in a passage which merits quotation in full:

> "At the time of the priority date, a lot of clinical conditions that were thought to be characterised by central sensitisation i.e. those that had hyperalgesia and allodynia had not actually been specifically shown to be the italicised version of central sensitisation. In fact, if you look at the class of drugs that were most commonly used to treat those conditions, whether it be neuropathic pain, fibromyalgia, any of the conditions that were characterised by the non-italicised version, central augmentation, amplification, the most commonly used class of drugs for all of those conditions were tricyclic drugs that were originally developed as anti-depressants. Amitriptyline is the one we have heard a lot about. That drug, although it binds very weakly to NMDA receptors, at the time and subsequent to the priority date, was really thought to be working more so by working on the inhibitory pathways. We have heard about disinhibition, those pathways that go from the brain areas, the peri-aqueductal grey – the Yunus chapter. We are just talking about those. So, compounds, which were the drugs most broadly used in clinical conditions, characterised by hyperalgesia, were probably not working on the italicised version of central sensitisation. They were working on the broader concept of central sensitisation. So that, clinically, in 1996, and even at present, the non-italicised version of central sensitisation is what we identify with hyperalgesia and allodynia and the classes of drugs that work in those conditions. Some may be working on the italicised version, but many are not working on the italicised version. They are treating hyperalgesia and allodynia via different mechanisms."

204. Prof Clauw also gave evidence that it was his experience that, in a group of 100 patients suffering from DPN, 40 would have pain, but 60 would have decreased sensitisation at the periphery.

205. Considering the evidence as a whole, I conclude that it was common general knowledge that:

i) Neuropathic pain was characterised by secondary hyperalgesia and allodynia, in the sense that these symptoms were present in the large majority of patients, but a significant minority did not display these symptoms.

ii) Secondary hyperalgesia and allodynia involved central augmentation. In some cases this would be central sensitisation, but not in all cases.

Rat paw formalin test

206. Another important issue in the validity case concerns the common general knowledge with regard to the rat paw formalin test. As described above, this consists of two phases. It is common ground that the first phase models the acute nociceptive pain caused by the injection of formalin. The issue concerns the second phase. During the course of the trial, this issue narrowed considerably, but a significant aspect remains in dispute.

207. Warner-Lambert contends that it was common general knowledge that the second phase had a central sensitisation component. Mylan and Actavis accepted this in their closing submissions. Given that Mylan and Actavis accept this, it is not necessary for me to go through all the 17 publications relied on by Warner-Lambert as supporting this proposition (which include the five papers mentioned in paragraph 212 below as well as the publications discussed in paragraphs 216 to 233 below).

208. Mylan and Actavis contend that the second phase was nevertheless regarded as a model of inflammatory pain. As Mylan and Actavis point out, this is how it was commonly referred in the pre-priority date literature, such as Chapter 15 of the *Textbook of Pain*, "Methods of assessing pain in animals", contributed by R. Dubner (at page 297). Warner-Lambert did not dispute this in their closing submissions, and therefore it is not necessary for me to consider all the publications relied on by Mylan and Actavis. Prof Woolf had suggested in his first report that, even though the formalin test was commonly described as a model of inflammatory pain, it was understood that the second phase was not linked to inflammatory pain. In his third report, however, he accepted that:

> "The second phase of the formalin test does model elements of inflammatory and neuropathic pain, specifically the phenomenon of central sensitisation which is present in both. It is therefore fair to say that the formalin model is a model of inflammatory pain in so far as inflammatory pain has a mechanistic central component (as does neuropathic pain)".

As he explained when cross-examined about the passage in his first report:

> "The linkage was not exclusively inflammatory pain, but obviously inflammatory pain has a central sensitisation component and that was certainly what I was attempting to say there, that the late phase of the formalin model was recognised to reflect the presence of central sensitisation, that certainly could be present in inflammatory pain, but equally could be present in other conditions, including neuropathic pain."

Consistently with this, what counsel for Warner-Lambert put to Prof Wood in cross-examination was that the (second phase of) the formalin test was not *purely* a test of inflammatory pain. Prof Wood accepted this.

209. It is therefore only necessary for me to deal with three points. The first concerns the role of inflammation, and in particular inflammatory mediators in the second phase of the formalin test. Although Prof Woolf accepted that the second phase was a model of

inflammatory pain, he did not accept that it was a model of inflammation. He was adamant that it was important to recognise that the immune system drove inflammation and that the immune response took place over several hours (i.e. after the period covered by the second phase). Prof Woolf accepted, however, that neurogenic inflammation started very soon after tissue damage occurred in the first phase, with the release of neuropeptides from the peripheral terminals of nociceptors which caused swelling. He also accepted that tissue damage released inflammatory mediators, such as bradykinin, histamine, serotonin and prostaglandins, which were present and active during the second phase. He emphasised, however, that central sensitisation greatly amplified this low-level input.

210. The second point concerns the relative importance of central sensitisation in the second phase of the formalin test. This is a topic in relation to which I think both sides lost sight of what was actually in issue. Counsel for Mylan and Actavis characterised Prof Woolf's evidence as having been that central sensitisation was the dominant mechanism. In fact, what Prof Woolf said in his second report was as follows (my emphasis):

> "In the years in the run up to the Priority Date there were many publications that made it clear that an inflammatory response could not *alone* be responsible for the second (late) phase of the formalin test and that a central sensitisation component must play *a role or even the dominant role*."

211. As I have already noted, Mylan and Actavis do not dispute that it was common general knowledge that central sensitisation played a role in the second phase. They dispute that it played the dominant role, but I do not read Prof Woolf as saying that it was generally accepted that central sensitisation played the dominant role.

212. Prof Woolf cited five papers in support of the proposition I have quoted from his report: (i) T.J. Coderre *et al*, "Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection", *Brain Research*, 535, 155-158 (1990); (ii) H. Wheeler-Aceto *et al*, "The rat paw formalin test: comparison of noxious agents", *Pain*, 40, 229-238 (1990); (iii) Acton *et al*, "Amitriptyline produces analgesia in the formalin pain test", *Experimental Neurology*, 117, 94-96 (1992); (iv) T.J. Coderre and R. Melzack, "The contribution of Excitatory Amino Acids to Central Sensization and Persistent Nociception after Formalin-induced Tissue Injury", *J. Neuroscience*, 12, 3665-3670 (1992); and (v) S.B. McMahon *et al* (cited above). Counsel for Mylan and Actavis submitted that the papers in question did not establish that central sensitisation played the dominant role in the second phase, but for the reason I have explained it is not necessary for me to try to decide whether this submission is well founded.

213. When Prof Wood was cross-examined about this topic, he said that there were other papers which took a contrary view, which were subsequently put to Prof Woolf: (i) B.K. Taylor *et al*, "Persistent cardiovascular and behavioural nocipetive responses to subcutaneous formalin require peripheral nerve input", *J. Neuroscience*, 15, 7575-7584 (1995); (ii) R. Dallel *et al*, "Evidence for a peripheral origin of the tonic nociceptive response to subcutaneous formalin", *Pain*, 61, 11-16 (1995); and (iii) K. Ren and R. Dubner, "Inflammatory models of pain and hyperalgesia", *ILAR J.*, 40 111-118 (1999) (post-priority date, but discussing earlier disagreement about the

mechanisms underlying the second phase). As counsel for Warner-Lambert pointed out, Prof Wood had not mentioned the latter group of papers in his reports. Accordingly, I agree with counsel for Warner-Lambert that they are unlikely to have been part of the common general knowledge (or in the case of the third paper, reflective of it). But I think this misses the point, which is whether it was generally accepted that central sensitisation played the dominant role.

214. In my view Prof Wood's evidence, and the papers to which he referred, confirm that this was not generally accepted. As I have said, however, I do not think this was a proposition advanced by Prof Woolf in the first place. As Prof Woolf said in cross-examination:

> "I think the disagreement was, was phase 2 exclusively central sensitisation? I think that some people interpret[ed] the Coderre work as such and there were others who said it was exclusively peripheral and driven only by primary activity. As is common in most cases, it is a mixture of both. There is some peripheral drive which continues to contribute to the phenomenon, but it is acting on a facilitated state. That was clear at the priority date."

215. The third point is the most important. Although counsel for Warner-Lambert did not articulate Warner-Lambert's case in this way, in effect Warner-Lambert contends that it was common general knowledge that the second phase of the rat paw formalin test was predictive of efficacy in treating neuropathic pain. Mylan and Actavis dispute this.

216. Prof Woolf's evidence was that, as he put it in his third report, "While the formalin model was not … a model of neuropathic pain, it was appreciated and well understood that activity in this model of central sensitisation *could* predict efficacy in neuropathic pain [my emphasis]". In his first report he relied upon Chapter 9 of the *Textbook of Pain*, "Central pharmacology of nociceptive transmission", contributed by T.L. Yaksh and A.B. Malmberg ("Yaksh and Malmberg"), in support of this proposition.

217. The introduction to Yaksh and Malmberg explains (at page 165, left-hand column, references omitted):

> "In the last 5 years, it has become increasingly appreciated that in addition to the acute component, protracted afferent drive for periods lasting minutes can evoke pronounced changes in pain behaviour, suggesting an augmented processing of the nociceptive response, i.e. a hyperalgesic state. Thus, the injection of an irritant, such as formalin, into the skin will lead to an acute barrage followed by a protracted ongoing low level of C fibre activity. In the animal so treated, one observes a multiphase component of behaviour in which the first phase reflects the acute afferent barrage, followed, after a brief period of quiescence, in a powerful second phase of agitation. "

It goes on (at page 166, right-hand column):

> "Tests, such as the hot plate or paw pressure, define substrates which are activated by an acute high-intensity stimulus. On the other hand as noted above, protracted afferent input, as generated by an injury state, may lead to a prominent hyperalgesia. Models, such as the formalin test, appear to define systems which are brought into play by such ongoing afferent input."

218. Yaksh and Malmberg proceeds to discuss some of the evidence for the involvement of central sensitisation in the second phase (at page 170, right-hand column – page 171, left-hand column):

> "The injection of an irritant such as formalin into the paw will result in an initial burst of small afferent activity, followed by a prolonged low level of afferent discharge (Heapy et al 1987). Behaviourally, the animal displays an initial transient phase of flinching and licking of the infected paw (phase 1), followed after a brief period of quiescence by a second prolonged phase of licking and flinching of the injected paw. Significantly, the spinal delivery of NMDA and NK-1 antagonists have little effect upon the first phase, but will significantly diminish the magnitude of the second phase response (Yamamoto & Yaksh 1991, 1992; Coderre & Melzack 1992). …
>
> Of equal importance, delivery of NMDA and NK-1 antagonists after the first phase of the formalin test results in a loss of their ability to alter the second phase response (Yamamoto & Yaksh 1991, 1992; Coderre & Melzack 1992). These observations indicate that the magnitude of the second phase response is dependent upon processes which were initiated by the activation of NMDA and NK-1 sites during the first minutes after the injection of the formalin, but these sites are not required for the sustenance of the second phase activity and occur independently of these sites.
>
> The mechanisms of this augmented responsiveness induced by repetitive C-fibre input and the activation of NMDA and sP are not completely understood. …"

219. Later, Yaksh and Malmberg discusses hyperalgesia (at page 183 left-hand column):

> "As noted above, the generation of a modestly protracted afferent barrage by the injection of an irritant into the skin or the generation of a state of inflammation will evoke an acute pain state, followed by a profound hyperalgesia. Models such as the formalin test in the rat have been shown to be associated with a two-phased response, with the magnitude of the second-phase behaviour being in excess of that anticipated on the basis of the afferent activity measured in the peripheral afferent at the corresponding time points (Heapy et al 1987; Wheeler Aceto et al 1990). Similarly, other models of hyperalgesia involving

> chronic inflammatory states may well be involved in such states of facilitated processing (though if the increased pain behaviour reflects upon a greater sensitivity of the peripheral nerve to the stimulus, then this hyperalgesia might reflect a model mediated by a peripheral mechanism). The spinal delivery of certain afferent transmitters, such as sP or NMDA will evoke a prominent decrease in the thermal nociceptive threshold of the unanaesthetized rat, corresponding to the presumed mechanisms set into play by repetitive afferent input. In man, the focal activation of cutaneous C-fibres by the subcutaneous injection of capsaicin results in a prominent acute pain behaviour followed by a profound hyperalgesia over an area of skin that greatly exceeds the focal site of the original stimulus. Importantly, this secondary hyperalgesia appears centrally mediated, for (as with the formalin test) if the acute afferent barrage is blocked by local anaesthetic, the secondary phase does not occur (Torebjörk et al 1992)."

220. Yaksh and Malmberg then returns to the phenomenon of central sensitisation (at page 184, right-hand column – page 185, left-hand column):

> "The observation that NK-l and NMDA antagonists given between phase I and phase 2 have little effect upon phase 2 supports the argument that these receptors systems serve to initiate, but not sustain the facilitated component of the second phase (Coderre & Melzack 1991, 1992; Yamamoto & Yaksh l99l, 1992). These agents, as described, thus serve as antihyperalgesics and, to the degree that a pain state is augmented by these processes, those classes of agents will serve to normalize the facilitated pain state.
>
> In contrast, agents such as the opioids on the formalin test serve as analgesics by blocking the afferent input responsible for evoking behaviour (as in phase 1 of the formalin test and the acute response on the hot-plate or tail-flick test)."

221. Consistently with his evidence discussed above, Prof Wood accepted that the discussion in these passages of Yaksh and Malmberg showed that central sensitisation amplified the effect of the afferent barrage which was triggered by the initial injection of formalin and immediate tissue damage in the first phase of the formalin test, although he maintained that central sensitisation was not the cause of the pain experienced in the second phase. This is consistent with Mylan and Actavis' acceptance that it was common general knowledge that the second phase had a central sensitisation component.

222. Yaksh and Malmberg goes on to discuss the Bennett model of neuropathic pain. In this context it states (at page 186 left-hand column):

> "… intrathecal agents such as the NMDA antagonists have no effect upon the normal paw latency, but will result in a dose-dependent increase in the latency of the hyperalgesia paw to

> normal (nonhyperalgesic) response latencies. In this sense, as with those agents which block in a limited, but dose-dependent fashion, phase 2 of the formalin test, such agents might also be classified as being antihyperalgesic."

223. It immediately continues under the subheading "Comparability of hyperalgesic pain states" (at page 186 left-hand column – right-hand column):

> "While there are certain parallels between the systems which underlie the mechanisms of the hyperalgesia observed in the formalin test and that in nerve injury, consideration of Table 9.7 emphasizes that the pharmacology of these two measured end-points are not the same. Thus, for the nerve injury evoked hyperalgesia, NK-l antagonists and cyclooxygenase inhibitors are not active. Moreover, it is not known if the spinal substrates through which the NMDA antagonists act to alter the two hyperalgesia states are the same. Thus heterogeneous spinal mechanisms may be involved in the different pain states. Still, at present it is not clear that all agents which block the hyperalgesia component observed following nerve lesion will block the facilitated component of phase 2 of the formalin test."

224. Prof Wood accepted that the skilled reader of these passages would understand that some agents, and in particular NMDA antagonists, would be active in both the second phase of the formalin test and the Bennett model, but said that the skilled reader would also understand that the mechanistic basis of the two types of hyperalgesia were quite distinct. It can also be seen that Yaksh and Malmberg points out that some agents, such as NK-1 antagonists, are active in the formalin test, but not the Bennett model. Significantly, it was not put to Prof Wood that Yaksh and Malmberg demonstrated that it was common general knowledge that the second phase of the formalin test was predictive of efficacy for neuropathic pain.

225. In his third report Prof Woolf cited three papers as examples showing that drugs that act on neuropathic pain have activity in the second phase of the formalin test. The first was Kristensen *et al* (cited above). This paper looks at the efficacy of CPP, an NMDA-receptor antagonist that had been shown to have effects in the second phase of the formalin test, when administered to a single patient. The summary states that the patient's "continuous deep pain component and allodynia were unchanged" after the intrathecal administration of CPP, "but the following 'wind up' phenomenon … was completely abolished" (page 249). Prof Wood's evidence was this showed that CPP was ineffective against neuropathic pain. Prof Woolf disagreed both with Prof Wood and with the authors. His interpretation was that CPP had effected a change in secondary hyperalgesia, and that the authors were incorrect to describe this as wind-up. He was forced to accept that it was a single case report, however, and therefore little weight could be placed on it (for consistency with his criticisms of Mellick).

226. The second paper was Acton *et al* (cited above). This is a study looking at the effect of amitriptyline, a drug that was known to be efficacious in treating neuropathic pain, on the second phase of the formalin test. Prof Wood's evidence was that this was an extremely flawed paper. A very high dose of 10 mg/kg had been administered with no statistical effect. Only at double that dose, 20 mg/kg, had a very small, albeit

significant, effect been observed in the second phase. By way of comparison, the usual dose of amitriptyline used to treat neuropathic pain in humans was about 1 mg/kg. So the rats needed 20 times the normal human dose before even a minimal effect was observed. Prof Woolf disagreed with Prof Wood and said that one of the major issues in drug development was the fact that you often needed to use higher doses of a treatment in the pre-clinical models than patients could tolerate.

227. The third paper was Coderre *et al* (1993) (cited above). This discusses the use of lidocaine to block activity in the second phase of the formalin test. As Prof Woolf accepted, however, lidocaine is a sodium-channel blocker which is used as a nerve blocker i.e. it acts peripherally.

228. In his third report Prof Woolf also mentioned K.J. Elliott *et al*, "Dextromethorphan shows efficacy in experimental pain (nociception) and opioid tolerance", *Neurology*, 45, Supp 8, S66-S68 (1995) as an example of a paper which referred to the formalin test as "a model of inflammatory pain" (at page S66. right-hand column), but went on to refer to the second phase as resulting from "both local inflammation and central sensitization", and used it to test a drug for PHN. This paper was not put to Prof Wood (or Dr Scadding), however, and it is not clear to me that the authors treated the formalin test as predictive of efficacy in PHN. Rather, their conclusion was that dextromethorphan should be considered for a controlled clinical trial in PHN as a result of a combination of experimental evidence, which included, but was not limited to, the formalin test results.

229. Finally in his third report Prof Woolf cited M.F. Jett *et al*, "The effects of mexilitine, desipramine and fluoxetine", *Pain*, 69, 161-169 (1997) ("Jett"), saying the introduction provided "a good summary of the common general knowledge relating to the formalin test, central sensitisation and neuropathic pain as at the Priority Date". In the US proceedings, Prof Woolf had stated that he had been unable to find a single publication explicitly linking the formalin model, central sensitisation and neuropathic pain despite doing a search. It is reasonable to assume, given the importance of this point, that Warner-Lambert's legal teams both here and in the USA will have also carried out extensive searches. Given that Prof Woolf was aware of Jett from his evidence in the USA, it is odd that he did not mention it in his first or second reports. The reason he gave in cross-examination, namely that it was post-priority date, was unconvincing given the manner in which he subsequently relied upon it in his third report.

230. Jett evaluated the efficacy of two drugs that were known to have efficacy in treating neuropathic pain (mexiletine and desipramine) and one drug that was known to be ineffective (fluoxetine) in rat models identified by the authors as involving central sensitisation, namely the formalin and L5/L6 nerve ligation models. Fluoxetine did not work in any of the models. Mexiletine reduced hyperalgesia and tactile allodynia in both models. Desipramine reduced hyperalgesia in both models, but not tactile allodynia. The authors therefore concluded that "the neuronal mechanisms underlying the two manifestations of neuropathic pain [i.e. hyperalgesia and tactile allodynia] are different" (summary at 161). It can therefore be seen that the paper provides little support for the proposition that the second phase of the formalin test was regarded as predictive of efficacy for neuropathic pain.

231. In any event, Prof Wood disagreed that Jett was reflective of the common general knowledge at the priority date. Futhermore, when it was put to him that "some people thought that the formalin test modelled neuropathic pain", Prof Wood disagreed, saying that "some people hoped that it might be", that the hope was not fulfilled and that it was not common general knowledge. Remarkably, counsel for Warner-Lambert submitted in his closing submissions that in this cross-examination counsel "was not attempting to establish that the theory was generally accepted, but that it would be recognised".

232. In cross-examination, Prof Woolf relied for the first time on J.C. Hunter and L. Singh, "Role of excitatory amino acid receptors in the mediation of the nociceptive response to formalin in the rate", *Neuroscience Letters*, 174, 217-221 (1994). It is correct that in this paper the authors (who included the inventor of the Patent) use the second phase of the formalin test to test certain agents for their effect on central sensitisation. As they explain, however, "since the tonic phase of the formalin response is accompanied by a prolonged inflammatory response, potential anti-inflammatory properties of these compounds were also investigated against carrageenin-induced inflammation in the rat". Thus they recognise that the second phase of the formalin test comprises both central sensitisation and inflammatory components. To try to ascertain which component the agents are acting on, they also test them in the carrageenin model. As the agents do not act in the carrageenin model, they are able to conclude that the agents attenuate central sensitisation.

233. As Prof Wood accepted, this supports the proposition that central sensitisation plays a role in the second phase of the formalin test and that the test is not purely one of inflammatory response. It was not put to Prof Wood that this paper shows that the second phase of the formalin test is predictive of efficacy for neuropathic pain. Nor was it put to Prof Wood that the paper was common general knowledge. He said that he read the journal in which it is appeared, but only to scan it rather than as core reading. Given that it was not mentioned by Prof Woolf in any of his reports, the paper is unlikely to have been common general knowledge.

234. Mylan and Actavis argue that it was known that the second phase of the formalin test was not predictive of efficacy for neuropathic pain. The basis for this is that, as Prof Woolf and Prof Wood agreed, it was known that NSAIDs were efficacious in the second phase, but not the first phase, of the formalin test. As I have already noted, the experts were agreed that NSAIDs were not effective for neuropathic pain. At least in relation to peripheral neurpathic pain, however, this is not quite as strong a point as it may appear, because Prof Woolf's evidence when it was put to him was that NSAIDs were effective in the Bennett model, albeit only when administered intrathecally at high doses, of the order of 100 to 1000 times higher than a patient could tolerate.

235. Considering the evidence as a whole, I am not satisfied that it has been established that it was common general knowledge that the second phase of the formalin test was predictive of efficacy for neuropathic pain.

The carrageenin and post-operative pain models

236. Mylan and Actavis contend that it was common general knowledge that both the carrageenin and post-operative pain models could be set up to look for tactile dynamic allodynia or primary or secondary thermal or mechanical hyperalgesia as desired by

selection of the appropriate stimulus and application of the appropriate stimulus at the appropriate site. Surprisingly, this is not something that was stated by Prof Wood in his reports, and therefore I have approached this proposition with scepticism. Nevertheless, the first of the two points made by Mylan and Actavis in this regard follows from Prof Woolf's own evidence in chief and the second point he readily accepted in cross-examination.

237. Mylan and Actavis' first point is that, in his first report Prof Woolf explained when setting out the common general knowledge that "*dynamic* mechano-allodynia, secondary hyperalgesia [emphasis added]" were manifestations of central sensitisation. Thus Prof Woolf drew a distinction between dynamic allodynia and static allodynia. This is consistent with Bennett (cited above) which draws the same distinction (at pages 212-213). It is clear from the literature that, as one would expect, if the experimenter is interested in dynamic allodynia as opposed to static allodynia, then different stimuli are required (for example, a light brush). I understood Prof Woolf to accept this.

238. Mylan and Actavis' second point is that, if it is secondary hyperalgesia that the experimenter is interested in, then it is necessary to make the measurement away from the site of injury. Not only is this is supported by the literature, but as Prof Woolf stated:

> "If you are exploring secondary hyperalgesia, you need to test it outside the zone of the injury. So, that logic is irrefutable, by definition."

Relationship between the formalin test, carrageenin test and post-operative pain model

239. Although Prof Woolf's evidence was that both the carrageenin test and the post-operative pain model had a central sensitisation component, he accepted that there was nothing in the literature to suggest either of these models could be used to predict efficacy for neuropathic pain either on its own or in combination with the formalin test.

Construction

240. The task for the court when construing a claim in a patent is to determine what the person skilled in the art would have understood the patentee to have been using the language of the claim to mean: *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2004] UKHL 46, [2005] RPC 9. The general principles applicable to this exercise were summarised by Jacob LJ giving the judgment of the Court of Appeal in *Virgin Atlantic Airways Ltd v Premium Aircraft Interiors UK Ltd* [2009] EWCA Civ 1062, [2010] RPC 8 at [5] in the following propositions.

> "(i) The first overarching principle is that contained in Article 69 of the European Patent Convention.
>
> (ii) Article 69 says that the extent of protection is determined by the claims. It goes on to say that the description and drawings shall be used to interpret the claims. In short the claims are to be construed in context.

(iii) It follows that the claims are to be construed purposively - the inventor's purpose being ascertained from the description and drawings.

(iv) It further follows that the claims must not be construed as if they stood alone - the drawings and description only being used to resolve any ambiguity. Purpose is vital to the construction of claims.

(v) When ascertaining the inventor's purpose, it must be remembered that he may have several purposes depending on the level of generality of his invention. Typically, for instance, an inventor may have one, generally more than one, specific embodiment as well as a generalised concept. But there is no presumption that the patentee necessarily intended the widest possible meaning consistent with his purpose be given to the words that he used: purpose and meaning are different.

(vi) Thus purpose is not the be-all and end-all. One is still at the end of the day concerned with the meaning of the language used. Hence the other extreme of the Protocol - a mere guideline - is also ruled out by Article 69 itself. It is the terms of the claims which delineate the patentee's territory.

(vii) It follows that if the patentee has included what is obviously a deliberate limitation in his claims, it must have a meaning. One cannot disregard obviously intentional elements.

(viii) It also follows that where a patentee has used a word or phrase which, acontextually, might have a particular meaning (narrow or wide) it does not necessarily have that meaning in context.

(ix) It further follows that there is no general 'doctrine of equivalents.'

(x) On the other hand purposive construction can lead to the conclusion that a technically trivial or minor difference between an element of a claim and the corresponding element of the alleged infringement nonetheless falls within the meaning of the element when read purposively. This is not because there is a doctrine of equivalents: it is because that is the fair way to read the claim in context.

(xi) Finally purposive construction leads one to eschew the kind of meticulous verbal analysis which lawyers are too often tempted by their training to indulge."

The nature of the claims

241. All of the claims of the Patent are in Swiss form. It has repeatedly been held that such claims are process claims (as distinct from product claims): see *John Wyeth &*

Brother Ltd's Application [1985] RPC 545, 563 (Whitford and Falconer JJ sitting *en banc*); *Monsanto & Co v Merck & Co Inc* [2000] RPC 77, 92-93 (Aldous LJ, with whom Auld LJ agreed); *Actavis UK Ltd v Merck & Co Inc* [2008] EWCA Civ 444, [2009] 1 WLR 1186 at [26]-[27] (Jacob LJ giving the judgment of the Court of Appeal); Case T 1780/12 *University of Texas Board of Regents/Cancer treatment* [2014] EPOR 28 at [18]-[27] (EPO Technical Board of Appeal); and *Warner-Lambert CA* at [45], [54], [56], [118] and [129] (Floyd LJ, with whom Arden and Ryder LJJ agreed)

242. It has also been held by the Court of Appeal that such claims are directed to the manufacturer of the medicament or pharmaceutical composition: *Actavis v Merck* at [10], [59], [75]; and *Warner-Lambert CA* at [128]-[129].

Technical features of claim 1

243. Claim 1 of the Patent requires that the use of pregabalin be for "treating pain". This gives rise to two issues of construction.

244. *Pain.* First, somewhat surprisingly, there is a dispute between the parties as to what is meant by "pain". Mylan and Actavis contend that the skilled team would interpret this in accordance with the IASP definition of "pain" (see paragraph 45 above), and hence as embracing all types of pain. Warner-Lambert contends that the skilled team would interpret "pain" in claim 1 as being restricted to types of pain characterised by hyperalgesia and/or allodynia and having a central sensitisation component.

245. Warner-Lambert's argument proceeds in two stages. The first stage is that the skilled team would understand the claim to be limited to the types of pain listed in [0003]. This requires the skilled team to read the words "Such disorders include, but are not limited to, …" as meaning "Such disorders are limited to …", the exact opposite of what the words say. This proposition only has to be stated to be seen to be untenable.

246. The second stage of the argument is that the skilled team would recognise that what the listed types of pain have in common is that they are characterised by hyperalgesia and/or allodynia and have a central sensitisation component. I do not accept this either, for a number of reasons.

247. First, there is no mention of central sensitisation anywhere in the Patent. Nor is there any suggestion at all there is a common mechanism or other link between the disparate kinds of pain listed in [0003].

248. Secondly, the list includes at least two types of pain which do not have a central sensitisation component, namely fibromyalgia and idiopathic pain (in the case of the latter, because by definition it is of unknown origin). For the reasons given in paragraph 194 above, I am not satisfied that phantom limb pain would be regarded as having a central sensitisation component either.

249. Thirdly, the argument depends on the references to "neuropathic pain" in the Patent being understood to be confined to peripheral neuropathic pain, and hence as excluding central neuropathic pain. For the reasons explained below, I do not accept this.

250. Fourthly, to his credit, Prof Clauw frankly volunteered during cross-examination that he had not read the Patent as being limited to central sensitisation, but as extending more broadly. This is consistent with the evidence of Prof Wood and Dr Scadding.

251. Accordingly, I conclude that Mylan and Actavis's construction is the correct one.

252. I should add that, in the light of Prof Clauw's evidence in cross-examination, counsel for Warner-Lambert advanced an alternative construction in his closing submissions, to the effect that "pain" should be interpreted as extending to any form of pain characterised by hyperalgesia and/or allodynia. I do not consider that this contention is open to Warner-Lambert given that it was not explored with any of the other witnesses, but in any event it suffers from many of the same defects as Warner-Lambert's primary construction.

253. *Treating.* Secondly, there is a dispute as to the effect of the word "treating". It is common ground that this is a functional technical feature of the claim, i.e. the actual attaining of the therapeutic benefit is a technical feature of the claimed invention: see G2/88 *Mobil Oil Corp/Friction reducing additives* [1990] EPOR 73 at [9], T609/02 *Salk Institute for Biological Studies/AP-1 complex* (unreported, 27 October 2004) at [9] and *Regeneron Pharmaceuticals Inc v Genentech Inc* [2013] EWCA Civ 93, [2013] RPC 28 at [56] (Kitchin LJ).

254. There is a dispute, however, as the relevant criterion for establishing such efficacy. Mylan and Actavis contend that the criterion for efficacy is a positive result in one of the three animal models used in the Patent. Warner-Lambert contends that the criterion for efficacy is evidence of efficacy in humans. After some prevarication, counsel for Warner-Lambert submitted that this meant success in a Phase II trial.

255. In my judgment Mylan and Actavis are correct for the following reasons. First, the only evidence presented in the specification is the evidence from the three animal models. The skilled team would understand that the patentee is relying upon these as being predictive of efficacy. Secondly, there is no reference to trials in humans, let alone Phase II trials. Thirdly, the specification makes it clear in [0014] that the claims are intended to cover the treatment of mammals, not just humans.

The mental element

256. Claim 1 of the Patent requires that the use be "for" treating pain. It is common ground that the word "for" in a Swiss form claim such as this does not simply mean, as it usually does in patent claims, "suitable for", but imports a mental element. A central issue in this litigation concerns the nature of the mental element. It is convenient to defer consideration of this question to the context of infringement, to which it is primarily relevant. Neither side suggested that the precise nature of the mental element was significant to the issues on obviousness (let alone insufficiency).

Claim 3

257. Claim 3 is limited to "neuropathic pain". Warner-Lambert contends that "neuropathic pain" would be interpreted by the skilled team as peripheral neuropathic pain, and hence as excluding central neuropathic pain. Strikingly, this contention was not foreshadowed in any of Warner-Lambert's evidence or in its skeleton argument for

trial, and was first raised during the cross-examination of Dr Scadding (and hence it was not put to Prof Wood). Mylan and Actavis dispute this interpretation, and contend that neuropathic pain should be interpreted as encompassing both types of neuropathic pain.

258. In my judgment Mylan and Actavis are correct for the following reasons. First, the expression used throughout the Patent is "neuropathic pain". The expression appears to be used quite generally, and there is no reference to "peripheral neuropathic pain", still less any indication that central neuropathic pain is not intended to be included.

259. Secondly, the IASP definition (see paragraph 50 above) encompassed both peripheral and central neuropathic pain. Prof Woolf accepted that the purpose of the IASP Classification was to provide clear and precise definitions. Prof Clauw's evidence was that the IASP Task Force lagged some 5-10 years behind the field. Thus, definitions adopted by the IASP had often been in common use for a number of years beforehand. Furthermore, he was clear that the term "neuropathic pain" encompassed central pain. Dr Scadding also gave evidence that by the priority date people were using the term "neuropathic pain" in its IASP sense to include central pain.

260. Thirdly, the only basis relied upon for Warner-Lambert's construction is the sentence at [0006] which states that neuropathic pain "is caused by injury or infection of peripheral sensory nerves". This is a correct statement whichever construction is adopted. Furthermore, the paragraph goes on to list various causes of neuropathic pain, finishing with a statement that it "includes, but is not limited to pain caused by nerve injury such as, for example" DPN. This is clearly non-limiting language.

261. Fourthly, the Patent contains specific subsidiary claims to phantom limb pain and fibromyalgia pain. I have already concluded that both these conditions were regarded as ones involving central neuropathic pain.

The prior art

262. Mylan and Actavis rely upon the following pieces of prior art:

i) C. P. Taylor *et al*, "Potent and stereospecific anticonvulsants activity of 3-isobutyl GABA relates to in vitro binding at a novel site labelled by tritiated gabapentin", *Epilepsy Research*, 14, 11-15 (1993) ("Taylor I").

ii) C.P. Taylor, "Mechanism of action of new anti-epileptic drugs" in Chadwick (ed.), *New trends in epilepsy management: the role of gabapentin* (Royal Society of Medicine Services), 13-40 (1993) ("Taylor II").

iii) L.B. Mellick and G.A. Mellick, "Successful treatment of reflex sympathetic dystrophy with gabapentin", *American Journal of Emergency Medicine*, 13(1), 96 (1995) ("Mellick").

iv) N.S. Gee *et al*, "The Novel Anticonvulsant Drug, Gabapentin (Neurontin), Binds to the $\alpha_2\delta$ Subunit of a Calcium Channel", *Journal of Biological Chemistry*, 271, 5768-5776 (1996) ("Gee").

v) L.L. Radulovic *et al*, "The Preclinical Pharmacology, Pharmacokinetics and Toxicology of Gabapentin", *Drugs of Today*, 31(8), 597-611 (1995) ("Radulovic").

Taylor I

263. Taylor I is a paper by a team from Parke-Davis led by Charles Taylor. The abstract says that 3-isobutyl GABA is "structurally related to the novel anticonvulsant gabapentin". The structures of GABA, gabapentin and (S)-3-isobutyl GABA (pregabalin) are shown in Figure 1. The introduction says that "there are only a small number of molecular targets that are generally accepted to be relevant for clinical therapy of epilepsies", that "gabapentin has been proven to be an effective treatment for prevention of partial seizures in patients refractory to available drugs" and that "the molecular site of action of gabapentin is not well understood" (page 11). It then says that a "novel binding site labeled by tritiated gabapentin has been described in membrane fractions from rat brain tissue" (page 12, left-hand column). It goes on to say that this binding site "has been used to evaluate a number of derivatives of gabapentin and structurally related compounds". Pregabalin is then identified as being "one of a series of GABA derivatives substituted at the 3-position and of these derivatives is the most potent anticonvulsant in vivo" (page 12, left-hand column).

264. Taylor I reports *in vivo* studies in mice showing the relative anticonvulsant effect of gabapentin, pregabalin and the R-enantiomer of 3-isobutyl GABA. In particular, the results depicted in Fig 2(B) on page 13 show that lower doses of pregabalin appear to result in mice being protected from seizures, compared with gabapentin. The R enantiomer was inactive, however. Taylor I also reports binding studies using radiolabelled gabapentin and partially purified synaptic plasma membranes from rat cortexes. The results in Figure 3 show that pregabalin binds to the same binding site as gabapentin, but more potently. In particular, the legend to Figure 3 states that pregabalin binds with an IC_{50} value of 0.037 µmol, compared with gabapentin which has an IC_{50} of 0.08 µmol, the racemate which has an IC_{50} of 0.083 µmol and the R enantiomer which has an IC_{50} of 0.062 µmol.

265. Taylor I concludes that the results "strongly suggest" that the novel gabapentin binding site is related to anti-convulsant effect *in vivo* and that pregabalin "was significantly more potent than gabapentin for preventing both low-intensity electroshock and conventional maximal electroshock seizures" (page 14, right-hand column).

Taylor II

266. Taylor II is a review article by Charles Taylor which looks at the mechanisms of action of a number of new anti-epileptic drugs (AEDs). After a short introduction, Taylor II successively discusses sodium-channel modulators and AEDs similar to phenytoin, anti-absence drugs relating to ethosuximide; GABA-modulating AEDs, glutamate antagonists, AEDs relating to felbamate and AEDs related to gabapentin. Mylan and Actavis rely upon the last section (pages 23 to 33). Notwithstanding the heading of this section, it is in fact mainly about gabapentin.

267. This section begins by providing some background to gabapentin. The structures of gabapentin and 3-isobutyl GABA (not stereospecifically depicted) are shown in

Figure 6 together with two other molecules. The legend to Figure 6 states that gabapentin binds to a specific protein site in the rat brain and has a novel pharmacological activity. It also explains that 3-isobutyl GABA has a similar pharmacological profile to gabapentin and exists as two enantiomers.

268. Taylor II states (at pages 23-26):

> "Gabapentin (Fig. 6) has been shown to prevent seizures in several animal models and in clinical studies. It has a mechanism of action that appears to be different from the AEDs described above. …
>
> Originally, gabapentin was synthesized as a structural analogue of GABA ….
>
> … gabapentin cannot be described as 'GABA-mimetic' and, despite activity in a variety of *in vivo* and *in vitro* models, its molecular site of action remains to be clearly defined. There has, however, been some study of a newly-discovered specific gabapentin binding site in neuronal tissues (see … below).
>
> Gabapentin has several properties in animals and humans that give it a desirable profile. It has a very low degree of toxicological effects …. It is readily absorbed from the gastrointestinal tract but is not significantly metabolized … ; Gabapentin does not bind significantly to plasma proteins ... Thus gabapentin is unusually easy to administer because of its simple pharmacokinetics, and it has few of the dose-related side effects that are common with other AEDs.
>
> …
>
> *In vitro*, gabapentin does not interact with neuronal sodium channels or L-type calcium channels, thus distinguishing it from phenytoin, carbamazepine and lamotrigine as well as from the dihydropyridine calcium-channel blockers. It is also inactive in standardized receptor-binding assays. …. These negative results support the idea of a novel mechanism of anti-convulsant action for gabapentin."

269. Taylor II then describes recent binding studies with radiolabelled gabapentin "which reveal a specific binding site in the brain, but not in other organs" (page 26). It goes on to say (at page 29):

> "Gabapentin-receptor binding is displaced by unlabelled gabapentin and by several structural analogues of gabapentin, including 3-isobutyl GABA (Fig 6). The two enantiomers of 3-isobutyl GABA have different potencies for binding at the gabapentin site, and the same difference in potency is seen in seizure models with whole animals (Fig. 11) [89] Several other compounds that are potent inhibitors of gabapentin binding *in*

> *vitro* [84] also prevent seizures in animal models [90]. Together these findings strongly suggest that the gabapentin-binding site is novel in comparison to commonly studied neurotransmitter and drug receptor sites of brain. These findings also indicated that the anti-convulsant actions of gabapentin and related compounds are correlated with binding at the gabapentin site, even though the physiological function of the binding site remains to be discovered.
>
> Future biochemical studies may lead to the purification and identification of a protein receptor for gabapentin, such as a functionally characterized membrane-bound receptor, uptake transporter, or enzyme."

270. Figure 11 of Taylor II is the same as Figures 2B and 3 of Taylor I. In particular, the legend to Figure 11 of Taylor II reproduces the information from Taylor I that pregabalin binds with an IC_{50} value of 0.037 µmol (37 nM), compared with gabapentin which has an IC_{50} of 0.08 µmol (80 nM), the racemate which has an IC_{50} of 0.083 µmol (80 nM) and the R enantiomer which has an IC_{50} of 0.062 µmol (62 nM). It also reproduces the information that the R enantiomer was ineffective against seizures.

271. Taylor II then describes additional biochemical and electrophysiological studies with gabapentin. Having summarised a number of studies, it states (at page 29):

> "These results indicate that gabapentin is unlikely to have direct pharmacological actions on the GABAergic synapses or calcium channels that are responsible for glutamate or GABA neurotransmitter release."

272. It goes on to say (at page 30):

> " … gabapentin (100µmol) failed to reduce or otherwise alter long-term potentiation in rat hippocampal slices *in vitro,* a response that is known to depend on activation of NMDA receptors [88]. …
>
> …. Depolarizing responses of cultured spinal cord neurons to the iontophoretic of GABA were not altered by the addition of gabapentin. Gabapentin is also inactive in other electrophysiological tests sensitive to antagonism or modulation of glutamate receptors. In addition, gabapentin had no effect on sustained repetitive firing of sodium-dependent action potentials in cultured spinal cord neurons.
>
> ….
>
> Considered together, biochemical and electrophysiological studies suggest that gabapentin interacts with a novel receptor or enzyme in neurons and thereby causes a biochemical change (poorly defined at present) to cause an anti-convulsant effect.

> Although gabapentin slightly reduces the release of monoamines, the relevance for anti-convulsant action is not clear."

273. The last section of Taylor II discusses the efficacy and pharmacological mechanism of gabapentin. This states (at 33-35):

> "Studies of gabapentin in tests for various anti-epileptics mechanisms are compared with results for prototype AEDS in Table 3. The results indicate that gabapentin does not interact with voltage-sensitive sodium channels, which may be the major site of action of phenytoin, carbamazepine and lamotrigine. …
>
> …
>
> Finally, unlabelled gabapentin and several structural analogues of gabapentin with anti-convulsant properties displace binding of tritiated gabapentin at a novel receptor site of brain membranes, and other AEDs do not displace binding. Stereospecific binding activity of 3-isobutyl GABA is related to stereospecific anti-convulsant activity in whole animals. Together, these data indicate that gabapentin prevents seizure by a mechanism different from those of other AEDS and related to a novel drug-binding site."

Mellick

274. Mellick is a case report in the form of a letter to the editor of the journal. It starts by describing the serious problem of pain conditions such as RSD. It then says that the authors "would like to describe a previously unreported and apparently successful new therapeutic intervention for reflex sympathetic dystrophy". Mellick goes on to say that gabapentin "has recently been found in our practice to be dramatically successful in the treatment of severe and refractory pain in patients with RSD".

275. The historical use of gabapentin as an anticonvulsant is then described. This section has footnotes citing six references including Taylor II and N. Suman-Chauhan *et al*, "Characterization of (^{3}H)- gabapentin binding to a novel site in rat brain: Homogenate binding studies", *Eur. J. Pharmacol.*, 244, 293-301 (1993) ("Suman-Chauhan").

276. Mellick goes on to say that the authors have successfully treated five consecutive patients with RSD with gabapentin and that each of them has experienced "dramatic pain relief and improvements in their conditions with this initiation of this new anticonvulsant". Table 1 sets out the characteristics of the five patients, the dosages which they were given and the levels of relief that the patients benefited from. The authors conclude:

> "To date, we have had no treatment failures. More extensive descriptions of these case studies are pending publication in the pain management literature. We look forward to future controlled investigations in order to confirm our recent

> discovery of successful pain control with gabapentin in patients with RSD."

Gee

277. Gee is another paper by authors from Parke-Davis. The abstract refers to gabapentin as being "a novel anticonvulsant drug, with a mechanism of action apparently dissimilar to that of other antiepileptic agents". The introduction states (at page 5768, right-hand column):

> "A single high affinity (K_D = 38 $\pm$ 2.8 nM) binding site for [^{3}H] gabapentin in rat brain has been described (7). Radioligand binding to brain membranes was potently inhibited by a range of gabapentin analogues and by several 3-alkyl-substituted analogues of GABA, although GABA itself was only weakly active. Other antiepileptic drugs including phenytoin, diazepam, carbamazepine, valproate, and phenobarbitone were inactive. Gabapentin (IC_{50} = 80 nM) and (RS)-3-isobutyl-GABA (IC_{50} = 80 nM) were the most active compounds identified (7). The (S+)-enantiomer of 3-isobutyl-GABA was significantly more active than the (R-)-enantiomer both in displacing [^{3}H] gabapentin binding and in preventing maximal electroshock seizures in mice (8). These data strongly suggest that the protein defined by [^{3}H] gabapentin plays an important role in controlling the excitability of neurons."

Reference 7 is Suman-Chauhan and reference 8 is Taylor I.

278. Gee goes on to describes how the authors identified the molecular target for gabapentin by purifying and characterising the protein from pig cerebral cortex membranes. It identifies the binding site of gabapentin as the $\alpha_2\delta$ subunit of a voltage-dependent calcium channel.

279. A subsection of the results section entitled "Pharmacological properties of the Purified Protein" describes how several compounds were evaluated in competition assays with the purified [^{3}H] gabapentin-binding protein. It states that pregabalin potently inhibited [^{3}H] gabapentin binding with an IC_{50} of 40 nM, compared to 50 nM for gabapentin and 370 nM for the R-enantiomer (page 5771, right-hand column and see also Figure 4 on page 5772).

280. A subsection of the discussion section entitled "Mechanism of action of gabapentin" states that the $\alpha_2\delta$ calcium channel subunit "may be the critical target at which gabapentin exerts its antiepileptic action" and that this "is supported by previous studies that have shown a correlation between the affinity of ligand at the [^{3}H] gabapentin binding site and the anticonvulsant activity (8)", although it is also stated that "the physiological role of the $\alpha_2\delta$ subunit is not well understood at present" (page 5775, left-hand column).

Radulovic

281. Radulovic is another review article by authors at Parke-Davis, including Charles Taylor. The summary refers to gabapentin's mechanism of action being identified, and states that gabapentin "prevents seizures in a variety of animal models and is also active in animal models of spasticity, analgesia and amyotrophic lateral sclerosis (ALS)" (at page 598, left-hand column). After an introduction, the article is divided into three main sections, "Pharmacology", "Disposition" and "Toxicology", each of which is further divided into a number of sub-sections. Mylan and Actavis primarily rely upon three sub-sections of the Pharmacology section.

282. In the introduction Radulovic states (at page 598, right-hand column):

> "Unlike GABA, gabapentin passes the blood-brain barrier. However, gabapentin itself is not active at $GABA_A$ or $GABA_B$ receptors, nor is it an inhibitor of GABA uptake. Numerous pharmacological studies have failed to pinpoint gabapentin's mechanism of action (6.7), but recent studies suggest that gabapentin increases the nonsynaptic release of GABA, perhaps by altering cellular GABA metabolism. In any case, the anticonvulsant activity of gabapentin has been demonstrated in numerous models (see below) and in clinical trials (8-10)."

283. In a subsection of Pharmacology on "Analgesia", Radulovic states (at page 601, left-hand column):

> "Gabapentin was not active in several models of analgesia in response to acute painful stimuli. … However results in a model of neuropathic pain due to constriction of rat sciatic nerve or nerve roots (19, 20) indicated that gabapentin reduces behavioural responses of heightened sensitivity to painful stimuli when administered either systematically or intrathecally. These results suggested that gabapentin alters spinal neuronal circuitry involved in the perception of pain from peripheral neuropathy."

284. Reference 19 is W.-H.Xiao and G.J. Bennett, "Gabapentin relieves abnormal pains in a rat model of painful peripheral neuropathy", *Soc. Neurosci. Abst*., 21, 897 (1995) ("Xiao and Bennett"). Reference 20 is a paper submitted to *Pain* by J.H Hwang and T.L. Yaksh. The evidence is that this paper had not been published by the priority date, and it appears that it was never published.

285. Radulovic goes on in a subsection headed "Potential mechanisms of action" to state (at page 601, left-hand column – right-hand column):

> "Biochemical and electrophysiological studies in vitro with gabapentin are summarized in Table II. Although a constellation of effects were observed, it is not clear which of these are most relevant for the anticonvulsant and/or other pharmacological actions of gabapentin.

> …
>
> Although there are still questions to be answered about the molecular and cellular mechanisms involved and how they might contribute to the prevention of seizures, alteration of nonsynaptic GABA in neuronal tissues is a reasonable explanation for the anticonvulsive effect of gabapentin. …
>
> Gabapentin has other actions that are less clearly associated with its anticonvulsant actions. …"

286. In a subsection headed "Receptor binding studies with [^{3}H] – gabapentin" Radulovic states (at page 602, left-hand column):

> "Gabapentin did not affect ligand binding at a wide variety of commonly studied drug and neurotransmitter binding sites and voltage-activated ion channels, including GABA, glutamate and glycine receptors of several types. However, experiments with [^{3}H]-gabapentin revealed gabapentin binding sites in mouse brain, but not in several peripheral organs (37)."

Reference 37 is Suman-Chauhan.

287. This subsection goes on to say (page 602, right-hand column - page 603, left-hand column):

> "The binding of gabapentin to its receptor was characterised in studies using rat, mouse and pig brain homogenates (37, 39). Unlabelled gabapentin displaced [^{3}H]-gabapentin from rat brain membranes (K_D = 0.08 μM). [^{3}H]-gabapentin was also displaced by the neutral branched-chain amino acids …, as well as by L-glutamine (39). Gabapentin was not displaced from its receptor by other anticonvulsants such as valproate or phenytoin, but it was displaced by several chemically related compounds (37, 40). The displacement of gabapentin from its binding site by various neutral branched-chain amino acids led to the proposal that the gabapentin binding site is related to the membrane transported for these amino acids (39).
>
> Recently, gabapentin was used to isolate and identify a protein from mammalian brain that binds with high affinity to gabapentin molecules (41). These studies indicated that the high-affinity gabapentin binding protein is identical with the $\alpha_2\delta$ subunit of voltage-sensitive calcium channels. However, since the function of $\alpha_2\delta$ subunits of calcium channels is not clear, the functional significance of the high-affinity gabapentin binding site remains to be established."

Reference 40 is Taylor I and reference 41 is Gee (then in press).

288. In a subsection headed "electrophysiological studies" relied on by Warner-Lambert, Radulovic states (at page 603, left-hand column):

> "Gabapentin did not alter voltage-clamped sodium currents in the same manner as phenytoin, carbamazepine or lamotrigine (43), but with longer *in vitro* incubation periods it did alter sustained firing of Na-dependent action potentials (44). In addition, a recent study suggested that gabapentin has other electrophysiological actions that may account for reduced excitability (45). It is not yet clear whether these *in vitro* findings are relevant to its anticonvulsant and/or other pharmacological actions in *in vivo*."

Obviousness

The law

289. In order for a claim in a patent to be valid, the claimed process or product must not be obvious. The structured approach to the assessment of allegations of obviousness first articulated by the Court of Appeal in *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd* [1985] RPC 59 was re-stated by Jacob LJ in *Pozzoli v BDMO SA* [2007] EWCA Civ 588, [2007] FSR 37 at [23] as follows:

> "(1)(a) Identify the notional 'person skilled in the art';
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the 'state of the art' and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?"

290. The correct approach to the fourth step in a case such as the present was summarised by Kitchin LJ, with whom Lewison and Moore-Bick LJJ agreed, in *MedImmune Ltd v Novartis Pharmaceuticals Ltd* [2012] EWCA Civ 1234, [2012] RPC 27 as follows:

> "90. One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of

technology such as pharmaceuticals and biotechnology which are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them worthwhile. But denial of patent protection in all such cases would act as a significant deterrent to research.

91. For these reasons, the judgments of the courts in England and Wales and of the Boards of Appeal of the EPO often reveal an enquiry by the tribunal into whether it was obvious to pursue a particular approach with a reasonable or fair expectation of success as opposed to a hope to succeed. Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way. Lord Hoffmann summarised the position in this way in *Conor* at [42]:

> 'In the Court of Appeal, Jacob LJ dealt comprehensively with the question of when an invention could be considered obvious on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, by saying that the notion of something being obvious to try was useful only in a case where there was a fair expectation of success. How much of an expectation would be needed depended on the particular facts of the case.'

92. Moreover, whether a route is obvious to try is only one of many considerations which it may be appropriate for the court to take into account. In *Generics (UK) Ltd v H Lundbeck*, [2008] EWCA Civ 311, [2008] RPC 19, at [24] and in *Conor* [2008] UKHL 49, [2008] RPC 28 at [42], Lord Hoffmann approved this statement of principle which I made at first instance in *Lundbeck*:

> '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.'
>
> 93. Ultimately the court has to evaluate all the relevant circumstances in order to answer a single and relatively simple question of fact: was it obvious to the skilled but unimaginative addressee to make a product or carry out a process falling within the claim…."

291. This approach has been followed and applied in a number of subsequent Court of Appeal and first instance decisions: see in particular *Regeneron v Genentech* in the Court of Appeal at [86] (Kitchin LJ).

292. Counsel for Warner-Lambert submitted that Mylan and Actavis must show that it would have been obvious to the skilled team that pregabalin *would* be effective to treat pain, but he nevertheless accepted that it was relevant to consider whether the skilled team would have a fair expectation of success if it were to try pregabalin for the treatment of pain. In my judgment this is the correct test for the reasons I gave in *Hospira UK Ltd v Genentech Inc* [2015] EWHC 1796 (Pat) at [108]-[115].

Overview of the obviousness case

293. Mylan and Actavis' obviousness case is focussed on the use of pregabalin for the treatment of neuropathic pain, i.e. claim 3 and subsidiary claims falling within the ambit of claim 3. It suffers from the basic difficulty that none of the prior art relied on discloses both pregabalin and use for the treatment of neuropathic pain (or any kind of pain). Mylan and Actavis advance a series of different arguments, which divide into two main groups. The first group starts from the proposition that the potential utility of gabapentin for treating neuropathic pain was common general knowledge. On this basis, Mylan and Actavis rely upon Taylor II alternatively Gee alternatively Radulovic (read with Taylor I or Gee) as starting points. If this was not common general knowledge, as I have concluded, Mylan and Actavis rely upon Mellick (read with Taylor II or Gee) alternatively Radulovic (read with Taylor I or Gee) as starting points. It can thus be seen that Mylan and Actavis' case depends on the skilled team reading (at least) two items of prior art together. It is well established that, in principle, this is a perfectly permissible line of argument; but it is more difficult to make good than a case based solely upon the disclosure of a single item of prior art (read with the common general knowledge).

General points relied on by Warner-Lambert

294. Warner-Lambert relies upon a number of general points in answer to the obviousness case. It is convenient to mention these before turning to the individual citations.

295. The first point is a matter of secondary evidence. This is that it is plain that Taylor I, Taylor II and Gee were fairly widely read and referred to at the time. Gee in particular appears to have made quite an impact. Despite this, none of the experts in this case, nor any of the other neuroscientists who might expected to have become aware of these papers, made the invention claimed in the Patent.

296. The second point is that, as both Dr Scadding and Prof Wood agreed, there was little understanding of the mechanisms of neuropathic pain at the priority date. As a consequence, drug development was a case of trial and error. I would comment that this point is rather contradictory of Warner-Lambert's case with regard to insufficiency. Moreover, it must be qualified by my findings as to the common general knowledge concerning central sensitisation and the reorganised state; but nevertheless I consider that the generality of the point is accurate.

297. The third point is that, as both Dr Scadding and Prof Wood agreed, an ion channel blocker (such as pregabalin) would have been thought to be an unattractive candidate for a pharmaceutical because it was likely to have effects all over the body, and thus to cause side effects.

298. I agree that all three matters are pointers against a conclusion of obviousness, although none is anywhere near conclusive.

Mellick

299. Mellick is concerned with the use of gabapentin for the treatment of RSD. Dr Scadding and Prof Clauw were agreed that, as noted in paragraph 54 above, the prevailing view at the priority date was that RSD included a neuropathic pain component. The only evidence that gabapentin is efficacious provided by Mellick is anecdotal. There is no mention of pregabalin in Mellick.

300. Mylan and Actavis rely upon Mellick as a starting point which takes the skilled team to either Taylor II (which is cited as a reference in Mellick) or Gee (which is not cited in Mellick and is later in time).

301. The first issue is whether the skilled team, and in particular the neuroscientist, would consider Mellick worth pursuing at all. Prof Woolf was trenchant in his criticism of Mellick, and gave a whole series of reasons as to why the skilled team would not regard the disclosure as credible or worth taking forward: the journal was not a mainstream one; it was unlikely that Mellick had been peer-reviewed given that it was a case report; he had not heard of the authors or their institutions; Mellick contained statements which lacked credibility, such as stating that patients with chronic pain often presented to the emergency department, or which were simply incorrect, such as that gabapentin is a GABA-mimetic; the lack of clarity as to which patients were included or excluded; the hyperbolic language used to describe the results; the statement that there had been no failure was not plausible; and, above all, the fact that the evidence presented was purely anecdotal.

302. Counsel for Mylan and Actavis pointed out that there was an inconsistency between Prof Woolf's criticisms of Mellick and his reliance on Kristensen *et al*, but as I have already noted, Prof Woolf's response to this was to accept that little weight could be placed on the latter.

303. Prof Wood's view was that the neuroscientist would be interested in the potential utility of gabapentin as a result of reading Mellick, although he accepted that the neuroscientist would not have any expectation based on Mellick as to what the results of animal model tests would be. As counsel for Mylan and Actavis pointed out, Prof Wood's evidence is supported by the unchallenged evidence of Prof Bennett that he

was interested in Gary Mellick's results (Dr Mellick contacted him directly with information equivalent to that in Mellick) and that it led him to try gabapentin in his model.

304. I prefer Prof Wood's evidence on this point, but I accept that the skilled team would regard Mellick's claims with caution given that the evidence is anecdotal.

305. Prof Woolf accepted that, if the skilled team were interested in the teaching of Mellick and wanted to take gabapentin further for treating pain, they would follow the reference to Taylor II. Prof Wood accepted that they would also follow the reference to Suman-Chauhan.

306. Suman-Chauhan describes gabapentin as a novel anticonvulsant with an unknown mechanism of action which does not exhibit analgesic activity (citing a 1986 abstract by Dooley *et al*). The paper reports studies of the binding characteristics of radiolabelled ([^{3}H]) gabapentin and a number of other GABA analogues to a binding site using purified synaptic plasma membranes prepared from rat cerebral cortex. Gabapentin and racemic 3-isobutyl GABA showed the highest binding to this site of those tested. The paper includes a note added in proof that the authors have subsequently found that "a number of neutral L-amino acids …. are potent inhibitors of [^{3}H] gabapentin binding" (page 301, left-hand column).

307. It is Mylan and Actavis' case that, in addition to following up the key references cited in Mellick, the skilled team would also carry out a literature search, and thus find Gee. Although Prof Wood gave evidence in his first report that the neuroscientist would carry out a literature search "to identify other scientific papers relating to gabapentin", and that he believed that the neuroscientist would find Gee as a result, he was not specific as to what search would be done or how. In cross-examination he accepted that he could not be sure what papers would be found. Nor was any case put to Prof Woolf in cross-examination as to the nature of the search that would be carried out. Still less was it put that the skilled team would inevitably find Gee. Accordingly, I am not persuaded that it has been established that the skilled team would find Gee as a result of reading Mellick.

Taylor II

308. For the reasons given above, I accept Mylan and Actavis' case that the skilled team would come to Taylor II from reading Mellick, but I accept Warner-Lambert's case that in that event the skilled team would also take into account Suman-Chauhan.

309. Mylan and Actavis contend that the skilled team reading Taylor II would appreciate the following:

    i) Gabapentin is an effective anticonvulsant, albeit with an unknown mechanism of action.

    ii) Gabapentin binds to a unique binding site.

    iii) The binding occurs throughout the synaptosomal membrane fraction, which is the place that the skilled team would be interested in as it looks at neuronal cells which are relevant to anticonvulsant activity. Whilst Taylor II does not

exclude the possibility of there being a non-neuronal binding site, there is no suggestion of that in Taylor II.

iv) The relative potency of the binding site is correlated with the therapeutic antiseizure activity. The correlation would not give the neuroscientist proof that the binding site was responsible for gabapentin's physiological function, but it would give him a reasonable expectation that the two were linked. The data in Taylor II certainly gave the author enough confidence to state that the findings "indicate that the anti-convulsant actions of gabapentin and related compounds are correlated with the binding at the gabapentin site".

v) Pregabalin has structural similarity with gabapentin, it binds with more potency to the gabapentin binding site than gabapentin and it is also more potent in preventing seizures.

310. Warner-Lambert does not dispute points (i) and (ii), but it takes issue with points (iii) and (iv). As for point (v), Warner-Lambert contends that this is an oversimplification.

311. The dispute as to point (iii) is essentially one of emphasis: Warner-Lambert emphasises Prof Woolf's evidence that Taylor II does not exclude the possibility of binding in non-neuronal cells.

312. The dispute with respect to point (iv) is more marked. Warner-Lambert relies on Prof Woolf's evidence that Taylor II provides "absolutely no evidence" that the binding site has pharmacological activity. Prof Wood's evidence was more nuanced: he maintained that Taylor II showed that there was a correlation (and indeed the contrary was not put to him), and that this would give one a reasonable expectation that the two were linked, but he accepted that there was no proof.

313. Counsel for Warner-Lambert relied upon two matters as supporting Prof Woolf's view. The first is a statement in a paper by O. Honmou *et al*, "Gabapentin potentiates the conductance increase induced by nipecotic acid in CA1 pyramidal neurons in vitro", *Epilepsy Res.*, 20, 193-202 (1995) at 194, following a reference to Taylor II, that "there is no evidence that the binding site correlates with the site of action of gabapentin". I am unimpressed with this point for two reasons. First, no basis was put to Prof Wood for thinking either that the skilled team would read this paper or that it accurately represented the reaction of the skilled team to Taylor II. Secondly and more importantly, Taylor II does present evidence of correlation, and as noted above, the contrary was not put to Prof Wood. The real issue is whether there is evidence of anything more than correlation.

314. Secondly, Prof Woolf pointed out there was a discrepancy between the binding data and the anticonvulsant data, namely that the R enantiomer had a binding affinity only 16 times lower than pregabalin and 8 times lower than gabapentin, but it was inactive against seizures even at much higher doses. Prof Wood agreed that this was an interesting observation, but he thought that it could be explained by the conditions under which the binding assay was carried out and the requirement for transport of the compounds into the cells. Accordingly, he would not be concerned by the discrepancy.

315. The conclusion I draw with regard to this point is that the skilled team would consider that Taylor II provided evidence of a correlation between binding to the binding site and anticonvulsant effect, and that that would suggest that there might be a link, but that there was no proof of this. Accordingly, the skilled team would appreciate that further work remained to be done.

316. Finally, so far as point (v) is concerned, Warner-Lambert relies upon the evidence with the respect to the R enantiomer that I have already mentioned.

317. Against this background, Mylan and Actavis argue as follows:

    i) The skilled team would be prompted by Mellick to test gabapentin in an animal model of neuropathic pain such as the CCI model.

    ii) As a result of reading Taylor II, the skilled team would be prompted to test pregabalin as well.

    iii) The models themselves are relatively inexpensive and there would be no risk (other than expense) in carrying out the tests.

    iv) The skilled team would be highly motivated to carry out such tests, given the need for more effective treatments for neuropathic pain.

    v) The skilled team would have a reasonable expectation of success because they would know that gabapentin was a clinically useful candidate for treating neuropathic pain, and Taylor II would provide them with information as to the binding site which was likely to relate to the pharmacological action of gabapentin and that pregabalin binds more potently to that site than gabapentin.

    vi) Accordingly, it would be obvious to try pregabalin for treating pain in an animal model.

318. I am not persuaded by this argument. In my view it is a step-by-step argument based on hindsight. I will consider the steps one by one.

319. Prof Woolf accepted that, if the neuroscientist was interested in taking gabapentin forward as a possible treatment for neuropathic pain, as I consider that the skilled reader of Mellick would be, an obvious step to take would be try it in an animal model of neuropathic pain, such as the Bennett model. Accordingly, I consider that it would be an obvious step in the light of Mellick to test gabapentin in an animal model for neuropathic pain.

320. I accept, as I have said, that the skilled team would follow up the references to Taylor II and Suman-Chauhan. I also consider that Taylor II would encourage the skilled team to test gabapentin for neuropathic pain notwithstanding the negative statement about its analgesic activity in Suman-Chauhan, which Prof Wood explained that he would not place weight on given that its source was solely an abstract from obscure authors dating from 1986.

321. In my judgment it is clear from the evidence of Prof Wood and Prof Woolf that the skilled team would have little expectation of success with gabapentin given that (a)

the evidence of efficacy in Mellick is purely anecdotal, (b) Taylor II contains no evidence of efficacy with respect to pain at all and (c) Taylor II indicates that gabapentin has a novel mechanism of action, which suggests that it is unlikely to act through any recognised pain pathway. As discussed above, the mere fact that gabapentin was an anticonvulsant would not give the skilled team any expectation that it would be effective for pain.

322. I do not accept that it would then be obvious to test pregabalin as well as gabapentin. Taylor II is a long review of a number of different classes of AEDs. I accept that the section on AEDs related to gabapentin would be of interest to the skilled team coming from Mellick, but most of the material in this section is about gabapentin itself. Pregabalin is mentioned, and some data relating to it is presented, but there is no emphasis on pregabalin in Taylor II. Once the skilled team moved beyond testing gabapentin, moreover, there are various other possibilities that they could explore. Thus Prof Wood accepted that he would be interested in testing the amino acids mentioned in the note added to Suman-Chauhan in proof, and that they would possibly be higher on his list than pregabalin. I accept that the skilled team would be motivated and that the tests would not be difficult or expensive to carry out, but nevertheless anything more than a test of gabapentin would still be a research project, as Prof Wood accepted. As Prof Woolf emphasised (albeit in the context of Radulovic), there are ethical issues with animal tests and they do take time and resources, and thus the skilled team would prioritise testing for compounds for which there was a clear rationale in the form of data.

323. Although it is not a matter that I have relied on in reaching this conclusion, I consider that my conclusion is supported by Prof Bennett's evidence. He was prompted by the information received from Dr Mellick to try gabapentin in his model of neuropathic pain. This led to Xiao and Bennett and then to a full paper (W.-H. Xiao and G.J. Bennett, "Gabapentin has an antinociceptive effect mediated via a spinal site of action in a rate model of painful peripheral neuropathy", *Analgesia*, 2, 267-273 (1996)) which was initially submitted on 10 June 1996 and submitted in revised form on 12 July 1996. As one would expect, Prof Bennett was aware of Taylor's work, and cited Taylor I in his paper. Yet Prof Bennett does not suggest in his evidence that he was prompted to test pregabalin in his model.

324. Finally, even if the skilled team considered testing pregabalin, Prof Wood accepted that the skilled team would have even less expectation of success with pregabalin than gabapentin. In my view they would have no expectation of success at all with pregabalin, since there was not even the anecdotal evidence in Mellick to suggest that pregabalin might be efficacious against pain.

Gee

325. Given that (a) I have concluded that it was not common general knowledge that gabapentin was being used to treat pain, (b) I have concluded that it has not been shown that the skilled team would find Gee as a result of reading Mellick and (c) for the reasons I shall explain, I do not consider that Gee adds anything to Mylan and Actavis' case based on Taylor II, I shall deal with Gee fairly briefly.

326. As Prof Woolf accepted, Gee represents a significant scientific advance on Taylor II in terms of identifying the binding site of gabapentin. On other hand, no function or

pharmacological effect is ascribed to it. So far as the obviousness argument is concerned, Gee simply repeats the key information in Taylor II, but adds nothing to it. Mylan and Actavis' argument based on Gee is very similar to its argument based on Taylor II. The only real difference is that Mylan and Actavis rely upon the allegation that it was common general knowledge that there was a relationship between the inhibition of calcium channels and analgesia; but I have concluded that it was not common general knowledge that there was any particular reason for thinking that calcium channel blockers were effective.

327. In my view it would be no more obvious to test pregabalin for neuropathic pain in the light of Gee than in the light of Taylor II. As Prof Wood accepted, the focus of Gee is entirely on gabapentin. Pregabalin is used purely as a tool to help characterise the binding site. Prof Wood accepted that mechanistic studies based on gabapentin would be a much simpler route forward than turning to pregabalin. Furthermore, Prof Wood and Prof Woolf were agreed that Gee invites further mechanistic studies on gabapentin. In any event, Gee would not give the skilled team any expectation of success if they did test pregabalin for pain. Prof Wood volunteered that this would be "an enormous logical leap".

Radulovic

328. Radulovic advances Mylan and Actavis' case with respect to gabapentin because it discloses that gabapentin has given positive results in the Bennett animal model of neuropathic pain; but it does not mention pregabalin.

329. Prof Woolf accepted that the neuroscientist would follow up the reference to Xiao and Bennett (for the reason explained above, it would not be possible for him to follow up the reference to Hwang and Yaksh). This abstract (which was for a poster presentation by Prof Bennett at the 25th Annual Meeting for the Society of Neuroscience in San Diego in November 1995) states that gabapentin is a "novel antiepileptic with an unique binding pattern in brain, and an unknown mechanism of action." It then states that Mellick and Mellick "suggests that it may have efficacy in the treatment of neuropathic pain". The abstract describes studies of gabapentin's effect on "heat-hyperalgesia" and "mechano-hyperalgesia (pin prick test) and mechano-allodynia (v. Frey hair test)". It reports that heat hyperalgesia and mechano-allodynia, but not mechano-hyperalgesia, were "significantly reduced in a dose-related manner". It concludes by saying "Our results suggest that [gabapentin] may be useful in the clinic and that its effects may be mediated by a spinal site of action".

330. Counsel for Warner-Lambert relied on the fact that Xiao and Bennett was one of over 12,400 abstracts of presentations at the Society of Neuroscience conference contained in a three-volume supplement, and on evidence given by Prof Woolf that abstracts are not included in the PubMed database, as showing that the skilled team would not have obtained Xiao and Bennett. In my judgment these points are immaterial because Xiao and Bennett is specifically cited in Radulovic, and in principle it could have been obtained by the skilled team (albeit that in reality this might take some effort).

331. Prof Wood's evidence was that, being recent and from Prof Bennett, this would be of interest to the neuroscientist. Counsel for Warner-Lambert submitted that Prof Wood appeared to have assumed that the skilled team would have access to Prof Bennett's full poster presentation. I do not accept this. Rather, I understood Prof Wood to be

saying that, because he would be interested in what was said in the abstract, he would go to the meeting (which he was in the habit of going to) to see the full poster in order to find out more information, and in particular the data underlying the conclusions presented in the abstract. He did not rely upon anything that might be contained in poster (which is not in evidence) as part of his analysis, however.

332. Prof Woolf accepted that there was no reason to doubt the accuracy of the results reported in Xiao and Bennett, but pointed to the absence of data from the abstract and the fact that it would not have been peer-reviewed. He expressed the view that, without the data, the abstract did not provide a compelling case for testing gabapentin for the treatment of neuropathic pain.

333. In my judgment it would be obvious in the light of Radulovic, read together with Xiao and Bennettt, to pursue the development of gabapentin for the treatment of neuropathic pain, in particular by conducting further animal studies. Furthermore, I consider that the skilled team would have a reasonable expectation of success in such studies given that a well-known author in the field had reported positive results, albeit without yet revealing his data. But this does not assist Mylan and Actavis unless it would also be obvious to test pregabalin with a similar expectation of success.

334. In this regard Mylan and Actavis rely upon the references to Taylor I and Gee. Prof Woolf accepted that the neuroscientist would follow up the references in the "receptor binding studies" section of Radulovic, which include Taylor I, Gee and Suman-Chauhan. But in my judgment this does not get Mylan and Actavis home for the following reasons.

335. As can be seen from the description above, the disclosure of Taylor I is essentially equivalent to that of Taylor II for present purposes (it contains a little more detail, but nothing turns on that). It is fair to say that Taylor I is more focussed than Taylor II. Nevertheless the skilled team starting from Radulovic is only reading Taylor I in order to follow up the references given by Radulovic. Thus the context is the skilled team's interest in what Radulovic has taught them about gabapentin. It is true that Taylor I teaches them that pregabalin is structurally related to gabapentin, binds more potently and is a more potent anticonvulsant, but it does not say anything about pregabalin's effect on neuropathic pain. For the reasons I have given when discussing Taylor II, I do not consider that it would be obvious to test pregabalin as well gabapentin. Indeed, as counsel for Warner-Lambert pointed out, Radulovic emphasises how much work has been done on gabapentin, and yet how little was known about its mechanism of action. As the skilled team would appreciate, much less work had been done on pregabalin. Furthermore, like Suman-Chauhan, which it cites, Radulovic draws attention to the neutral L-amino acids as another possibility to investigate.

336. As for the reference to Gee, this does not advance Mylan and Actavis' case any further than Taylor I/Taylor II for the reasons discussed above.

337. In any event, Prof Wood accepted that there would have been no expectation of success, and that was also Prof Woolf's opinion.

Overall conclusion

338. For the reasons discussed above, I conclude that none of the claims of the Patent is obvious over any of the prior art relied upon by Mylan and Actavis.

Insufficiency

The law

339. In *Eli Lilly & Co v Human Genome Sciences Inc* [2012] EWCA Civ 1185. [2013] RPC 22 Sir Robin Jacob quoted with apparent approval at [11] the following summary of the relevant principles given by Kitchin J (as he then was) at first instance in the same case [2008] EWHC 1903 (Pat), [2008] RPC 29 at [239]:

> "The specification must disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. The key elements of this requirement which bear on the present case are these:
>
> (i) the first step is to identify the invention and that is to be done by reading and construing the claims;
>
> (ii) in the case of a product claim that means making or otherwise obtaining the product;
>
> (iii) in the case of a process claim, it means working the process;
>
> (iv) sufficiency of the disclosure must be assessed on the basis of the specification as a whole including the description and the claims;
>
> (v) the disclosure is aimed at the skilled person who may use his common general knowledge to supplement the information contained in the specification;
>
> (vi) the specification must be sufficient to allow the invention to be performed over the whole scope of the claim;
>
> (vii) the specification must be sufficient to allow the invention to be so performed without undue burden."

340. Failure to enable the invention to be performed without undue burden is often referred to as "classical insufficiency" and failure to enable the invention to be performed over the whole scope of the claim is often referred to as "*Biogen* insufficiency" or "excessive claim breadth", although these are aspects of the same objection and often shade into one another. In the present case, Mylan and Actavis' case is one of excessive claim breadth.

341. I reviewed the law with regard to excessive claim breadth at some length in *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2011] EWHC 1699 (Pat) at

[458]-[484] and summarised that analysis in *Sandvik Intellectual Property AB v Kennametal UK Ltd* [2011] EWHC 3311 (Pat), [2012] RPC 23 at [121]-[124]. As Kitchin LJ stated in *Regeneron v Genentech*:

> "100. It must therefore be possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim or, put another way, the assertion that the invention will work across the scope of the claim must be plausible or credible. The products and methods within the claim are then tied together by a unifying characteristic or a common principle. If it is possible to make such a prediction then it cannot be said the claim is insufficient simply because the patentee has not demonstrated the invention works in every case.
>
> 101. On the other hand, if it is not possible to make such a prediction or if it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within the scope of the claim then the scope of the monopoly will exceed the technical contribution the patentee has made to the art and the claim will be insufficient. It may also be invalid for obviousness, there being no invention in simply providing a class of products or methods which have no technically useful properties or purpose."

342. As counsel for Warner-Lambert pointed out, the question of what is meant by "plausible" has been considered in the context of an objection of lack of industrial applicability by the Supreme Court in *Human Genome Sciences Inc v Eli Lilly & Co* [2011] UKSC 51, [2012] RPC 6, where Lord Hope said at [149]:

> "I would not quarrel with Jacob L.J.'s comment, after consulting the *Shorter Oxford English Dictionary*, that the sense [the word 'plausibly'] conveys is that there must be some real reason for supposing that the statement is true: para. 111. The important point, however, is that the standard is not any higher than that."

The same sense is conveyed by some of the other expressions which can be found in the case law on industrial applicability, and which are mentioned by Lord Neuberger in his judgment in that case, such as "reasonably credible".

Assessment

343. Mylan and Actavis accept that the specification makes it plausible that pregabalin is efficacious for the treatment of inflammatory pain, and accordingly do not challenge the validity of claims 2, 5, 7, 8 and 9 on this ground. Mylan and Actavis contend that the specification does not make it plausible that pregabalin is efficacious for the treatment of neuropathic pain, idiopathic pain or fibromyalgia, and therefore challenge the validity of claims 1, 3, 4, 6, 10, 11, 12, 13 and 14 on this ground. (Mylan and Actavis also rely on the same contention as leading to invalidity of these claims by the alternative route of so-called *Agrevo* obviousness referred to by Kitchin

LJ at the end of my citation from *Regeneron* above, but it is not necessary to consider this separately.)

344. It is convenient to begin with some general observations. The first is that, even on Warner-Lambert's construction, claim 1 is extremely broad. Prof Woolf accepted that the idea that a compound would be useful for all the conditions listed in [0003] was really quite extraordinary. The second is that the specification expressly states that the data presented show that pregabalin is effective in the treatment of inflammatory pain, a statement which it is common ground that the skilled team would regard as entirely plausible. By contrast, the specification does not claim that the data presented show that pregabalin is effective in the treatment of neuropathic pain, let alone conditions such as idiopathic pain. Thirdly, the specification expressly mentions two recognised models of neuropathic pain, but presents no data from such models. Fourthly, as already noted, there is no mention in the specification of the unifying principle relied upon by Warner-Lambert, namely central sensitisation. Indeed, there is no suggestion in the specification that there is any unifying characteristic or principle which enables a prediction to be made in respect of conditions other than inflammatory pain. Fifthly, the skilled team would note that the specification does not refer to either hyperalgesia or allodynia when discussing the formalin test. Sixthly, the skilled team would appreciate that the data presented in the Patent do not discriminate between primary and secondary hyperalgesia, but it is only the latter that indicates the presence of central sensitisation. Furthermore, the skilled team would appreciate that it would have been quite easy to design the experiments in way that did measure secondary hyperalgesia. Seventhly, as counsel for Mylan and Actavis pointed out, it is telling that counsel for Warner-Lambert suggested to Dr Scadding and Prof Wood in cross-examination that there was sufficient data in the Patent to make obvious to try pregabalin for neuropathic pain. That is not enough for sufficiency.

345. Having made those general observations, I shall consider the objection claim by claim. It is convenient to start with claim 13, which is in a category of its own, before turning to the claims relating to neuropathic pain.

346. *Claim 13: idiopathic pain*. In my judgment there is nothing in either the specification or the common general knowledge which renders the claim that pregabalin would be effective to treat idiopathic pain remotely plausible. Prof Wood was clear that this was overdoing it, and it is not hard to see why. Dr Scadding's evidence was to similar effect. Neither Prof Clauw nor Prof Woolf gave any evidence which supports the sufficiency of this claim.

347. *Claim 3: neuropathic pain*. It is necessary to divide consideration of neuropathic pain into central neuropathic pain and peripheral neuropathic pain.

348. So far as central neuropathic pain is concerned, as discussed above, the common general knowledge was that central sensitisation was not thought to have a role in central neuropathic pain. It follows that Warner-Lambert cannot rely upon central sensitisation as a unifying characteristic or principle which embraces central neuropathic pain. Even if the skilled team reading the Patent with their common general knowledge as to central sensitisation regarded it as plausible that pregabalin would be effective for peripheral neuropathic pain, they would not consider that that rationale extended to central neuropathic pain. Thus Prof Woolf accepted that, based on the data in the Patent, it would be impossible for the skilled team to make any

reasonable prediction that pregabalin would be effective for treating central neuropathic pain, whereas he maintained that it could be predicted that it would be effective for peripheral neuropathic pain. It is for this reason that counsel for Warner-Lambert argued that claim 3 should be construed as limited to peripheral neuropathic pain.

349. In the alternative, counsel for Warner-Lambert argued that a unifying characteristic or principle which embraced central neuropathic pain was the presence of hyperalgesia and/or allodynia. I do not consider that this argument is open to Warner-Lambert, since it was not pleaded, advanced in Warner-Lambert's evidence or opening skeleton argument, was not put to Dr Scadding or Prof Wood, was not supported by Prof Woolf and was first suggested by Prof Clauw (who gave evidence last) in cross-examination. In any event, I do not accept that, considered as a whole, the evidence supports it. As I have said, the only expert who espoused it was Prof Clauw and then only very late in the day. Furthermore, as counsel for Mylan and Actavis pointed out, this argument is difficult to reconcile with the fact that NSAIDs were known to be effective for the treatment of inflammatory pain, but not neuropathic pain, a problem that becomes particularly acute when one is dealing with central neuropathic pain. (While this is also an obstacle to Warner-Lambert's case with respect to peripheral neuropathic pain, it is less of an issue for the reason explained in paragraph 234 above.)

350. Finally, counsel for Warner-Lambert prayed in aid the fact that pregabalin had subsequently been authorised for central (as well as peripheral) neuropathic pain; but as counsel for Mylan and Actavis pointed out, later work does not justify a claim which was speculative when it was made.

351. Turning to peripheral neuropathic pain, I consider that the evidence is finely balanced. In addition to the general points made above, Warner-Lambert's case suffers from the problem that it has not been established that it was common general knowledge that the rat paw formalin test was predictive of efficacy for neuropathic pain. Moreover, as discussed above, Prof Woolf accepted that the carrageenin and post-operative pain models did not assist in this regard. Nevertheless, I have concluded on balance that, given that plausibility is a relatively low threshold, the data contained in the specification, when read with the common general knowledge, just make it plausible that pregabalin would be effective to treat peripheral neuropathic pain. This is because the common general knowledge as to (i) the involvement of central sensitisation (at least as an amplifying mechanism) in both inflammatory pain and peripheral neuropathic pain and (ii) the role played by central sensitisation in the rat paw formalin test would have suggested to the skilled team that it was possible that a drug which was effective for inflammatory pain, in particular as modelled by the second phase of the formalin test, would also be effective in peripheral neuropathic pain, although this would not necessarily be the case. This conclusion is supported by the evidence not only of Prof Woolf, but also of Dr Scadding and Prof Wood in cross-examination. Dr Scadding said that, when he read the Patent, he thought that it "could be the case" that pregabalin would be effective for (peripheral) neuropathic pain, although a demonstration of that was missing. Prof Wood more or less accepted that it was a credible suggestion, although he made it clear that he would want to test it experimentally.

352. Given that claim 3 is not restricted to peripheral neuropathic pain (and there is no application to amend it so as to restrict it in that way), however, this conclusion does not save the validity of claim 3.

353. *Claims 4: cancer pain.* As I understand it, it is common ground that cancer pain could be peripheral or central neuropathic pain, depending on the location of the tumour. It follows that claim 4 is invalid.

354. *Claim 6: phantom limb pain*. I have already concluded that phantom limb pain was regarded as a form of central neuropathic pain and that it has not been established that it was known to have a central sensitisation component. Accordingly, claim 6 is invalid.

355. *Claim 14: fibromyalgia pain*. In my judgment it was not plausible that pregabalin would be effective to treat fibromyalgia. Whether or not fibromyalgia was regarded as a type of neuropathic pain, it was not common general knowledge that it had a central sensitisation component. Dr Scadding accepted that the claim was credible on that assumption, but not otherwise. Prof Wood did not consider this claim plausible. Prof Woolf's evidence was predicated upon it having a central sensitisation component. Prof Clauw's evidence I have discussed above.

356. *Claims 10 (trigeminal neuralgia pain), 11 (PHN pain) and 12 (causalgia pain)*. There was barely any mention of these claims in closing submissions. If I have understood the position correctly, Mylan and Actavis accept that these types of pain were regarded as falling within peripheral neuropathic pain. Accordingly, I conclude that they are valid.

357. *Claim 1: pain*. It follows from my conclusions above that claim 1 is also invalid. I would add there is simply no basis for saying that it was plausible that pregabalin would be effective for all types of pain.

Overall conclusion

358. I conclude that claims 1, 3, 4, 6, 13 and 14 are invalid on the ground of insufficiency.

Infringement: introduction

359. For convenience, in the sections of this judgment dealing with infringement and threats, I shall refer to Warner-Lambert and Pfizer without distinction as "Pfizer". Pfizer's claim for infringement is made pursuant to section 60(1)(c), alternatively section 60(2), of the 1977 Act. For the purposes of its claim for infringement, Pfizer relies on claims 1 and 3 of the Patent. I have concluded above that those claims are invalid, but I shall consider the infringement claim on the assumption that I am wrong about that. I shall nevertheless proceed on the basis that my construction of claims 1 and 3 is the correct one, which was how counsel for Pfizer argued the infringement case, while paying lip-service to the proposition that the claims must be interpreted in the same way for validity and infringement. This avoids the additional complications which ensue if the narrower construction is accepted.

Infringement: the facts

360. Unusually, the infringement claim in this case involves consideration of an extensive factual background. Although I set out much of the relevant background in earlier judgments, and in particular *Warner-Lambert I*, at that time the evidence was incomplete and untested. Accordingly, in this judgment I shall approach these matters afresh.

NHS England, CCGs, GPs and pharmacies

361. NHS England was established on 1 October 2012 as an executive non-departmental public body pursuant to the National Health Service Act 2006 as amended by the Health and Social Care Act 2012. With effect from 1 April 2013, NHS England has taken on many of the functions of the former Primary Care Trusts with regard to the commissioning of primary care health services, as well as some nationally-based functions previously undertaken by the Department of Health. The new arrangements comprise a single operating model for the commissioning of primary care services in England. Among the duties imposed on NHS England by the 2006 Act is a duty to publish guidance for CCGs on the discharge of their commissioning functions. Under the National Health Service Act 2006 as amended, the Secretary of State is under a duty to promote the autonomy of NHS England and may only give it directions if NHS England is guilty of a significant failure properly to discharge its functions.

362. CCGs are statutory bodies responsible for commissioning a range of medical services in their respective areas of England. All providers of primary medical services in England (other than purely private providers) are required to be members of a CCG. There are 211 CCGs.

363. In 2013 there were 35,561 GPs in England (not including locum GPs, of whom there appear to be a considerable number given the number of doctors who are registered). As at 31 March 2014 there were 11,647 pharmacies providing NHS pharmaceutical services in England (generally referred to as "community pharmacies").

The NHS in Wales, Scotland and Northern Ireland

364. As noted above, in Wales, Scotland and Northern Ireland, healthcare is a devolved matter. There is no counterpart to either NHS England or the CCGs in any of those nations. As I understand it, NHS Wales (GIG Cymru), NHS Scotland and NHS Northern Ireland are simply the names used to refer to the Welsh, Scottish and Northern Irish systems, which are the responsibility of the Welsh Government, the Scottish Government and the Northern Ireland Executive.

365. In Wales, there are seven local Health Boards, which are responsible for delivering most NHS services within their respective geographical areas. (In addition, there are three NHS Trusts (the Welsh Ambulance Trust, Velindre NHS Trust, which provides a range of specialist services, and Public Health Wales) that operate nationwide, as does the Health Commission Wales, which organises and funds all tertiary care and other specialist services.)

366. In Scotland, there are 14 regional Health Boards, which are responsible for delivering most NHS services within their respective geographical areas. There are also seven

Special Health Boards (including NHS Health Scotland, the Scottish Ambulance Service and NHS Education for Scotland) which provide various services nationwide.

367. In Northern Ireland, there are six Health and Social Care Trusts. Five of these are regional Trusts, which are responsible for delivering most NHS services within their respective geographical areas. In addition there is the Health and Social Care Board of Northern Ireland and the Northern Irish Ambulance Service, which provide services nationwide.

Lyrica

368. As noted above, Pfizer markets pregabalin under the trade mark Lyrica. It is one of the Pfizer Group's most successful products, with global sales in 2013 of approximately $4.6 billion. UK sales over the same period amounted to approximately $310 million. Sales have rapidly increased in recent years: according to NHS England, there was a 53% increase in pregabalin prescribing in England between 2011 and 2013. On average, approximately 260,000 packs of Lyrica were sold per month over the 12 month period to the end of January 2015. Net monthly sales in the UK over the same period were just under £18 million. Thus the average price of a pack was a little under £70.

369. Lyrica is available as a capsule in a range of doses, as follows: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg. Some doses come in packs of 56 capsules, whilst others come in packs of 84 capsules.

370. Lyrica is sold by Pfizer to pharmacies via a "direct to pharmacy" distribution system. About 94% of all Lyrica sales are made to community pharmacies. Approximately 5% of sales are to hospitals.

371. Prior to generic launch in mid-February 2015, Lyrica was the only pregabalin product on the market in the UK. About 30% of the sales of Lyrica were of parallel imports (i.e. Lyrica sold by Pfizer's sister companies elsewhere within the European Union).

Recommended doses of pregabalin

372. The recommended starting dose of pregabalin for neuropathic pain is 150 mg daily, split into two equal doses of 75 mg. The dosage can be increased in accordance with the patient's needs up to a maximum dose of 600 mg daily. For epilepsy, the recommended starting dose is 25 mg twice daily, although again the dose can be titrated upwards as required to a maximum of 600 mg daily. As for GAD, the recommended starting dose is 150 mg daily, split into two or three equal doses. Thus the same form and dosage of pregabalin can be used for each of the three licensed indications. It is normal practice to prescribe the right size of capsule for the appropriate dose, rather than a combination of smaller sizes.

Misuse of pregabalin

373. There is a relatively high incidence of misuse of pregabalin. As a result, in July 2014, following extensive discussions with the European Medicines Agency ("EMA"), Pfizer updated the EU product labelling for Lyrica to add the following warning:

> "Misuse, abuse potential or dependence
>
> Cases of misuse, abuse and dependence have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behaviour have been reported)."

374. In December 2014 Public Health England and NHS England jointly issued guidance entitled "Advice for prescribers on the risk of the misuse of pregabalin and gabapentin". This guidance draws doctors' attention to the problem of misuse of these drugs and contains advice as to how to deal with it. The guidance notes that pregabalin appears to be more sought after for misuse than gabapentin, that there is a growing illegal market, that the drugs are also being bought from online pharmacies and that prescribing per capita in secure settings is double that in the community. One of the actions advised is that, if a decision is made to prescribe these drugs for unlicensed indications, "the rationale should be discussed with the patient, appropriate consent acquired and all discussions clearly documented".

375. The DrugScope Street Drug Trends Survey 2014 published on 15 January 2015 reported as follows:

> "**Pregabalin and gabapentin misuse widespread among drug users and prisoners**
>
> Most of the 17 areas covered by the survey highlighted the significant increase in misuse of two prescription drugs, pregabalin and gabapentin, chiefly among Britain's opiate-using and prison populations. These anticonvulsant medications are increasingly prescribed to treat epilepsy, neuropathic pain and anxiety.
>
> People who misuse the drugs do so because of the feelings of euphoria they can create; they are commonly used alongside - and as enhancers to - other drugs, such as alcohol, opiates such as heroin or methadone, and diazepam. Pregabalin and gabapentin are easily available on the illicit market in 25mg to 800mg capsules, changing hands for between 50p and £2.
>
> Drug workers reported users displaying extreme intoxication and uninhibited, risky behaviours while on the drugs. Mixing these medications with other central nervous system depressants such as opiates and alcohol significantly increases the risk of overdose. Deaths involving pregabalin and gabapentin are on the rise and the Office for National Statistics told DrugScope that pregabalin and gabapentin were mentioned on 41 death certificates in 2013 (pregabalin on 33 and gabapentin on 9)."

Prescribing practices

376. It is standard practice for a prescribing doctor to identify the drug prescribed by reference to its international non-proprietary name ("INN"), that is to say, its generic name (such as "pregabalin"). As Ms Howe explained, the starting point of any consideration of prescribing practice is the fundamental principle of the prescriber's clinical freedom. Nevertheless, generic prescribing is encouraged at all levels of the healthcare system, including by the Department of Health, NHS England, CCGs and Health Boards and by the professions. This is for both clinical and financial reasons. The clinical reasons are that prescribing generically helps remind clinicians of the therapeutic action of the drug, enables greater certainty amongst healthcare professionals when treating a patient (e.g. when the patient moves between care providers) and promotes dispensing flexibility (and hence speed).

377. There are some circumstances where prescribing by brand is clinically justified or required, such as where small differences between the branded and generic product (e.g. changes in the absorption rate of the active ingredients or in excipients) can have a detrimental effect on the patient. This can occur, for example, with some epilepsy medicines. The Selected List Scheme covers certain drugs which have been prescribed for a particular purpose to a particular class of patients.

378. According to statistics published by the HSCIC, in 2013 83.9% of all prescriptions in primary care were written generically. In relation to pregabalin specifically, the evidence is that generic prescribing is even higher. Mr Wilson's evidence was that 90–93% of all prescriptions for pregabalin were written generically in April 2014. Ms Tully's evidence was that over 99% of prescriptions for pregabalin in England in January 2015 were written generically.

379. It is rare for prescriptions to identify the condition for which the drug has been prescribed. Although hard data is difficult to come by, it appears that no more than 5% of GPs routinely state the indication on their prescriptions. It seems clear from the evidence that there is considerable resistance to changing this. One reason for this is patient confidentiality.

380. In general, prescribing doctors will be unaware of what stocks or sources of supply the dispensing pharmacy will have available to it for fulfilling the prescription. In particular, if the prescribing doctor writes a prescription generically, and generic versions of the drug are available, the doctor will not know whether the branded product will be dispensed or a generic version, and if the latter, which one.

Clinical software

381. Almost all prescribers use clinical software systems to create prescriptions. The current market leader is EMIS, which supplies 53% of GP practices in the UK. For reasons that will appear, it is important to note that, prior to about September or October 2013, the market leader was iSoft and that, at around that time, many GP practices switched from iSoft to EMIS. The other current major suppliers are TPP (whose system is called SystmOne) and INPS (whose system is called Vision). Such software generally encourages the doctor to prescribe drugs generically. This is achieved by presenting the generic name as the default name for the drug, at the top of the list of options on screen. It is only if the GP deliberately scrolls down the menu

past the different generic doses that he/she can find the brand name. Alternatively, the GP can type in the brand name.

382. Where appropriate, the clinical software systems provide prescribing doctors with alerts about the drug being prescribed. These alerts are graded into low, medium and high severity.

383. In addition to the basic clinical systems, there are two specific programs called ScriptSwitch (supplied by Optum UK) and OptimiseRX (supplied by First Databank Europe, "FDB") which sit on top of the basic clinical software and which encourage GPs to prescribe drugs generically. These programs are generally adopted by CCGs and rolled out to GP practices under their control. ScriptSwitch is used by approximately 160 CCGs and OptimiseRx by eight CCGs.

Dispensing practices

384. Where the prescription is written generically, the pharmacist is free to dispense a branded drug or a generic one. Where the prescription specifies a particular brand (such as Lyrica), however, the pharmacist must dispense that brand in order to avoid (a) breaching regulation 214 of the Human Medicines Regulations 2012 (SI 2012 No. 1916) and (b) committing trade infringement and/or passing off.

385. In the future, pharmacists will have access to patients' Summary Care Records, but this is only just starting to be rolled out and at present does not include the condition for which a drug has been prescribed. As matters stand, therefore, pharmacists do not usually know the indication for which a drug has been prescribed, because this is not stated on the prescription. Unless the pharmacist happens to have ascertained and recorded this information in the past, the only ways in which the pharmacist can find this out are (i) by asking the patient and (ii) by asking the prescriber.

386. So far as asking the patient is concerned, community pharmacists are now required to ensure appropriate levels of privacy for conversations with patients. In principle, therefore, a pharmacist can ask a patient what indication he or she has been prescribed pregabalin for. There are two problems with this approach, however. The first is that the patient may not be present when the prescription is filed. The second is that, even if the patient is present, the patient may not be able accurately to answer the question.

387. Surprisingly, there appears to be no national data available as to the extent to which prescriptions are collected from pharmacists by persons other than the patient. At the hearing in January 2015, Actavis adduced evidence from a pharmacist who examined his pharmacy's prescription records for December 2014. During that month they received 55 prescriptions for Lyrica. Of those, only 17 were filed by the patient in person, while the remaining 38 were filed either by patients' representatives or were sent to the pharmacy as a part of its delivery service. This is clearly a small sample, but it is the only evidence on this point before the court. (In saying this, I should make it clear that Actavis did not tender this witness at trial; but no party adduced any other evidence on this point.) What this indicates is that, in a very substantial proportion of cases, a pharmacist who receives a prescription for pregabalin cannot ask the patient what indication the drug has been prescribed for.

388. About 80% of patients with neuropathic pain are over 35, and over 27% are over 65. In the case of those over 65, they will often be receiving multiple medications for a variety of conditions. Furthermore, in many cases the conditions will be long-term ones, and so the original prescription may have been written some time ago. It may therefore be questioned to what extent such patients will be able accurately to answer a question as to the indication for which they have been prescribed pregabalin. There is no evidence before the court as to the age profiles of patients with epilepsy or GAD, but at least some of these patients will be in a similar position.

389. It follows that in many cases the only way, and in others the only reliable way, for the pharmacist to ascertain this information is to contact the prescriber. It will be appreciated, however, that it may not be at all easy for the pharmacist to get through to the doctor on the telephone (or by email or other means) while the person who has brought the prescription is waiting. Once the information has been obtained, however, the pharmacist can make a record for the future.

The NHS Drug Tariff

390. The NHS Drug Tariff ("the Drug Tariff") sets out the main mechanism by which pharmacists are paid by the NHS for dispensing drugs against NHS prescriptions. The Drug Tariff sets out both the remuneration pharmacists receive for their services and the reimbursement price they receive for dispensing drugs. Part VIII contains a range of commonly used drugs, of which pregabalin is one. Part VIII is divided into five categories: Category A (readily available drugs, where the reimbursement price is calculated from a weighted average of the list price for four suppliers, provided that the drug is available from both of two of the suppliers or from one of those two and the other two), B (where usage has declined over time), C (price based on a particular brand or supplier), E (extemporaneously prepared) and M (the most widely available drugs, where the reimbursement price is calculated by the Department of Health in accordance with an agreement negotiated between the Department and the British Generic Manufacturers Association under section 261 of the National Health Service Act 2006). The Drug Tariff is produced monthly by the Pharmaceutical Directorate of the BSA.

391. Category C products are not generally available as generics. To be in Category A or M, the drug must be available as a generic. The decision as to whether or not to move a drug from Category C to Category A or M once generic versions become available is taken by the Secretary of State after consultation with the Pharmaceutical Services Negotiating Committee ("PSNC"), which represents NHS pharmacy contractors. These discussions are treated as commercially sensitive and hence highly confidential.

392. It should be noted that, for the purpose of Category M, a generic medicine is one to which the proprietor does not apply a brand name that enables the product to be identified without reference to the generic name. It follows that Lecaent is not a generic medicine for this purpose. It further follows that the launch of Lecaent, and other branded generic pregabalin products, would not have prompted a move of pregabalin to Category M. By contrast, the launch of true generic pregabalin products may do so.

393. At present, pregabalin is listed in Category C. Thus pharmacists can claim reimbursement at the branded product rate, whether or not the prescription is written

by reference to the brand name Lyrica. If pregabalin were to be moved to Category M or Category A, the pharmacist could only claim reimbursement for the generic value of the drug listed in Part VIII.

394. Ms Howe gave evidence that pregabalin would only be moved from Category C to Category M or Category A once unbranded generic pregabalin became available and then only after careful consideration by the Department of Health and negotiation with the PSNC. She made it clear that such a move would not be automatic.

Medicine margin

395. Under the community pharmacy contractual framework in England, pharmacies are paid for NHS pharmaceutical services through a combination of (i) fees and allowances (in particular, the flat fee for each prescription item dispensed) and (ii) "medicine margin". Thus under the 2014/15 settlement of £2.8 billion, it was expected that £2 billion would be from fees and allowances (paid by NHS England with a proportion recharged to CCGs) and £0.8 billion from medicine margin (paid for by CCGs as part of drug costs).

396. Medicine margin is the difference between the purchase price paid by the pharmacy and what they are reimbursed by the NHS for the product. It is assessed by an annual margin survey. This survey identifies, from invoices supplied by a sample of independent pharmacy contractors in confidence, the actual price they have paid for a sample of medicines (generic, branded and unlicensed) and compares this to the amount reimbursed by the NHS. This data is used to calculate the average amount of medicine margin retained during the year. It should be noted that the pharmacies who submit invoices do not know which medicines are within the sample.

397. The difference between the medicine margin found in the survey and the agreed target medicine margin as part of the contractual framework determines whether there needs to be any adjustment to the payments made to community pharmacies. If too much medicine margin is being made, downward adjustments are needed. If not enough medicine margin is being achieved, upward adjustments are needed. The adjustments are usually made to the reimbursement prices of products in Category M.

398. The medicine margin system means that, on average, the reimbursement paid to pharmacies covers the price paid by the pharmacy to its supplier plus the medicine margin. The difference between the price actually paid and the reimbursement price means that pharmacists have a financial incentive to stock and dispense cheaper generic drugs where available. Nevertheless, the extent of this financial incentive should not be exaggerated given that the total amount of medicine margin is fixed and that the differential between the price paid and the reimbursement price is averaged across a large number of products. Furthermore, as Ms Howe explained, it is inherent in the system that pharmacies sometimes dispense at a loss.

The percentage of pregabalin prescribed for each indication

399. One of the main factual issues investigated at trial was the percentage of pregabalin prescribed for each indication. Before turning to the figures, it is convenient to note that it is common ground that pregabalin is prescribed off-label to some extent, at

least for pain conditions other than neuropathic pain and for psychiatric conditions other than GAD.

400. At the hearing of Pfizer's application for an interim injunction, it was Pfizer's own evidence that the best evidence on this question was an analysis of the IMS data which indicated that sales of Lyrica in the UK in January to September 2014 broke down as follows: 54% for treating pain (of which 44% was for neuropathic pain), 12% for psychiatric conditions (of which 18% was for GAD), 2% for epilepsy and 32% for unspecified other diseases. This suggested quite a high level of off-label prescribing, and moreover off-label prescribing for conditions which extended beyond pain and psychiatric conditions.

401. Applying the same methodology to annual data for the preceding years, two points are evident. The first is a slow but steady decline in the percentage of pregabalin prescribed for pain from 69% in 2010 to 63% in 2013, together with a slow but steady increase in the percentage prescribed for psychiatric conditions from 7% to 11% (and a slight increase in "other diseases"). The second is that in January to September 2014 there appears to have been a sharp drop in percentage of pregabalin prescribed for pain (from 63% to 54%) and a sharp increase in "other diseases" (from 24% to 32%) compared to 2013.

402. At trial, Pfizer contended that the true percentage of pregabalin prescribed for pain was at least 78%. In support of this contention Pfizer relied on the evidence of Dr Phillips.

403. As explained above, IMS obtains prescribing data (referred to by Dr Phillips as "medical audit" data) from a panel of about 500 GPs. The GPs record their diagnoses using Read codes. IMS maps the Read codes to ICD 10 codes using a proprietary correlation. Towards the end of 2011, Pfizer and IMS agreed a set of allocations of ICD 10 codes that would allow prescriptions to be divided between different disease and indication categories in the field of pain, psychiatry and epilepsy. This exercise was undertaken by Pfizer's then European Medical Lead for Pain/CNS in conjunction with its European Business Analytics and Insight team. As Dr Phillips confirmed, thereafter Pfizer used these allocations on a daily basis in its business to allow Pfizer to ascertain the relative proportions of prescriptions written for each drug for each indication in any given period. The allocations were not specific to pregabalin. Importantly, it was these allocations that underpinned the 54% figure quoted above.

404. After the hearing in January 2015, Pfizer reconsidered these allocations. There were two stages to this exercise. In the first stage, Pfizer sought to align the figure attributable to pain with the figure on which Pfizer was basing its Brand Equalisation deals (as to which, see below), namely 59% for pain. In the first stage of the exercise, Pfizer decided to reallocate seven ICD 10 codes from "other diseases" to pain.

405. In the second stage, Pfizer revisited the allocations again. This time Pfizer decided to reallocate 50 (out of 280) ICD 10 codes from "other diseases" to pain. In addition, 13 ICD 10 codes were re-allocated to "psychiatry" and 18 ICD 10 codes to "unspecified". As noted in paragraph 33 above, this work was initially done by two scientists who were not medically qualified.

406. The result of this reallocation for the period to September 2014 was as follows: pain 64.7%, psychiatry 12.6%, epilepsy 1.7%, other diseases 4.0% and unspecified 17.0%. It should be noted, however, that these figures do not present the raw percentages from the reallocated IMS medical audit data. Rather, these percentages are the result of combining the medical audit data with "moving annual total" sales figures for pregabalin from IMS. The medical audit data is published quarterly and averages four quarters, with the result that the moving annual total analysis reflected seven quarters of medical audit data. Thus these figures essentially reflect an average of seven quarters of medical audit data. For example, the 59% figure for pain originally proposed by Pfizer in its Brand Equalisation deals (as to which, see paragraph 506 below) was based on an analysis of the June 2014 moving annual total of sales proportioned in accordance with the medical audit data, whereas the 54% figure in evidence at the January hearing was based on the September 2014 moving annual total. Dr Phillips was unable to explain why the medical audit data had been combined with the sales data in this way. Nevertheless, this does not appear to matter greatly for present purposes.

407. Finally, Pfizer reallocated all the "unspecified" prescriptions pro-rata across the three main disease categories (i.e. excluding the "other diseases" category). This produced the following figures: pain 78.6%, psychiatry 15.3%, epilepsy 2.1% and other diseases 4.0%. Applying the same approach to the data for the quarter to December 2014 produced the following figures: pain 78.1%, psychiatry 16.1%, epilepsy 2.2% and other diseases 3.6%.

408. Of the ICD 10 codes which were reallocated by Pfizer, by far the most frequently occurring was "R693", corresponding to "Diagnosis Not Stated". As noted above, the IMS data appears to show an increase in the "other diseases" category from 24% in 2013 to 32% in September 2014. It appears that this was due to the GPs on the IMS panel changing from iSoft to EMIS in September/October 2013. Unlike iSoft, EMIS does not routinely prompt users to link prescriptions to a diagnosis. This resulted in a significant increase in use of the code R693. (It also resulted in a temporary dip in the number of GPs on the IMS panel for the fourth quarter of 2013, to just under 300.) The percentage of prescriptions attributed to R693 increased still further in the first quarter of 2015.

409. Counsel for Actavis submitted that Pfizer's reallocation exercise should be treated with caution because it had been done for the purposes of the litigation. I accept that submission.

410. Counsel for Actavis also submitted that the evidence showed that there were a number of flaws in the exercise, and in particular the following. First, Dr Phillips accepted that the exercise included allocating conditions to the pain category which were very unlikely to have been treated with pregabalin, such as cystitis, and thus were more likely to reflect a coding error. Secondly, Dr Phillips accepted that for some conditions pregabalin could just as easily be treating anxiety as it could pain. Thirdly, in several instances Dr Jones considered the diagnoses to be poorly defined, which Dr Phillips accepted was a reasonable view. Fourthly, and perhaps most importantly, Dr Jones' evidence was that the pro-rating of unspecified diagnoses was inappropriate.

411. Dr Jones gave a number of reasons for this. First, it assumed that there was no off-label use (or least no off-label use outside the categories of pain and psychiatry),

whereas the evidence suggested that there was wider off-label use. Secondly, it assumed that the failure to link the prescription to a diagnosis was equally likely for all three categories, whereas Dr Jones' view was that the link between pregabalin and epilepsy was firm, the link between pregabalin and pain less so and the link between pregabalin and anxiety disorders considerably less so. Moreover, Dr Jones considered it likely that a considerable proportion of the unspecified prescriptions related to the use of pregabalin to deal with anxiety states that were associated with addiction (which might initially be addiction to another substance, although it could become pregabalin). Thirdly, it assumed that pregabalin was only ever prescribed for one condition, whereas it may in fact be prescribed for both pain and anxiety.

412. Overall, it was Dr Jones' clear and convincing evidence that the most reliable data were the IMS medical audit data dating from before the switchover from iSoft to EMIS. The most recent such data are those from 2013 (although this includes the quarter in which the switchover occurred, the full effect of the switchover was not felt until 2014). This would suggest that the figure for pain was 63%.

413. Dr Jones accepted in his report, however, that some of the reallocations of the ICD 10 codes which Pfizer had made were appropriate. In particular, he agreed that the reallocations of 20 of the 50 codes reallocated to pain were fair. Thus he accepted that the figure for pain in January to September 2014 should be increased to 58.7%. Furthermore, in cross-examination, he accepted that in some additional instances it was more likely than not either that the code reflected a diagnosis for pain or that the prescriptions could be apportioned between pain and anxiety.

414. As counsel for Actavis pointed out, it should not be forgotten that the IMS data is based on returns from a small sample of GPs or that it is based on mapping Read codes to ICD 10 codes. Accordingly, it should be regarded as an estimate, albeit an estimate that IMS tries to ensure is as accurate as possible. It follows that precision is neither possible nor appropriate.

415. Doing the best I can on the evidence, I conclude that the correct figure for pain in 2013 was about 70%. As for 2014 and 2015 to date, the probability is that the figure will have been no higher than this. It may well have been lower if the trend towards greater prescribing of pregabalin for psychiatric conditions continued, as seems likely.

The abridged procedure for marketing authorisations and skinny labels

416. Article 10 of European Parliament and Council Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use ("the Directive") lays down an abridged procedure for the authorisation of generic versions of drugs on the basis of bioequivalence with the originators' products. This enables generic suppliers like Actavis to obtain marketing authorisations for generic versions of a drug like pregabalin without generating their own safety and efficacy data once the originator's data exclusivity has expired.

417. Article 11 of the Directive provides that, for authorisations under Article 10, those parts of the Summary of Product Characteristics ("SmPC") of the reference product referring to indications or dosage forms which are still covered by patents need not be included. This enables the generic suppliers to carve out indications which are protected by second medical use patents from their SmPCs, and hence their marketing

authorisations and patient information leaflets ("PILs"). Marketing authorisations containing such carve-outs are commonly referred to as "skinny labels" (as opposed to "full labels", which cover all the indications and dosage forms for which the reference product is authorised.) Article 3 of European Parliament and Council Regulation 726/2004/EC of 21 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency ("the Regulation") contains a similar provision.

418. Where a generic product such as Lecaent has been authorised on the basis that it is bioequivalent to a product such as Lyrica, the fact that the SmPC for the former omits an indication included in the SmPC for the latter does not prevent doctors from prescribing or pharmacists from dispensing the former for that indication. Furthermore, both doctors and pharmacists will know that the product is the same despite the difference in the indications. In the present case, there is not even a difference in the dosage regime for the different indications, as in some other cases.

An unprecedented situation

419. An important point which both Ms Tully and Mr Wilson made in their evidence, and which is also reflected in the evidence of Ms Howe, is that the situation faced by Pfizer and Actavis and by the UK healthcare systems in this case was unprecedented. Thus no one could look to any precedent for guidance as to what to do. This needs to be borne constantly in mind when reading what follows.

Pfizer's preparations for loss of exclusivity

420. Loss of exclusivity ("LOE") is an important issue for a company like Pfizer, particularly for a product like pregabalin. Pfizer has a dedicated team whose job it is to prepare for loss of exclusivity ("LOE") in relation to such products. Even though Actavis had placed the steps taken and not taken by Pfizer in this regard squarely in issue, Pfizer did not adduce evidence from any member of the relevant team. Ms Tully knew little about this topic. Dr Phillips was able to supplement her evidence in one respect, but again he was not the right person to give evidence about it. Accordingly, the evidence is mainly documentary. Even the documentary evidence is somewhat exiguous since Pfizer has disclosed few documents addressing this question (despite disclosing additional documents as late as the last day of the trial).

421. It appears from the documents that Pfizer was preparing for LOE in relation to pregabalin by no later than 22 October 2012. At that stage Pfizer was expecting the first generic product to enter the market six months post-LOE at the end of 2014/beginning 2015. (Note that this suggests that Pfizer planned to allow the SPC to lapse, and hence LOE would occur on 8 July 2014.) Furthermore, Pfizer planned to launch a "dual brand" at that time. Ms Tully accepted that that was a reference to a Pfizer generic pregabalin product (an "auto-generic" product). It is fairly plain from this that Pfizer was anticipating that generic competitors would launch pregabalin products with skinny label marketing authorisations.

422. This was certainly the case by 6 June 2014, when Pfizer wrote to Birmingham Cross City CCG explicitly anticipating that generic manufacturers of pregabalin would only seek skinny labels.

423. On 10 June 2014 there was a meeting of a Lyrica Advisory Board attended by two representatives of IMS and some unidentified clinicians. It is clear from a presentation discussing feedback from this meeting dated 16 June 2014 that Pfizer was contemplating launching Pfizer pregabalin. It is also clear that Pfizer anticipated that there was likely to be "quite intense" confusion as a result of the patent situation, that communication "on a global scale" would be a challenge and that "local/global prescription guidelines/guidance to support the prescribers' decision would be preferred".

424. Despite planning for generic entry, Pfizer took no action to address the situation that would arise when this happened until late September 2014. I shall discusss the steps which Pfizer took at that point below. Counsel for Actavis put it to Ms Tully that this inaction was deliberate. Ms Tully's only answer was that Pfizer was facing an unprecedented situation and therefore did not know what to do. I entirely accept that Pfizer was facing an unprecedented situation. Nevertheless it is clear that Pfizer had carefully considered what steps were open to it, and identified at least two possible steps: first, launching a Pfizer pregabalin product; and secondly, trying to ensure that prescribers received appropriate guidance. Pfizer did not attempt to take either of these steps until late September 2014. I infer that this inaction was deliberate, and that Pfizer considered that it was in its commercial interest.

Actavis' preparations to launch Lecaent

425. Mr Wilson explained in his evidence how Actavis operates generally and how the Lecaent product came to be launched. Actavis operates through separate teams operating independently so as to achieve their functions as quickly as possible. This means that different teams will be unconcerned with matters that have no direct impact on their particular sphere. For a UK launch, the final decision is taken by the UK Portfolio Committee, which Mr Wilson chairs.

426. To begin with, Actavis had not planned to market pregabalin in the UK while the SPC covering pregabalin as such was in force. As explained above, that had been due to expire in 2018, but Pfizer allowed it to lapse. Actavis became aware that the SPC had been allowed to lapse on 19 March 2014. Given the size of the pregabalin market, Actavis decided to begin preparations to launch a generic pregabalin product as soon as data exclusivity expired.

427. Actavis were aware of the Patent. To begin with, Actavis considered two options: (i) bringing revocation proceedings in respect of the Patent, which if successful would clear the way for a launch with a full label; and (ii) launching under a skinny label. The preferred option was a full label, but Actavis knew that, from a regulatory perspective, it would be possible to restrict their application for a marketing authorisation to a skinny label later on if appropriate.

428. Actavis prepared initial sales forecasts for a full label launch in April 2014. These were based on the assumption that Actavis would achieve a market share of a certain percentage. This figure is confidential, and I will refer to it as X%. Mr Wilson explained that Actavis frequently used the X% figure when planning product launches, because experience had shown that it was a figure that allowed for considerable flexibility: if Actavis planned for X%, then they could quite easily cope with selling either more or less than that figure in the initial period after the launch. It

is important to appreciate that Actavis continued to base its plans on the X% figure throughout the period until launch.

429. Pregabalin was one of the first applications to be made under a new initiative by Actavis to achieve faster marketing authorisations. By May 2014, Actavis' Regulatory and Launch Teams were cautiously optimistic that they could obtain a marketing authorisation in December 2014 or January 2015. The Regulatory and Launch Teams omitted to communicate this optimism to the IP Team, however, and therefore Actavis did not commence revocation proceedings at that stage.

430. In order to allow for the possibility of an early launch, Actavis placed an initial order for generic pregabalin at the end of May 2014. The product was to be manufactured "at risk" i.e. the packaging and PIL were to be subject to granting of the marketing authorisation. The quantity ordered was estimated to be enough for 4-5 months. The product was manufactured by Balkanpharma in Bulgaria, part of the Actavis Group.

431. As noted above, Actavis filed their application for a marketing authorisation on 9 July 2014, the day after data exclusivity expired. At that stage, the application was for a full label marketing authorisation.

432. At around the same time, Actavis began to look at the breakdown of the pregabalin market by indication. For this purpose, data was obtained from IMS in August 2014. Actavis carried out a rather crude analysis of the IMS data which suggested that about 71% of the market was for pain and about 29% for non-patented uses. This was done by Stephen Harrison, a business information manager who was not medically qualified. Mr Wilson's evidence was that it was regarded as no more than an approximate estimate. Subsequently Actavis re-analysed the figures in October 2014. This produced a figure of 74% for pain, as result of re-distributing 5% of other uses between pain, seizure and anxiety. The figure which was most consistently used by Actavis in its forecasts and plans was 70%, however. This is the 71% figure rounded down.

433. Also in August 2014 Actavis decided to prepare a skinny label SmPC and PIL as well as a full label SmPC and PIL, so as to enable Actavis to launch with either a full or skinny label swiftly on the grant of the marketing authorisation.

434. Also in August 2014 Actavis became aware of Mylan's action to revoke the Patent and decided to start their own revocation action, which they did on 12 September 2014. It was not until after the revocation action was started that Actavis' IP Team became aware for the first time of the possibility of the marketing authorisation being granted quickly (i.e. more rapidly than the normal timetable, which would have led to launch in late 2015). As a result, the IP Team recommended that Actavis launch initially with a skinny label and launch with a full label later if the revocation action was successful.

435. The UK Portfolio Committee accepted this recommendation. Given that Actavis were hoping to obtain a marketing authorisation quickly, Actavis were hopeful that they would face no or limited generic competition for the non-patented indications when they launched, and therefore would achieve a better than X% share. In addition, Actavis knew that they could, if necessary, sell the product over a longer period of time given that it has a shelf life of two years. In any event, the initial quantity of

product had already been ordered by that point in time. Accordingly, Actavis did not revise their sales forecasts for pregabalin to reflect the fact that they would only be targeting an estimated 30% of the pregabalin market.

436. Pfizer was told of Actavis' intention to launch with a skinny label shortly after the decision was made, namely on 30 September 2014 (see paragraph 449 below).

437. At that stage, Actavis' best estimate for the grant of the marketing authorisation was December 2014, although it was thought that it could be as early as November 2014. Actavis' Supply Team had confirmed the product would be ready by around the middle of December 2014. Actavis provided Balkanpharma with the final version of the skinny label PIL in mid October 2014 and the packaging process started shortly after that. Thus Actavis had product ready for launch under quarantine in the UK by mid December 2014.

438. In December 2014 Actavis learnt that Pfizer was offering Brand Equalisation deals to customers based on pain being 59% of the pregabalin market (see further paragraph 506 below).

439. Mr Wilson gave evidence that, typically, Actavis would place a second order for the manufacture of a product shortly before launch. He was unable to give a date as to when this occurred in the present case. I will assume for the purposes of this judgment that the order was placed in mid-January 2015.

440. As things turned out, Actavis' marketing authorisation was granted on 16 February 2015 and the product was launched the next day.

441. After launch, and as a result of demand in March 2015, Actavis increased its forecast market share until July 2015, at which point Actavis forecast that its share would reduce back to the original level forecast (i.e. X%). By this time NHS England had issued guidance with respect to the prescribing and dispensing of pregabalin (as to which, see below).

442. Actavis' sales projections have always been well within what would be available to them based on their rough estimate of 30% of the pregabalin market being for non-patented indications and even more significantly within the 46% figure that was put forward in Pfizer's evidence on the application for an interim injunction.

The wording of Actavis' SmPC and PIL

443. Pfizer complains about the wording of Actavis' SmPC and PIL. As described above, the SmPC and PIL state that the conditions for which Lecaent is indicated are epilepsy and GAD. Pfizer points out, however, that the SmPC and PIL include warnings as to adverse events when pregabalin is taken for the treatment of neuropathic pain. The inclusion of such warnings is optional from the regulatory perspective. As I understand it, Pfizer accepts that the inclusion of the warnings was in accordance with good practice. Pfizer contends, however, that this shows that Actavis foresaw that Lecaent would be dispensed for neuropathic pain. I do not accept this. I find that the warnings were included because the inclusion of all the warnings from the originator's full label is generally regarded as good practice where a skinny label marketing authorisation is applied for.

444. More significantly, Pfizer complains that Actavis have included what is known as "blue box" wording in its PIL. This is optional text which a generic supplier may include in the PIL for a skinny label product to notify patients that the same product is also authorised for other indications.

445. The optional inclusion of such wording has been approved by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – human ("CMDh"), which was set up pursuant to European Parliament and Council Directive 2004/27/EC of 31 March 2004, which amended the Directive, for the examination of any question relating to the marketing authorisation of a medicinal product in two or more Member States in accordance with the mutual recognition procedure or the decentralised procedure. The wording approved by CMDh is as follows:

> "[The product in question] is also authorised to treat other conditions which are not mentioned in this leaflet. Ask your doctor or pharmacist if you have further questions."

446. Pfizer complains first that Actavis have included blue box wording at all, when other generic companies that have launched pregabalin have not done so; and secondly that the wording using by Actavis is not precisely in accordance with the approved wording, but is as follows:

> "Lecaent may be prescribed to treat other conditions not listed in this leaflet. If you have any questions, ask your doctor or pharmacist."

447. Again, Pfizer relies on this as showing that Actavis foresaw that Lecaent would be dispensed for pain. Again, I do not accept this. It is clear that the reason why CMDh approved the optional inclusion of blue box wording was to provide reassurance to patients. While receipt by a patient of a generic drug dispensed for an indication which remains covered by a second medical use patent, and which has therefore been carved out of the skinny label, is one possible circumstance where such reassurance would be useful, it is not the only one. This point is highlighted by the wording which is used by Actavis. Counsel for Pfizer implied during her cross-examination of Mr Wilson that the change in wording was somehow improper or suspicious. It has the advantage, however, that it covers the situation where the doctor has prescribed pregabalin off-label. I find that this wording was included because it was perceived by Actavis to be good practice.

Genesis of the proceedings

448. As noted above, on 12 September 2014 Actavis commenced revocation proceedings in respect of the Patent. On 23 September 2014 Pfizer's solicitors asked Actavis' solicitors about Actavis' intentions with regard to obtaining a marketing authorisation for, and launching, a pregabalin product. On 25 September 2014 Actavis' solicitors replied that Actavis had filed an application for a marketing authorisation, but gave no further details. On 29 September 2014 Pfizer's solicitors asked for a copy of Actavis' marketing authorisation application and for answers to the questions they had previously asked about Actavis' proposed launch date and expected date of grant of a marketing authorisation.

449. On 30 September 2014 Actavis' solicitors disclosed that the application for a marketing authorisation had been filed on 9 July 2014, and said that the application was being expedited and that it could be granted "as early as November 2014". They also stated:

> "Actavis is therefore preparing to launch a pregabalin product in the UK with a summary of product characteristics ('SmPC') limited to the treatment of epilepsy and general anxiety disorders (a so-called 'skinny label') in December 2014 or January 2015.
>
> Actavis also wishes to launch a pregabalin product with a full label in the UK, including for the treatment of neuropathic pain, as soon as possible, but wishes to clear the way first by seeking revocation of EP(UK) 0 934 061. Such a full label launch will therefore not take place until after the hearing [of] Actavis's revocation proceedings."

450. On 1 October 2014 Pfizer's solicitors asked Actavis' solicitors to explain "what measures your client has put in place to ensure that your client's generic product is not used for the treatment of pain" and for the finalised launch date to be provided as soon as it was decided upon.

451. On 3 October 2014 Actavis' solicitors repeated that they anticipated the marketing authorisation would be granted in November 2014 and that Actavis would launch in December 2014/January 2015. They also stated:

> "Our client's product will be marketed in conjunction with the attached Product Information Leaflet, which you will note does not include indication for the treatment of neuropathic pain. On launch our client also intends to notify superintendent pharmacists specifically that its product is not indicated for the treatment of neuropathic pain."

They went on to indicate that Actavis considered that they would not infringe the Patent, but recognised that Pfizer might disagree.

452. On 10 October, 4 November, 19 November and 24 November 2014 Pfizer's solicitors requested copies of Actavis' marketing authorisation application, SmPC and proposed notice to superintendent pharmacists.

453. In the letter dated 24 November 2014 Pfizer's solicitors also stated:

> "We are of the opinion that, if your client intends to launch a generic product, it is required to take appropriate steps to ensure that it is not dispensed for the treatment of pain, including by ensuring that all pharmacists are aware that its generic product is not authorised for and should not be dispensed for the treatment of pain. As a starting point, this would seem to require an appropriate notice being placed on the outside of the packet of your client's product to ensure that

> this matter is brought to the attention of the pharmacist handling the product."

This was the first time that Pfizer had made this request.

454. On 25 November 2014 Actavis' solicitors sent Pfizer's solicitors copies of Actavis' proposed SmPC and notice to superintendent pharmacists. On 26 November 2014 Pfizer's solicitors informed Actavis' solicitors that Pfizer did not consider the proposed notice to be sufficient.

455. On 2 December 2014 Actavis' solicitors replied to Pfizer's solicitors' letters dated 24 and 26 November 2014, stating:

> "Further, the late raising by your client of the packaging point appears to us and our client to be a tactical attempt to delay the imminent launch by our client of the pregabalin product targeted to the non-patent market. Our client is already packaging its product and the additional notice is in any event unnecessary, inappropriate, and, in our client's experience, unprecedented."

456. This crossed with a letter from Pfizer's solicitors of the same date stating:

> "Given your client's approach, there is an urgent need to take steps that will prevent infringement of our client's patent, whilst allowing your client to market its product in respect of its authorised indications."

457. On 3 December 2014 Actavis' solicitors replied, stating:

> "You have our client's position that in its view its planned launch of the Skinny Label Product will not infringe your client's patent. However, we remain in the dark as to your client's position on what would or would not constitute patent infringement beyond the piecemeal raising of late objections to aspects of our client's launch. Please provide us with the steps which your client considers to be sufficient to prevent infringement of your client's patent by our client's Skinny Label Product."

458. In a letter dated 5 December 2014 which was not received by Actavis' solicitors until 8 December 2014, Pfizer's solicitors reiterated the request that the packaging of Actavis' product include a statement that the product should not be dispensed for pain. They also requested that Actavis make this an express condition of supply to any pharmacy and that Actavis inform "the prescribing authorities at the Department of Health" that their product should not be prescribed for the treatment of pain. This was the first time that Pfizer had made these requests.

Steps taken by Pfizer to prevent generic pregabalin being prescribed or dispensed for pain

459. Since late September 2014, Pfizer has taken extensive steps to try to ensure that generic pregabalin is neither prescribed nor dispensed for the treatment of pain. This has involved communications with a variety of stakeholders. Actavis contend that a number of these communications amount to threats of proceedings for patent infringement. I shall deal with these communications stakeholder by stakeholder (or classes thereof) rather than in one chronological sequence.

460. *Department of Health and NHS England*. By 21 August 2014 Pfizer had decided to seek a meeting with Dr Keith Ridge CBE, the Chief Pharmaceutical Officer at the Department of Health, NHS England and Health Education England. At that stage no contact was made, however. On 8 September 2014 Pfizer decided to contact Dr Ridge's personal assistant the following day to request a meeting in the last week of September 2014 and started planning for the meeting. By this date Pfizer was also planning to contact a "second wave of stakeholders" within a few days of the meeting with Dr Ridge.

461. In the event it does not appear that the request for a meeting with Dr Ridge was made until 22 September 2014. His response to the request was to agree to a conference call between himself and his deputy and a number of Pfizer representatives including Ms Tully. This took place on 7 October 2014. During the call, Pfizer explained that it believed that "the current prescription, dispensing and reimbursement framework is likely to contribute to generic infringement of the pain patent". During the call, Dr Ridge agreed to put Pfizer in touch with a number of other stakeholders. He immediately sent an email about this to a number of colleagues, including Ms Howe.

462. Ms Tully followed this up with a letter to Dr Ridge on 8 October 2014 making the same point. Therefore, she stated:

> "… certain players in the prescription, dispensing and reimbursement chain may, albeit potentially unwittingly, be involved in such infringing activities".

This point was reiterated by Pfizer in the same or similar language in many subsequent communications.

463. Ms Tully went on to identify four areas which Pfizer believed needed to be addressed. The first was "official central communication to inform the NHS of the Lyrica pain patent situation and how to ensure that it is respected (i.e prescriptions of pregabalin for pain should specify the brand Lyrica)". The second was prescription software adjustments to alert GPs to this. The third was hospital tendering guidance. The fourth was Drug Tariff clarification.

464. On 22 October 2014 representatives of Pfizer met Ms Howe and two colleagues. Pfizer articulated its position in the same way as it had to Dr Ridge. On 28 October 2014 Pfizer followed this up with a letter to Ms Howe. This letter is alleged to be a threat and I shall deal with that aspect of it below. At this stage I note that it identifies the same four areas to be addressed as the letter dated 8 October 2014. It also records that the Department of Health considered that prescribing by brand name for Lyrica would be acceptable, but that the Department was unable to send out an official

central communication. It also records that the Department had suggested various other stakeholders to contact, including software suppliers.

465. On 17 November 2014 Pfizer sent Ms Howe an email asking for a further discussion about various aspects of the situation.

466. On 1 December 2014 Pfizer contacted Dr Ridge by email requesting a further discussion. In a further email later the same day, Pfizer asked whether Dr Ridge could request CCGs and other appropriate bodies to issue guidance. On 2 December 2014 Dr Ridge replied that he could not see NHS England asking for guidance to be issued.

467. On 10 December 2014 Pfizer's solicitors sent the Department of Health copies of its statements of case, application notice and evidence relating to its application for an interim injunction against Actavis.

468. On 16 December 2014 representatives of Pfizer attended a meeting with representatives of the Department of Health. I have only seen Pfizer's note of this meeting, which was sent by Pfizer to the Department as an enclosure to a letter from Ms Tully to Ms Howe dated 9 January 2015. The letter is alleged to be a threat and I shall deal with that aspect of it below. At this stage it is sufficient to record that in the note of the meeting Pfizer states that:

> "… you said that the Department of Health was not able to issue guidance under the new NHS structure. However, you believed the issuing of guidance was important for Pfizer in achieving a solution, and that the PAG/Nick Beavon's communication was clear and gave those healthcare professionals who received it what they needed to act within the law. Your view is that getting prescribers to act appropriately, since it is they who hold the discretion as to whether to prescribe by reference to INN or brand, is key."

469. During the run-up to, and during, the hearing before this Court in January 2015, there was correspondence between Pfizer's solicitors and the Government Legal Department on behalf of the Department of Health. Some of this correspondence is referred to in *Warner-Lambert I*. The details do not matter for present purposes.

470. On 22 January 2015 Pfizer wrote to Dr Ridge at NHS England, enclosing a copy of *Warner-Lambert I*, drawing attention to what I had said at [73]-[77] and requesting NHS England to issue guidance promptly. Following telephone conferences between representatives of Pfizer and representatives of NHS England on 23 January, 28 January, 4 February and 9 February 2015, on 10 February 2015 Professor Sir Bruce Keogh, NHS England's National Medical Director, wrote to Pfizer stating:

> "… at present I do not think that the correct formulation of prescriptions for pregabalin is an issue on which we should express a view on behalf of NHS England, at least on a timescale that is likely to be material to the litigation under way."

Instead, he suggested, if the Royal Colleges or the British Medical Association ("BMA") were to issue guidance, NHS England could draw attention to it. A copy of this letter was sent to Actavis' solicitors.

471. On 12 February 2015 Actavis' solicitors wrote to Pfizer's solicitors suggesting that both parties discuss this suggestion with Sir Bruce. On 16 February 2015 Pfizer's solicitors replied saying that Pfizer would be happy for Actavis to contact Sir Bruce and asking what Pfizer could do to assist. On 18 February 2015 Actavis' solicitors wrote to Sir Bruce saying that they would like to take up the suggestion made in his letter. This was overtaken by Pfizer's application against NHS England (as to which, see below), however.

472. *NPSG and PMSG*. On 16 October 2014 Pfizer had a conference call with representatives of the National Pharmaceutical Supply Group ("NPSG") and the Pharmaceutical Market Support Group ("PMSG") identifying the risk of patent infringement. On 20 October and 17 October 2014 respectively Ms Tully followed up with letters to NPSG and PMSG in similar terms to the letter to Dr Ridge dated 8 October 2014.

473. *Welsh Government, Northern Ireland Executive and Scottish Government*. On 24 October 2014 Pfizer met Professor Roger Walker, the Chief Pharmaceutical Officer of the Welsh Government. Pfizer's position on patent infringement and the ways in which NHS Wales could assist were summarised in a subsequent letter dated 29 October 2014. Similar discussions were held with Dr Mark Timoney, the Chief Pharmaceutical Officer of the Northern Ireland Executive during a teleconference on 29 October 2014, summarised in Pfizer's letter of 31 October 2014; and with Professor Bill Scott, the Chief Pharmaceutical Officer of the Scottish Government, on 30 October 2014, summarised in Pfizer's letter of 3 November 2014.

474. Pfizer met Prof Scott on 26 November 2014 and followed this up with a letter on 12 December 2014. The letter recorded that Pfizer had said that it believed that the simplest solution was for clinicians to be advised to prescribe Lyrica by brand when prescribing pregabalin to treat neuropathic pain, but that Prof Scott had replied that he and his colleagues did not consider that it was the role of the Scottish Government to provide guidance to clinicians on this topic. On the other hand, Prof Scott had no issue with Pfizer communicating on this issue with the 14 regional Health Boards.

475. On 22 January 2015 Pfizer wrote to Prof Scott, Prof Walker and Dr Timoney, enclosing a copy of *Warner-Lambert I*, drawing attention to what I had said at [73]-[77] and requesting that guidance be issued promptly.

476. On 28 January 2015 Pfizer spoke to Prof Walker and Dr Timoney. On 29 January 2015 Pfizer followed this up with emails attaching copies of the guidance issued by the National Pharmacy Association ("NPA") and PSNC (as to which, see below). Both emails stated:

> "… we share the Hon Mr Justice Arnold's view that issuing guidance to prescribers that pregabalin should be prescribed by brand name (ie LYRICA) when pregabalin is being prescribed for pain is the simple fix to this problem."

477. On 17 February 2015 Dr Timoney replied to Pfizer stating that the updated NICE Clinical Guideline (as to which, see below) had been brought to attention of the Health and Social Care Board, that he had alerted Community Pharmacy NI to the PSNC guidance and that he was liaising with the Department of Health (the letter was copied to Ms Howe).

478. *PSNC*. On 3 November 2014 Pfizer met with representatives of the PSNC. Pfizer followed this up with a letter dated 5 November 2014. This letter is alleged to be a threat and I shall deal with that aspect of it below. At this stage I note that it recorded that the PSNC had advised that Pfizer should try to find a way of ensuring that prescribers specify the brand Lyrica on prescriptions of pregabalin for pain. It is convenient to note also that on 7 November 2014 Sue Sharpe of the PSNC replied by email querying whether it was Pfizer's argument that a pharmacy receiving a prescription for "pregabalin" that dispensed the generic, knowing it to be prescribed for neuropathic pain, was infringing the patent. Richard Cullen of Pfizer's Legal Department responded by email on 13 November 2014. This email is also alleged to be a threat.

479. On 26 January 2015 Pfizer wrote to the PSNC enclosing a copy of *Warner-Lambert I* and requesting discussion of the best way forward with respect to Drug Tariff categorisation once generic pregabalin was launched. On 28 January 2015 the PSNC issued guidance to its members saying that, if they were minded to dispense generic pregablin, they should first satisfy themselves that it was not being provided for the patented indications.

480. On 11 February 2015 Pfizer sent the PSNC an email requesting amendments to this guidance which were specified in a further email on 12 February 2015. On 13 February 2015 the PSNC agreed to amend its guidance and updated its website accordingly. The guidance includes a template letter that can be sent to GPs if pharmacists are presented with a prescription for generic pregablin for the treatment of neuropathic pain. The letter requests the GP to re-issue the prescription to specify Lyrica.

481. *NICE*. On 3 November 2014 there was a meeting between Pfizer and the Medicines and Prescribing Centre ("MPC") of the National Institute for Heath and Care Excellence ("NICE") to discuss the situation. Pfizer followed this up with letters dated 13 November and 11 December 2014. The letter dated 13 November 2014 is alleged to be a threat and I shall deal with that aspect of it below. It also recorded that the MPC did not propose to provide any guidance at that stage, although it would recommend to CCGs and others that they carefully consider the situation, but asserted that the MPC might be obliged to offer such guidance. The letter dated 11 December 2014 specifically requested NICE to consider making an amendment to the relevant NICE Clinical Guideline.

482. On 22 December 2014 NICE replied stating that it had taken steps to amend NICE Clinical Guideline 173 "Neuropathic pain – pharmaceutical management", specifically the footnote to recommendation 1.1.8 ("offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)"). The amendment inserted the following statement:

> "In addition, the Lyrica (Pfizer) brand of pregabalin has patent protection until July 2017 for its licensed indication of peripheral and central neuropathic pain; until such time as this patent expires generic pregabalin products will not be licensed for this indication and their condition would be off-label and may infringe patent."

Pfizer has complained that this guidance is insufficiently prominent and that it is unlikely to have come to the attention of prescribers anyway, but it will be appreciated that that is a matter for NICE.

483. *RPS*. On 4 November 2014 Pfizer met the Royal Pharmaceutical Society ("RPS"). This was followed up in Pfizer's letter of 12 November 2014. This recorded that the RPS had encouraged Pfizer to engage with prescribers and relevant prescriber and medical associations to ensure awareness of the Lyrica pain patent situation throughout the prescription, dispensing and reimbursement chain.

484. *Pharmacy customers.* On a date which is not clear to me, but no later than 14 November 2014, Pfizer wrote to its pharmacy customers concerning Lyrica's loss of exclusivity. This letter explained the background, stated that Actavis intended to launch generic pregabalin with an authorisation and label that only covered epilepsy and GAD and said that "we therefore think it is important for you to understand that we believe the supply of generic pregabalin for use in treatment of pain, whist the pain patent remains in force in the UK, would be infringing Pfizer's patent protection and would constitute an unlawful act". The letter also stated that Pfizer expected to be in touch with the recipients in the near future "to discuss our commercial proposals for Lyrica in relation to the epilepsy and [GAD] indications". Subsequently Pfizer entered into Brand Equalisation deals with a number of these customers (see further paragraph 506 below).

485. *BPS and RCGP*. On 14 November 2014 Pfizer had a conference call with Dr Martin Johnson of the British Pain Society ("BPS") and the Royal College of GPs ("RCGP") to discuss how Pfizer could make sure how its rights for Lyrica's use in pain were respected. This was followed up in a letter dated 15 November 2014.

486. *Pharmacy Voice*. On 17 November 2014 Pfizer met Professor Rob Darracott, the Chief Executive of Pharmacy Voice, which represents community pharmacies, to discuss its position with regard to the Patent. Pfizer followed this up with a letter dated 28 November 2014. The letter recorded that Prof Darracott had advised Pfizer to ensure that prescribers specify the brand Lyrica on prescriptions of pregabalin for pain and to reach out to software companies to help with this.

487. *Software providers*. On 24 November 2014 Pfizer had a conference call with the Chief Medical Officer of EMIS. It appears from Pfizer's note of the conversation that much of the discussion was about whether GPs were liable for contributing to infringement of the Patent, although there was also discussion of the sources of data used by EMIS.

488. On 30 January 2015 Pfizer wrote to Optum UK enclosing a copy of *Warner-Lambert I* and requesting that ScriptSwitch be modified so as to prompt prescribers to

prescribe Lyrica for pain. During a telephone conversation on 2 February 2015 Optum UK said that it was unable to implement a central solution.

489. On 5 February 2015 Pfizer wrote to EMIS, TPP, INPS and other providers requesting them to modify their respective systems to prompt prescribers to prescribe Lyrica for pain. By 17 February 2015 INPS had agreed to do this in March 2015, whereas EMIS stated that it would await guidance from NHS England.

490. On 5 March 2015 Pfizer wrote to all the software providers enclosing the guidance issued by NHS England. On the same day EMIS confirmed that it would reflect that guidance in its systems. On 12 March 2015 FDB confirmed that it would be modifying OptimiseRx and a component of SystmOne which it supplied. I shall discuss the changes made by the software providers below.

491. *MHRA*. On 1 December 2014 Pfizer had a conference call with representatives of the Medicine and Healthcare Products Regulatory Agency ("MHRA"), and followed this up with a letter dated 10 December 2014. On 23 December 2014 Pfizer sent the MHRA copies of its statements of case, application notice and evidence relating to its application for an interim injunction against Actavis.

492. *Community Pharmacy Wales and the RPS's Director for Wales*. On 4 December 2014 Pfizer had a conference call or meeting with a representative of Community Pharmacy Wales and the RPS's Director for Wales. This was followed up by letters dated 12 January 2015 which stated Pfizer's belief that retail pharmacists could be liable for patent infringement, even potentially unwittingly.

493. *Community Pharmacy Scotland*. It appears that at some point Pfizer also contacted Community Pharmacy Scotland. In about January 2015 Community Pharmacy Scotland issued guidance saying that the patented product (Lyrica) should be dispensed for the patented indication (neuropathic pain).

494. *Superintendent pharmacists*. Every retail pharmacy business that is a body corporate is required to have a "superintendent pharmacist" who is responsible in regulatory terms for the supervision of any other pharmacists which the body corporate may employ (who may be many or none). The superintendent pharmacist may or may not be the "responsible pharmacist" who is on duty in a particular pharmacy at a particular time. On 10 December 2014 Ms Tully wrote a circular letter to the superintendent pharmacists of at least 62 pharmacy chains setting out Pfizer's position with regard to the Patent and generic pregabalin and noting that Pfizer had been informed that Actavis intended to launch generic pregabalin with an authorisation that only covered epilepsy and GAD. This letter is alleged to be a threat and I shall deal with that aspect of it below.

495. On 20 February 2015 Ms Tully wrote a circular letter to the superintendent pharmacists of at least 60 pharmacy chains, including Ms Wright, re-iterating Pfizer's position with regard to the Patent. Again, this letter is alleged to be a threat and I shall deal with that aspect of it below.

496. *BNF*. On 8 December 2014 Pfizer had a conference call with Karen Baxter, the RPS Director responsible for the *British National Formulary*, a pharmaceutical reference book published annually by the RPS which is the prescribing "bible" used by most

GPs and many other healthcare professionals in the UK. It appears that Pfizer requested that the next edition of the BNF (which was published in March 2015) should include guidance that Lyrica should be prescribed by brand name for pain. On 18 December 2014 Ms Baxter sent Pfizer an email stating that the RPS did not consider that this would be appropriate, although it was considering adding a general statement to the BNF acknowledging that differences existed in licensing between products and that users should check that they were prescribing the most appropriate product.

497. *CCGs and Health Boards*. On 12 December 2014 Ruth Coles, Pfizer's Legal Director, wrote to all CCGs in England, all Health Boards in Scotland, all Health Boards in Wales and the Northern Ireland Health and Social Care Board. This letter explained the patent situation and stated that Pfizer expected generic manufacturers to launch generic pregabalin with authorisations, SmPCs and PILs that only specified epilepsy and GAD. The letter is alleged to be a threat and I shall deal with that aspect of it below. The letter also said:

> "In view of the above, Pfizer requests that you issue appropriate guidance prescribing clinicians within your CCG [or Health Board] to help ensure that our pain patent is respected and that all prescribing clinicians are aware of the pain patent situation.
>
> There are a number of ways in which this might be achieve but the simplest solution, we believe, is for clinicians to be advised to prescribe Lyrica® by brand when prescribing pregabalin to treat neuropathic pain. Pharmacists will then be able to dispense Lyrica® against such prescriptions and this will ensure that they do no infringe the pain patent."

498. *PAG*. On 8 December 2014 Pfizer met Nick Beavon, who is Chief Pharmacist of Wandsworth CCG and Chair of the Pharmaceutical Advisers Group ("PAG"), which provides advice to CCGs. On 12 December 2014 Pfizer emailed Mr Beavon a copy of Pfizer's letter to CCGs. This email is alleged to be a threat and I shall deal with that aspect of it below. On 15 December 2014 Mr Beavon sent an email circular to the PAG network and the London CCG Chief Pharmacists' network about Lyrica's loss of exclusivity in which he stated:

> "It is my view that when prescribing for neuropathic pain within licence, the only appropriate action at this point in time is to prescribe by Lyrica brand to avoid confusion and infringement of patent law."

He also attached a copy of the Pfizer letter to CCGs.

499. *NHS Highland and NHS Grampian*. On 18 December 2014 Pfizer's solicitors wrote to the Highland Health Board ("NHS Highland") alleging that NHS Highland had procured infringement of the Patent as a result of an article concerning the prescribing of pregabalin published by NHS Highland in the October-November 2014 edition of *The Pink One*. On 29 December 2014 Pfizer issued an application to join NHS Highland as an additional defendant to the claim against Actavis and to seek interim

relief. As noted in *Warner-Lambert I* at [7], NHS Highland disputed the jurisdiction of this Court. Nevertheless, by 11 January 2015 NHS Highland had agreed to remove the offending article from its website and expressed its intention to issue revised guidance. Subsequently Pfizer and NHS Highland settled the dispute between them on confidential terms. By 24 March 2015 NHS Highland had issued revised guidance.

500. On 30 January 2015 Pfizer wrote to the Grampian Health Board ("NHS Grampian") expressing concern about a letter sent by NHS Grampian to GPs and community pharmacists in Grampian on 19 December 2014, drawing attention to *Warner-Lambert I*, referring to what NHS Highland were doing and requesting NHS Grampian to withdraw the advice provided in its letter. On 20 February 2015 NHS Grampian said that it would update its guidance, and on 4 March 2015 NHS Grampian confirmed that it had done so.

501. *SIGN*. On 9 January 2015 Pfizer wrote to the Scottish Intercollegiate Guidelines Network ("SIGN"), which is responsible for issuing clinical guidance in Scotland, requesting it to amend its guidance in line with the amendments made by NICE. I do not know whether SIGN did so.

502. *NPA*. On 13 January 2015 Pfizer wrote to the NPA, the main trade association for community pharmacies in the UK, explaining the position with regard to the Patent. It appears that this letter may have been followed by a telephone conversation. On 22 January 2015 the NPA issued guidance to its members that they should take steps to ensure that generic pregablin was not dispensed for pain and warning them that dispensing generic pregabalin for pain might be deemed by Pfizer to be patent infringement.

503. *RCP*. On 26 January 2015 Pfizer met Professor Jane Dacre, President, and another representative of the Royal College of Physicians ("RCP") and followed this up with a letter dated 6 February 2015. The letter set out Pfizer's belief that pharmacists could be liable for patent infringement by dispensing generic pregabalin for pain and that the simplest solution was for clinicians to be advised to prescribe Lyrica by brand for pain.

504. *GMC and GPhC*. On 6 February 2015 Pfizer wrote to the General Medical Council ("GMC", the regulatory body for doctors) and the General Pharmaceutical Council ("GPhC", the regulatory body for pharmacists) drawing attention to *Warner-Lambert I* and requesting that those bodies issue guidance to prescribers and pharmacists respectively. It also wrote to George Freeman MP, Parliamentary Under Secretary of State for Life Sciences on the same day.

505. *BMA*. On 18 February 2015 Dr Phillips wrote to the Chief Executive Officer of the British Medical Association ("BMA", which represents doctors) drawing attention to *Warner-Lambert I* and requesting the BMA's assistance in ensuring that prescribers were given appropriate guidance. On 6 March 2015 the BMA replied that it had issued advice to GPs via Local Medical Committees to the effect that doctors should prescribe Lyrica by brand name for pain.

Pfizer's Brand Equalisation deals

506. In addition to the steps described above, Pfizer has entered into so-called "Brand Equalisation" deals with its main customers. This is a common step taken by originators when a generic version of a drug is about to be launched. Brand Equalisation deals involve the originator discounting the price of the branded product offered to specific customers so as to compete with the price of the generic product. Pfizer has entered into Brand Equalisation deals in respect of Lyrica with a number of its largest pharmacy customers. These include three of the four largest chains, namely Boots, Lloyds and The Well Group. Ms Tully's evidence was that the customers with whom Brand Equalisation deals had been agreed had a combined share of the UK market for prescription medicines of about 42%. Pfizer's original proposals for these Brand Equalisation deals were based on the percentage of pregabalin being prescribed for pain being 59%, but this was subsequently changed to 78%.

Pfizer's application for interim relief

507. As noted above, on 8 December 2014 Pfizer commenced proceedings for infringement and launched an application for interim relief. As a temporary measure, Actavis undertook not to launch their product without giving Pfizer seven days' notice. At the hearing, Actavis undertook not to launch prior to judgment on the application.

508. As explained in *Warner-Lambert I* at [78], the relief sought by Pfizer evolved over the course of the application. By the conclusion of the hearing, Pfizer sought an order in the following terms:

> "1. The Defendants: (a) shall make it a condition of any oral or written agreement entered into with a pharmacy for the supply of Lecaent that the pharmacy shall use reasonable endeavours not to supply or dispense Lecaent to patients who have been prescribed pregabalin for the treatment of pain, by making reasonable enquiries of a person presenting a prescription for 'pregabalin' as to whether the prescription is for pain and/or making reasonable checks of pharmacy records for the same; and (b) shall make it a condition of any oral or written agreement entered into with an intermediary (such as a distributor) for the supply of Lecaent that, in any onward supply of Lecaent by the intermediary, such intermediary must in turn make it a condition of any onward supply agreement for the supply of Lecaent that the receiving pharmacy shall use reasonable endeavours as specified in (a) above.
>
> 2. Insofar as the Defendants are to supply Lecaent to intermediaries (such as a distributor) they inform the Claimant's solicitors of the name of that intermediary prior to supply.
>
> 3. No later than the date of first supply of Lecaent to a pharmacy in the United Kingdom, the Defendants shall write a letter, in

the form attached, to the superintendent pharmacist responsible for the pharmacy to which Lecaent is to be supplied.

4. Prior to launch of Lecaent in the United Kingdom the First, Second and Third Defendants and each of them shall ensure that each pack of Lecaent supplied to a pharmacist is accompanied by removable notification that is easily legible stating:

'This product is not authorised for the treatment of pain and must not be dispensed for such purposes.'

5. The Defendants shall notify in writing forthwith, and in any event before the date of first supply of Lecaent to a pharmacy in the United Kingdom, the NICE Medicines and Prescribing Centre of the Department of Health informing it that Lecaent should not be prescribed or dispensed for the treatment of pain.

6. No later than the date of first supply of Lecaent to a pharmacy in the United Kingdom, the Defendants shall write a letter, in the form attached, to all Clinical Commissioning Groups in the UK."

509. As discussed in *Warner-Lambert I*, at the hearing of the application, the principal bones of contention were paragraphs 1 and 4. For the reasons given in *Warner-Lambert I*, I decided not to order Actavis to take those steps pending trial, and that decision was upheld by the Court of Appeal in *Warner-Lambert CA*.

Pfizer's application against NHS England

510. On 16 February 2015 Pfizer's solicitors wrote to NHS England stating that Pfizer intended to make an application to the Court for an order requiring NHS England to issue guidance to CCGs. On 18 February 2015 NHS England's solicitors wrote to Pfizer's solicitors stating, in summary, that (i) NHS England was an innocent bystander in the present dispute, (ii) NHS England was unwilling for various reasons to issue guidance of its own motion, but (iii) NHS England would not oppose an application by Pfizer for an order requiring it to issue guidance provided certain conditions were met. On 20 February 2015 Pfizer duly issued an application for such an order. As noted above, on 26 February 2015 I duly made an order for the reasons given in *Warner-Lambert IV*. The order required NHS England to issue guidance in the terms set out in Schedule 1 to the Order, which is reproduced in the Annex to *Warner-Lambert IV*.

Guidance issued by NHS England, NHS Wales and NHS Northern Ireland

511. The guidance was issued by NHS England to CCGs and the BSA on 27 February 2015. In turn, CCGs were obliged to distribute the guidance to GPs by 6 March 2015 and the BSA was obliged to distribute it to pharmacists by the same date. The key paragraphs of the guidance are as follows:

> "1. Pregabalin should only be prescribed for the treatment of neuropathic pain under the brand name Lyrica® (unless there are clinical contra-indications or other special clinical needs e.g. patient allergic to an excipient, branded product unavailable etc which apply to Lyrica®, when you should not prescribe Lyrica® or pregabalin).
>
> …
>
> 4. When dispensing pregabalin, if you have been told that it is for the treatment of pain, you should ensure, so far as reasonably possible, that Lyrica®, the branded form of pregabalin, is dispensed. However, when dispensing pregabalin for the treatment of anything other than pain, you are not restricted to dispensing Lyrica®."

512. Pfizer provided copies of the guidance to the Welsh, Scottish and Northern Irish Governments on 2 and 3 March 2015. Equivalent guidance was subsequently issued by the All Wales Chief Pharmacists Committee on 6 March 2015, and by the Health and Social Care Board of Northern Ireland on 16 March 2015. No equivalent guidance has been issued by the Scottish Government. So far as I am aware, neither Pfizer nor Actavis have applied for an order requiring it to do so.

513. There is no direct evidence as to the extent to which the NHS guidance (and the Welsh and Northern Irish equivalents) has been successfully communicated to individual GPs and community pharmacists or implemented by recipients.

Changes to clinical software

514. By no later than 10 June 2015, the clinical software providers, and in particular EMIS and TPP, had modified their software. EMIS is a web-based system where updates are made by EMIS on central servers. Generally, updates are rolled out by EMIS to all users once a month (though if an urgent issue arises an ad hoc update may be implemented as and when needed). EMIS has been modified so as to display a "Low Severity Warning" alert if pregabalin is selected as follows: "Alert If treating neuropathic pain, prescribe Lyrica (brand) due to patent protection. For all other indications, prescribe generically". If the user overrides this warning, the alert is shown again on the next screen. If Lyrica is selected, the "Low Severity Warning" alert is not shown. Similarly, SystmOne now displays a "Warning" as follows: "Neurological disorder: Neuropathic pain: Only the Lyrica brand is licensed for this indication".

515. Similarly, since the hearing in January 2015 and by no later than 10 June 2015, ScriptSwitch and OptimiseRx have been modified to display alerts as follows:

    i) In the case of ScriptSwitch: "If treating neuropathic pain, prescribe Lyrica (brand) due to patent protection".

    ii) In the case of OptimiseRx: "Consider prescribing as Lyrica (by brand) if for the treatment of pain. NHS England advise that, due to licensing and patent protection, all prescribing of pregabalin for pain should be with explicit

reference to the brand Lyrica. For all other indications, continue to prescribe generically."

Actavis' knowledge as to the effect of a skinny label on the dispensing of Lecaent

516. Actavis admit that at all material times they knew that a skinny label alone would not prevent Lecaent from being dispensed for the treatment of pain. Accordingly, Actavis accept that it was foreseeable that, unless further steps were taken, it was likely that some Lecaent would be dispensed for the treatment of pain as a result of pharmacists being presented with generic prescriptions for pregabalin which did not state the indication for which the drug had been prescribed. I will consider the effect of the steps that were taken by Actavis, Pfizer and others below.

Actavis' foresight and knowledge of the steps taken by Pfizer

517. It is not suggested by Actavis that they foresaw Pfizer taking any of the specific steps which Pfizer has taken to try to prevent generic pregabalin being prescribed and dispensed for pain. On the other hand, Actavis became aware of many of the steps taken by Pfizer in the run up to, or during, the hearing of Pfizer's application for an interim injunction (i.e. during mid-December 2014 to mid-January 2015). Actavis became aware of the full story when Pfizer gave disclosure in the infringement proceedings.

Steps taken by Actavis to ensure Lecaent was not dispensed for pain

518. Mr Wilson gave evidence that, following the decision to proceed with a skinny label, Actavis considered what other measures could be taken to ensure Lecaent was not dispensed for pain. At that stage it was unclear to Actavis what to do, partly because it was an unprecedented situation, but also because it would depend upon the situation on the ground at launch and upon the steps taken by others, including Pfizer. Nevertheless, Actavis decided to take the step of informing pharmacists that Lecaent was not indicated for neuropathic pain. Actavis informed Pfizer of this on 3 October 2014 (see paragraph 449 above).

519. As I have explained, this led to correspondence between Pfizer's solicitors and Actavis' solicitors both as to the wording of Actavis' proposed letter to pharmacists and as to what other steps Actavis should take. Both in the run-up to, and during the hearing of, Pfizer's application for an interim injunction, and thereafter, Pfizer presented a continually evolving set of demands as to the steps Actavis should take. Remarkably, this included the presentation of new demands during Pfizer's counsel's cross-examination of Mr Wilson and yet further new demands in Pfizer's closing submissions at trial.

520. In the meantime, Actavis have taken the following steps.

    i) On 17 February 2015 Actavis wrote to over 7,500 pharmacists in the terms indicated in *Warner-Lambert I* at [79]-[80].

    ii) Also on 17 February 2015 Actavis wrote to every CCG in England and every Health Board in Wales and Scotland and every Trust in Northern Ireland in the terms indicated in *Warner-Lambert I* at [81]-[82]. Actavis first offered to write

to CCGs in a witness statement made by their solicitor Timothy Powell on 2 January 2015.

iii) Actavis have emphasised that Lecaent is not indicated for pain in their promotional materials included in trade publications when launching Lecaent.

iv) Actavis have provided their sales team with a sales brief to ensure that they all know Lecaent is not to be used for pain.

v) Actavis have provided a script for their telemarketing team so as to communicate consistent information about Lecaent in response to customer enquiries.

vi) Actavis have provided copies of their letters to prescribers and pharmacists, and subsequently the NHS England guidance, when contacted with queries about pregabalin.

521. Pfizer complains that these steps were both inadequate and late. In particular, Pfizer complains that the letters which Actavis sent to pharmacists and CCGs were inadequate, because they did not state that Lyrica should be prescribed for pain (for the reasons briefly explained in *Warner-Lambert I* at [80] and [82]), and late, because they were only sent when Lecaent was launched. These complaints give rise to one of a number of side issues as to regulatory law which have arisen in these proceedings, namely whether Actavis was able to send such letters prior to receiving its marketing authorisation. I shall consider that below (see paragraphs 576-584).

Further steps demanded by Pfizer

522. In her opening submissions at trial, counsel for Pfizer identified four steps which Pfizer contended that Actavis could and should have taken, but had not. As noted above, additional steps were identified for the first time in her cross-examination of Mr Wilson. In her closing submissions counsel for Pfizer presented a list of seven steps which Actavis could and should take, some of which were brand new. I will consider each of these steps in turn, indicating in each case when they were first raised.

523. *Contractual terms (opening).* In her opening submissions at trial counsel for Pfizer maintained that Actavis should have imposed contractual terms on its customers as sought by Pfizer as part of its application for an interim injunction (see paragraph 1 quoted in paragraph 508 above).

524. I remain of the view that there are a number of problems with this demand. The first is that Actavis deal almost entirely with wholesalers. Thus Actavis would have to require its wholesalers to impose contractual terms on pharmacies. In order to make such terms enforceable by Actavis, provision would have to be made in accordance with the Contracts (Rights of Third Parties) Act 1999. While in theory this is possible, the practical reality is that enforcing contractual terms at one remove is never as easy as enforcing them between contracting parties. Secondly, it puts the dispensing pharmacist in a difficult position: how does he or she know what would amount to "reasonable enquiries" and "reasonable checks"? Thirdly, for this reason, it would be likely to discourage wholesalers and pharmacists from selling Lecaent.

525. This was not among the list of seven steps presented by counsel for Pfizer in her closing submissions. Accordingly, it appears that Pfizer no longer contends that Actavis should adopt this measure.

526. *Labelling (opening).* In her opening submissions at trial counsel for Pfizer maintained that Actavis should have supplied Lecaent packs wrapped (either individually or in multiples) in a removable cellophane wrapper bearing a notice stating "This product is not authorised for the treatment of pain and must be not be dispensed for such purposes" as sought by Pfizer as part of its application for an interim injunction. Actavis contend that they could not do this for regulatory reasons. I will consider that issue below (see paragraphs 585-589). Even if it was permissible, I remain of the view that there are two problems with this demand. The first is that it would be unlikely to be very effective in the absence of knowledge as to the indication for which pregabalin had been prescribed. The second is that it would deter pharmacists from stocking Lecaent, both because of the (small amount of) extra work required to remove the wrapper and because of a concern that they would be unable to comply with the notice.

527. Again, this was not among the list of seven steps presented by counsel for Pfizer in her closing submissions. Accordingly, it appears that Pfizer no longer contends that Actavis should adopt this measure.

528. *A reminder letter to CCGs and Health Boards (opening).* Counsel for Pfizer suggested in her opening submissions at trial that Actavis' letter to CCGs and Health Boards had not been effective and that Actavis should send a reminder letter. I see no reason to think that a reminder letter would be any more effective. At one point counsel for Pfizer also appeared to suggest that Actavis should also write to all GPs in the UK. Again, I see no reason to think that this would be any more effective than the guidance issued by NHS England and other bodies.

529. Again, this was not among the list of seven steps presented by counsel for Pfizer in her closing submissions. Accordingly, it appears that Pfizer no longer contends that Actavis should adopt this measure.

530. *A letter to software providers (opening).* Counsel for Pfizer suggested in her opening submissions that Actavis should have written to the software providers requesting them to change their software to facilitate the prescribing of Lyrica by brand name. I regard this is a fairly extraordinary suggestion, since it involves Actavis requesting the software providers to take steps to preserve Pfizer's market under the Patent. Leaving that aside, however, I consider that it is unlikely that the software providers would have changed their software until encouraged to do so by the NHS England guidance or other guidance with independent and official status.

531. In cross-examination counsel for Pfizer suggested that Actavis should encourage the software providers to make changes. Mr Wilson replied that Actavis would write if this would help, and Actavis followed this up in correspondence. This is no reason to think that this was necessary, however, since all of the software providers had modified their software by then anyway.

532. In her closing submissions counsel for Pfizer submitted for the first time that Actavis should "procure and maintain" (how was not specified) that all the software providers

should implement warnings that Lyrica should be prescribed for the treatment of pain as a high severity warning and ensure that such warnings are applied in all GP practices. This is an extraordinary suggestion: high severity warnings are reserved for the clinically most severe situations. In my view it is plainly inappropriate to treat the prescribing of Lyrica by brand name in the same way. In any event, I cannot conceive how Actavis are supposed to be able to procure that the software providers do this.

533. *Contractual restriction on wholesalers (cross-examination).* Counsel for Pfizer suggested to Mr Wilson that Actavis should impose a contractual restriction on its wholesalers requiring them not to supply pharmacies exclusively with pregabalin. As Mr Wilson explained, this would be pointless, since pharmacies typically acquire products from multiple wholesalers anyway. In addition, as counsel for Actavis pointed out, no pharmacy would acquire just generic pregabalin, since it would need to have Lyrica to dispense against branded prescriptions.

534. Again, this was not among the list of seven steps presented by counsel for Pfizer in her closing submissions. Accordingly, it appears that Pfizer no longer contends that Actavis should adopt this measure.

535. *NHS guidance (cross-examination).* Counsel for Pfizer suggested to Mr Wilson that Actavis should have requested the NHS to issue guidance before Actavis received their marketing authorisation. It was not explained why the NHS would have acted upon such a request given that (a) the purpose of the request would be to protect Pfizer's market under the Patent and (b) at that point in time Actavis was one of several generic companies planning to sell generic pregabalin under a skinny label, but which did not yet have a marketing authorisation enabling them to do so.

536. In her closing submissions counsel for Pfizer submitted that Actavis should "procure and maintain" that authoritative NHS guidance on prescribing Lyrica by brand name for pain across the UK. Such guidance has already been issued in England, Wales and Northern Ireland. Counsel for Pfizer emphasised that similar guidance had not been issued in Scotland. I do not understand what Actavis are supposed to do, however, given that Pfizer has already tried to persuade the Scottish Government to issue such guidance and the Scottish Government's position is that it is a matter for the regional Health Boards (see paragraph 474 above).

537. *Change to dm+d (cross-examination).* The Dictionary of Medicines and Devices ("dm+d") is an NHS standard dictionary for medicines and devices. dm+d provides a unique code for each medicine and device together with a textual description of the item. Electronic systems that exchange or share information about medicines and devices relating directly to an NHS patient's care must adhere to this standard by using dm+d identifiers and descriptions when transferring information about medicines relating directly to the patient's care. This provides interoperability between different systems. For example, dm+d is a cornerstone of the Electronic Prescription Service, a service used by GP practices to send prescriptions electronically to community pharmacies.

538. A limited number of "flags" can be assigned to entries in dm+d to give additional information about the entries. One such flag is a warning flag that a product is unsuitable to be prescribed generically for patient safety reasons. The criteria for assigning such flags are set by the Editorial Board of dm+d, which is chaired by a

colleague of Ms Howe's in the Department of Health. The Senior Responsible Officer for dm+d is another colleague of Ms Howe's.

539. In a letter from Pfizer's solicitors to the Government Legal Department dated 24 June 2015, Pfizer raised a question as to whether the dm+d entry for pregabalin could have a flag added to it to state that Lyrica should be prescribed by brand for pain. Ms Howe addressed this question in her second witness statement. She pointed out that, leaving aside the technical and cost considerations involved in making such a change, the clinical software providers were not reliant upon dm+d flags when determining the alerts they applied within their systems, and indeed were not obliged to use dm+d flags in their systems at all. Accordingly, she expressed the view that a new flag in dm+d would not, in itself, make any difference to prescribing or dispensing behaviour. As noted above, her evidence was not challenged by Pfizer.

540. Despite this, counsel for Pfizer suggested to Mr Wilson that Actavis should request a change to dm+d. She did not specify what change Actavis should request, still less how it would have effect.

541. In her closing submissions counsel for Pfizer advanced a new suggestion, namely that Actavis should "procure and maintain … a split of pregabalin Virtual Medicinal Product ('VMP') in DM+D into two VMPs 'pregabalin – pain' and 'pregabalin – non pain' to ensure that 'pregabalin – pain' VMP selection automatically leads to branded Lyrica prescriptions and 'pregabalin – non pain' VMP pain selection automatically leads to generically written pregabalin prescriptions". Since this suggestion was not put to Ms Howe or Ms Wilson (or any other witness), there is no evidence as to how effective it might be assuming that the Department of Health was prepared to make this change.

542. *A letter to hospitals (cross-examination).* Counsel for Pfizer suggested to Mr Wilson that Actavis should contact hospitals who tendered for pregabalin. Mr Wilson explained that Actavis had asked the hospital contracting body whether it was tendering for pregabalin, but was told that so far there had been no tenders for pregabalin.

543. In her closing submissions counsel for Pfizer submitted that Actavis should "procure and maintain" that any UK tender process for hospital demand for pregabalin should be conducted on the basis that pregabalin for pain was tendered separately from non-pain and that only Lyrica was awarded for pain. It was not explained how it lay within Actavis' power to procure this, particularly on a UK–wide basis.

544. *An order against the Department of Health (cross-examination).* Ms Howe gave evidence that the Department of Health would not support pharmacists endorsing prescriptions written generically with "Lyrica". Counsel for Pfizer suggested to Mr Wilson that Actavis should have sought an order against the Department of Health to allow this to happen. The legal basis for this suggestion was not explained, nor how it was supposed to work in practice. I regard it as a bizarre suggestion.

545. Again, this was not among the list of seven steps presented by counsel for Pfizer in her closing submissions. Accordingly, it appears that Pfizer no longer contends that Actavis should adopt this measure.

546. *The modified Consilient scheme (cross-examination).* Ms Tully suggested in her evidence that Actavis should adopt the Consilient scheme for marketing pregabalin (as to which, see paragraph 559(ii) below). Mr Wilson explained in his evidence that this was impracticable and would effectively prevent Actavis from selling Lecaent. Similar evidence was given by Ms Howe. Counsel for Pfizer suggested to Mr Wilson that the scheme could be modified to allow pharmacists to stock the product. Mr Wilson said that this would be cumbersome. As counsel for Actavis pointed out, it would require GPs to prescribe by brand for the non-patented indications (rather than generically). The scheme would have to apply to all generic entrants into the market, each of whom would have to adopt their own brand name. Thus it would also require the GPs to memorise the new brand names for each and every generic entrant and to choose arbitrarily between them when writing the prescription (which would also require the clinical software to be modified). It would also require pharmacists to stock all of the branded generic products. In short, it would be unworkable. In addition, Ms Howe said that the Department of Health would regard prescribing by brand in this way as unsatisfactory from a pharmacy policy perspective, because it ran counter to the advantages of generic prescribing.

547. Again, this was not among the list of seven steps presented by counsel for Pfizer in her closing submissions. Accordingly, it appears that Pfizer no longer contends that Actavis should adopt this measure.

548. *Guidance to hospital doctors (closing).* In her closing submissions counsel for Pfizer submitted for the first time that Actavis should "procure and maintain" that authoritative guidance on prescribing Lyrica for pain was issued to hospital doctors by the relevant Medicine Management Teams in CCGs and Health Boards. It was not explained how it lay within Actavis' power to procure this.

549. *Compensation to CCGs, Health Boards and others (closing).* In her closing submissions counsel for Pfizer submitted for the first time that Actavis should compensate CCGs, Health Boards and others in respect of any costs incurred in implementing NHS guidance or of any of the other steps demanded by Pfizer.

Effect of the guidance issued by NHS England and others

550. Pfizer has previously described the issuing by NHS England of guidance to doctors to prescribe Lyrica by brand name for pain as "the simple fix to this problem" (see paragraph 476 above). In a witness statement made on behalf of Pfizer in support of the application against NHS England, Ms Dagg expressed the belief that such guidance would be "highly effective" and that GPs and pharmacists would be likely to follow it. Ms Tully described the guidance issued by NHS England in her evidence as "the key development in terms of communication with pharmacists, CCGs and other stakeholders". She also quoted from a press release issued by Prof Darracott of Pharmacy Voice welcoming the NHS England guidance and the clarity it would bring. In an open letter to clinicians and pharmacists from Dr Phillips and a colleague which was published in the *British Medical Journal* on 8 June 2015, reference was made to "the much-needed central guidance issued by NHS England and senior NHS bodies within Wales and Northern Ireland". It is evident from all of this evidence that Pfizer anticipated that the guidance would be effective. At trial, however, Pfizer contended that it had not been as effective as had been hoped.

551. Ms Howe explained that NHS GP contracts take one of three forms: General Medical Services ("GMS") contracts, for which there are mandatory terms in the National Health Service (General Medical Services) Regulations 2004; Personal Medical Services ("PMS") contracts, for which there are mandatory terms in the National Health Service (Personal Medical Services) Regulations 2004; and Alternative Provider Medical Services ("APMS") contracts, for which there are mandatory terms in the Alternative Provider Medical Services Directions 2013. Most GP services are provided under GMS or PMS contracts. Both the GMS and the PMS Regulations require such contracts to include a term requiring contractors to have regard to all relevant guidance issued by NHS England. There is no equivalent provision in the APMS Directions. The upshot is that most GPs are required to have regard to guidance issued by NHS England, but are not bound to follow it.

552. It is common ground that by May 2015 the level of branded prescriptions had risen to about 30% of the total for pregabalin (from as little as 1% in January 2015). It is also common ground that this level is expected to continue to rise.

553. It is clear from the evidence that the main reason why it has taken time for the guidance issued by NHS England and others to translate into a higher level of branded prescribing is that many patients who take pregabalin for pain have chronic conditions which require long-term treatment and thus they have repeat prescriptions. Practice with regard to repeat prescriptions varies from surgery to surgery, but typically a patient will be able to obtain repeat prescriptions for 6 or 12 months without seeing a doctor. In the ordinary course, it will only be at the point that the patient sees the doctor that the opportunity will arise to switch that patient's prescription from generic pregabalin to Lyrica.

554. It is possible, however, for a GP practice to arrange for all prescriptions for pregabalin to be reviewed and to switch any prescriptions for generic pregabalin for pain to Lyrica. It would not be necessary for this work all to be done by a GP: the review could be done by an administrator, although a GP would then need to issue the new prescriptions. This would require the expenditure of time and money, however. It is clear from the evidence that, even though the expenditure of time and money is not large, there has been an understandable degree of reluctance on the part of GP practices to expend their own resources on the task. As a result, some practices have requested Pfizer to fund the exercise. Pfizer did not agree to this until counsel for Actavis asked Ms Tully on cross-examination why not. Towards the end of the trial, on 16 July 2015, Pfizer did offer to fund such work, but on the basis that it could recover the costs from the generic companies.

555. It was suggested by counsel for Pfizer in her opening submissions, on the basis of some reports in the medical press, that, in addition to the cost issue, some GPs might refuse to follow the guidance issued by NHS on the ground that they regarded it as an interference with their clinical freedom. She did not pursue this suggestion in her closing submissions, and there is no firm evidence to support it. As noted above, there are other circumstances in which prescribing by brand name is established practice, and it does not affect the doctor's freedom to prescribe whatever drug they consider clinically most appropriate. It seems to me that the negative reactions suggested by the press reports are more likely to be attributable to GPs' concerns about the spectre of patent infringement (see further below for discussion of the position of doctors in this regard).

556. Counsel for Pfizer did suggest that it was likely that, even now, not all GPs were aware of the guidance issued by NHS England. In my judgment this is unlikely. Still less is it likely that there are any GPs who have not become aware of the guidance issued by at least one of the various bodies who have issued it. As I have just touched on, this litigation, and in particular the guidance issued by NHS England, has been extensively covered by the medical and pharmaceutical press.

557. Accordingly, I conclude that it is reasonable to expect that, if it has not already happened by now, in the fairly near future most prescriptions for pregabalin for pain will be written by reference to the brand name Lyrica. This is, of course, subject to NHS England and other bodies changing their guidance in the light of my decision with respect to the validity of claims 1 and 3 of the Patent (taking into account any appeal against that decision).

558. Turning to the position of pharmacists, it is common ground that most pharmacists who were aware of the NHS England guidance would be likely to follow it so far as possible. Ms Dagg's evidence includes examples of this (see paragraph 562 below). In my judgment it is unlikely that many pharmacists will be unaware of it. Of course, this still leaves the situation where the pharmacist is presented with a prescription for generic pregabalin, does not know what indication it has been prescribed for and cannot readily find out (e.g. because the prescription has been presented by someone other than the patient). The more that prescribers prescribe Lyrica for pain, however, the more pharmacists will be justified in assuming that prescriptions written generically are for the non-patented indications.

Other generic suppliers of pregabalin

559. A number of other generic suppliers of pregabalin have come into the market in addition to Actavis, all under skinny labels:

    i) Dr Reddy's launched a pregabalin product under the trade mark Alzain on 13 February 2015. Pfizer has brought proceedings against Dr Reddy's for infringement of the Patent.

    ii) Consilient Health launched a pregabalin product under the trade mark Rewisca on 9 March 2015. This product is only available from two wholesalers subject to a bespoke ordering process. Pursuant to this process, Rewisca will only be supplied if it is prescribed by brand. Even then, pharmacies cannot stock the product, but are only supplied it upon proof of the branded prescription. The evidence suggests that, as a result, Consilient has made negligible sales of Rewisca. Pfizer accepts that, as a result of implementing this process, Consilient has not infringed the Patent.

    iii) Sandoz launched a generic pregabalin product at the beginning of July 2015. So far as I am aware, Pfizer has not (yet) brought proceedings against Sandoz for infringement of the Patent.

    iv) Teva launched a generic pregabalin product shortly after Sandoz. Pfizer has brought proceedings against Teva for infringement of the Patent.

v) Sanofi intends to launch a generic pregabalin product. So far as I am aware, Pfizer has not (yet) brought proceedings against Sanofi for infringement of the Patent

560. It is common ground that the overall level of sales of Lecaent, Alzain and Rewisca from 16 February to 19 May 2015 was about 17.4% of the total volume of pregabalin sold during this period.

Has generic pregabalin been dispensed for pain?

561. Pfizer contends that some generic pregabalin, including some Lecaent, has been dispensed for the treatment of pain. Ms Tully advanced several arguments in support of this contention, but her evidence on this topic was completely unconvincing (it included evidence which, as noted above, made no sense and which Ms Tully was unable to explain).

562. Ms Dagg gave evidence about six instances:

i) Example 1 concerned a patient who had been prescribed pregabalin for neuropathic pain for over two years. The patient had a "repeat card" for the prescription. As at 23 March 2015, the prescription was written generically. By the beginning of June 2015, the patient had received a new repeat card for the prescription, which was now for Lyrica. Thus this example shows the NHS England guidance being implemented. There is no evidence that the patient was dispensed generic pregabalin by his or her pharmacy during the period when the prescription was written generically.

ii) Example 2 concerns a patient who took pregabalin for neuropathic pain. The patient's prescription for pregabalin 200 mg and 75 mg was written generically. On 13 April 2015 the patient took a repeat prescription to a pharmacy in Tamworth. The pharmacist dispensed Lyrica for the 200 mg dosage and Alzain for the 75 mg dosage. There is no evidence that the patient received generic pregabalin on any other occasion. Nor does the evidence reveal whether or not the patient's prescription has been switched to Lyrica, as one would expect to have happened by now.

iii) Example 3 concerns a patient who received a prescription dated 9 April 2015 for pain which was written generically. A colleague of Ms Dagg presented the prescription to a branch of a large pharmacy chain in London and specifically requested that the pharmacist dispense Lecaent. When the pharmacist asked if he meant Lyrica, he repeated the request for Lecaent. The pharmacist duly complied with the request, but did not ask what indication the prescription was for. I was not addressed by the parties on the trade mark and passing off implications if the pharmacist had supplied Lyrica instead. In any event, I agree with counsel for Actavis that this example is contrived and unrealistic. There is no evidence that ordinary patients ask for Lecaent by brand name or are likely to do so.

iv) Example 4 concerns a patient who is a friend of Ms Dagg's. The patient is being treated with pregabalin for pain. The patient had a prescription written generically dated 8 April 2015. Ms Dagg took the prescription to a branch of

the large pharmacy chain in Hampshire and handed it to an assistant. She heard the duty pharmacist tell the assistant "If it's for pain, we give Lyrica, the old one, if it's not we give the new one Lecaent". The pharmacist then asked Ms Dagg if it was for pain. The pharmacist only had one pack of Lyrica, and gave Ms Dagg an owing note for a second pack. The following week Ms Dagg's daughter's nanny took the owing note to the pharmacy and was provided with a pack of Lecaent without any questions being asked. As counsel for Actavis submitted, this probably occurred because a different person presented the owing note. If the same person had done so, ordinarily that person would be likely to query why Lyrica was not dispensed. The same patient was later given a prescription dated 17 June 2015 which was written generically. The patient presented the prescription at a pharmacy and was dispensed Lecaent without any questions being asked.

v) Example 5 concerns an unidentified patient from Scotland who had been following this litigation closely and had pronounced views about it. In my judgment no weight can be placed on this example.

vi) In addition to the examples set out above, Ms Dagg herself visited a pharmacy on 4 July 2015. She spoke to the pharmacist on duty and asked what a person with a prescription for pregabalin would receive. The pharmacist explained that the protocol was that she would need to ask the patient what she was taking the medicine for and would then dispense either Lyrica or generic pregabalin depending on the illness being treated.

563. The strongest example from Pfizer's perspective is example 4. This confirms what one would expect from the inherent probabilities, namely that on occasion Lecaent has been dispensed where the prescription has been written generically for a patient who is in fact being treated for pain. Even in this instance, there is no reason to believe that the patient's prescription will not at some point be switched to Lyrica.

564. Overall, there is no evidence that Lecaent has been dispensed for patients who are being treated for pain on a substantial scale. On the contrary, Ms Tully's evidence was that Lyrica had retained over 80% of the market for pregabalin in the UK. As noted above, generics have achieved about 17.4% of the market. Lecaent has only achieved a proportion of that 17.4%, albeit a substantial proportion. Accordingly, whatever the precise split between patented and non-patented indications may be, the quantities of Lecaent sold are lower than the size of the non-patented market.

Regulatory issues

565. A number of side issues as to regulatory law have arisen during the course of the proceedings which have an indirect bearing on the question of infringement, because they affect the parties' ability to take certain steps which one party suggests that the other could and should have taken.

Could Pfizer have launched a skinny label product?

566. The first issue is whether it was possible for Pfizer itself to launch a skinny label generic pregabalin product. Actavis contend that this was possible, while Pfizer

contends that this was not permissible for regulatory reasons, given that it already had a full label marketing authorisation for Lyrica.

567. The relevant legislative provision is Article 82(1) of the Regulation. This provides:

> "Only one authorisation may be granted to an applicant for a specific medicinal product.
>
> However, the Commission shall authorise the same applicant to submit more than one application to the Agency for that medicinal product when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to healthcare professionals and/or patients, or for co-marketing reasons."

568. The Commission has issued guidance as to how it will apply this provision. The guidance points out that the second subparagraph constitutes a derogation from the general rule contained in the first subparagraph, and therefore should be restrictively interpreted. It makes it clear that the public health ground must be related to the availability of the product, and it covers certain common scenarios. The guidance also makes it clear, however, that the issue will be considered on a case-by-case basis and it recognises that other situations may arise.

569. The guidance explains that a common case for a duplicate authorisation is where there is patent protection in one or more Member States covering an indication or a pharmaceutical form, but not in one or more other Member States. A skinny label excluding that indication or form may be granted to enable marketing in the Member States where there is patent protection. The duplicate marketing authorisation must be surrendered when the relevant patent expires. It is common ground, however, that this scenario would not apply to Pfizer since it is the owner of the Patent.

570. Actavis rely on the fact that the guidance indicates that it is also considered to be within the public health ground for the holder of the reference marketing authorisation to obtain a second marketing authorisation for generic entry. It explains that this is because generic entry increases accessibility (i.e. it reduces the price for the medicine). It also says that further applications (i.e. beyond a second) by the holder of the reference marketing authorisation would need to be justified by further arguments.

571. It is common ground that Pfizer did in fact obtain a second marketing authorisation for Pfizer pregabalin on this basis, which was a full label authorisation (except that it had a particular pharmaceutical form carved out of it, namely an oral solution which is only used for the treatment of pain). The issue between the parties is whether Pfizer could have obtained a second marketing authorisation which was a skinny label marketing authorisation.

572. It is again common ground that this scenario is not expressly addressed by the existing guidance. It is also common ground that there is no known precedent for such an application. Thus it is impossible to be sure how the Commission would react.

573. Actavis contend that the crucial question is whether it can be shown that the grant of a second (or third) marketing authorisation to the holder of the reference marketing authorisation will increase accessibility of the product. If it will, then a second (or

third) marketing authorisation will be granted. I accept that reading of Article 82(1) and the Commision guidance.

574. Actavis then argue that, if Pfizer had obtained a skinny label marketing authorisation for Pfizer pregabalin, and had educated GPs to prescribe Lyrica by brand for the patented indication, that would have increased the accessibility of pregabalin for the non-patented indications while preserving the patented market. In principle, this appears to me to be correct. The difficulty with this suggestion is that it depends on Pfizer being able to persuade GPs to prescribe Lyrica by brand for the patented indication. Absent guidance being issued by NHS England and other responsible bodies, I consider that this would have been an uphill task.

575. In the alternative, Actavis rely upon the co-marketing ground under Article 82(1). Actavis contend that Pfizer could have enabled a third party to market an authorised generic with a skinny label by allowing its access to Pfizer's regulatory dossier under the informed consent procedure provided in Article 10(a)(i) of the Directive and used the authorised generic to service the non-patented market. Again, this appears to me to be correct. Again, however, the difficulty that remains is that Pfizer would have had to educate GPs to prescribe Lyrica by brand for the patented indication.

Could Actavis have communicated with CCGs and others prior to receipt of their marketing authorisation?

576. The second regulatory issue is whether Actavis could have sent CCGs and pharmacists letters of the kind which they sent at the time of launching Lecaent prior to receiving their marketing authorisation. Actavis contend that this was not permissible for regulatory reasons, but Pfizer disputes this.

577. Title VIII (Articles 86-110) of the Directive regulates the advertising of medicinal products, both to the general public and to persons qualified to prescribe or supply such products.

578. Article 86(1) defines "advertising of medicinal products" as including "any form of … inducement designed to promote the prescription, supply, sale or consumption of medicinal products" and as including various specific forms of promotion. Article 87 prohibits any advertising of a medicinal product in respect of which a marketing authorisation has not been granted in accordance with EU law. Accordingly, it is common ground that Actavis were prohibited from advertising Lecaent to anyone prior to 16 February 2015, when Lecaent received its marketing authorisation. Even following receipt of a marketing authorisation, Article 88 prohibits advertising of prescription medicines to the general public. Advertising to prescribers and dispensers is permitted provided that it conforms to the requirements of Article 91.

579. Pfizer relies, however, on Article 86(2) of the Directive. This excludes from Title VIII:

> "- correspondence, possibly accompanied by material of a non-promotional nature, needed to answer a specific question about a particular medicinal product,

- factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provide they include no product claims."

580. In Case C-421/07 *Damgaard* [2009] ECR I-2629 the Court of Justice of the European Union held at [24] that, in order to determine whether a communication constitutes advertising, it was relevant to consider the situation of the author of the communication about a medicinal product, his relationship with the company which manufactured the product together with other circumstances, such as the nature of the activity carried out and the content of the message.

581. The Code of Practice for the Pharmaceutical Industry ("the Code") published by the Association of the British Pharmaceutical Industry, which applies to the promotion of medicines to health professionals in the UK, defines "promotion" as "any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines". While this is not authoritative with respect to the interpretation of the Directive, it is consistent with it.

582. Pfizer argues that it was permissible for Actavis to have notified doctors and pharmacists at any time that: (i) Pfizer had patent protection for the use of pregabalin for the treatment of pain; (ii) while the Patent was in force, generic pregabalin products would only be indicated for the treatment of the non-patented indications; (iii) pregabalin should be prescribed for the treatment of pain by reference to the brand name Lyrica; and (iv) pharmacists should take all reasonable steps to check whether a generic prescription for pregabalin was for the treatment of pain and, if so, dispense Lyrica against that prescription.

583. I do not accept this argument. I accept that references to the patent situation and to Lyrica would have been permissible. But the fundamental problem is that, for the communication to make sense to the recipient, Actavis would have needed to make it clear in some way that generic pregabalin was shortly to become available in the UK. But Actavis would not have been able to do this without implicitly promoting their own product. This is particularly so given that most recipients would be aware that Actavis are major suppliers of generic products.

584. In my judgment, therefore, Actavis are correct to say that they would have contravened the Directive (and hence the implementing Regulations in the UK) if they had sent communications of the kind proposed by Pfizer before receiving their marketing authorisation. (Actavis would also have contravened the Code for the same reason.)

Could Actavis have supplied Lecaent packs in a cellophane wrapper bearing a notice?

585. The information which must or may appear on medicinal products is governed by the Directive. Information which must appear on the packaging is listed in Article 54. This does not require the outer packaging to include the indications for which a product is licensed. Article 62 allows additional information to appear on outer packaging provided it is consistent with the SmPC, useful for the patient and non-promotional.

586. As part of its application for an interim injunction, Pfizer sought an order requiring Actavis to ensure that Lecaent was supplied in packaging bearing a notice stating that the product should not be dispensed for pain, in particular by means of a cellophane wrapper: see *Warner-Lambert I* at [78], [85] and [121]. Ms Howe gave evidence that, following the interim application, the MHRA, which is an executive agency of the Department of Health, had sought the view of two EU working groups on this question.

587. The first was CMDh. The second was the Working Group on Quality Review of Documents ("QRD"), which provides assistance to the EMA's scientific committee and to companies on linguistic aspects of the product information for medicines. One of its tasks is to contribute to the development of a common understanding on the implementation of legislation and guidelines in relation to product information and labelling.

588. Although CMDh thought that a wrapper covering several packs which is removed before reaching the patients formed part of the transport packaging, rather than the outer packaging, under the Directive, it opposed its use in the way proposed by Pfizer. For its part, QRD considered that the wrapper fell within the scope of the labelling requirements of the Directive. Accordingly, Ms Howe stated that the MHRA would oppose the use of a wrapper in this way.

589. I therefore conclude that Actavis cannot be criticised for not having used such a wrapper. As noted above, it does not appear that Pfizer maintains this suggestion anyway.

Did Actavis intend Lecaent to be dispensed for the treatment of pain?

590. Pfizer alleges that Actavis have at all material times intended that Lecaent would be dispensed for the treatment of pain, and in particular neuropathic pain. This was not an allegation made by Pfizer when it launched its claim for infringement. Pfizer only sought to introduce the allegation after I had ruled in *Warner-Lambert I* that infringement of a Swiss form claim required an intention on the part of the manufacturer that the product would be used for treating the patented indication. When Pfizer applied to amend its Particulars of Infringement to introduce this allegation, I ruled in *Warner-Lambert II* that the facts and matters relied upon did not support the inference that Actavis had had the intention alleged, but nevertheless permitted Pfizer to make the amendment for the reasons explained in that judgment. (Subsequently Pfizer further amended the Particulars of Infringement to plead a case that it was foreseeable to Actavis that others would intentionally administer pregabalin to treat pain.)

591. Before proceeding further, I should note two points which are not in dispute. First, intention is a subjective state of mind, but it must be objectively assessed and may be inferred from appropriate facts. Secondly, Actavis do not seek to distinguish between their own knowledge and intention and that of Balkanpharma (the manufacturer of Lecaent).

592. At trial Mr Wilson's evidence in chief was unequivocal that Actavis did not intend and never had intended its skinny label pregabalin to be used for the treatment of pain. The allegation that Actavis had intended this was only put by counsel for Pfizer to Mr

Wilson in cross-examination in the most formal and cursory way. Unsurprisingly, he denied it. Not only that, but in addition counsel for Pfizer cross-examined Mr Wilson at some length about the fact that most of Actavis' sales forecasts had been based on their estimate that the non-patented share of the pregabalin market was 30%. As counsel for Actavis pointed out, this would not have been the case if Actavis had been targeting the entire pregabalin market.

593. In her closing submissions counsel for Pfizer relied upon four matters as justifying the inference that Actavis had had the intention alleged by Pfizer notwithstanding Mr Wilson's denial. The first was the fact that Actavis' forecasts were based on the X% market share. The second was that Actavis knew that a skinny label alone would not prevent Lecaent being dispensed for pain. The third was that Actavis knew that the measures it took prior to launch were insufficient to prevent this. The fourth was the modified blue box wording used by Actavis on their PIL.

594. In my view these points are wholly unpersuasive. So far as the first concerned, as I have explained, Actavis made its original forecasts, and indeed placed its first orders for pregabalin, before it had decided whether to launch under a full label or a skinny label. Moreover, the X% market share was a figure Actavis had frequently used before. The second point is correct, but does not show that Actavis intended Lecaent to be dispensed for pain. As for the third point, I do not accept that Actavis knew that the steps it proposed to take would be ineffective. I find that they did not know whether they would be effective or not. I have already discussed the fourth point in paragraph 447 above.

595. In my judgment there is no proper basis for inferring that Actavis intended Lecaent to be dispensed for the treatment of pain, and I have no hesitation in accepting Mr Wilson's denial.

596. Counsel for Pfizer submitted in the alternative that I should conclude that Actavis had had the intention alleged by Pfizer on the basis that Actavis should be taken to have intended the natural and probable consequences of their acts. This is an allegation of imputed intention: see *O v Rhodes* [2015] UKSC 32, [2015] 2 WLR 1373 at [45] (Baroness Hale of Richmond and Lord Toulson, with whom Lord Clarke of Stone-cum-Ebony and Lord Wilson agreed). Baroness Hale and Lord Toulson went on at [81]:

> "There is a critical difference, not always recognised in the authorities, between imputing the existence of an intention as a matter of law and inferring the existence of an intention as a matter of fact. Imputation of an intention by operation of a rule of law is a vestige of a previous age and has no proper role in the modern law of tort. It is unsound in principle. It was abolished in the criminal law nearly 50 years ago and its continued survival in the tort of wilful infringement of the right to personal safety is unjustifiable. It required the intervention of Parliament to expunge it from the criminal law, but that was only because of the retrograde decision in *Director of Public Prosecutions v Smith* [1961] AC 290. The doctrine was created by the courts and it is high time now for this court to declare its demise."

597. Counsel for Pfizer submitted that this statement of principle was only binding authority in relation to the tort of intentionally causing harm. That I accept. She also submitted that it should not be treated as persuasive authority in the present context. Other than the difference in context, she advanced no reasoned justification for disregarding it. In my judgment this statement of principle is both highly persuasive and of general application throughout the law of tort. Accordingly, I decline to impute the alleged intention to Actavis.

Pfizer's claim under section 60(1)(c): the law

The statutory framework

598. Section 60 of the 1977 Act sets out the acts which amount to an infringement of a patent. So far as relevant, it provides as follows:

> *"*(1) Subject to the provisions of this section, a person infringes a patent for an invention if, but only if, while the patent is in force, he does any of the following things in the United Kingdom in relation to the invention without the consent of the proprietor of the patent, that is to say —
>
> (a) where the invention is a product, he makes, disposes of, offers to dispose of, uses or imports the product or keeps it whether for disposal or otherwise;
>
> (b) where the invention is a process, he uses the process or he offers it for use in the United Kingdom when he knows, or it is obvious to a reasonable person in the circumstances, that its use there without the consent of the proprietor would be an infringement of the patent;
>
> (c) where the invention is a process, he disposes of, offers to dispose of, uses or imports any product obtained directly by means of that process or keeps any such product whether for disposal or otherwise.
>
> (2) Subject to the following provisions of this section, a person (other than the proprietor of the patent) also infringes a patent for an invention if, while the patent is in force and without the consent of the proprietor, he supplies or offers to supply in the United Kingdom a person other than a licensee or other person entitled to work the invention with any of the means, relating to an essential element of the invention, for putting the invention into effect when he knows, or it is obvious to a reasonable person in the circumstances, that those means are suitable for putting, and are intended to put, the invention into effect in the United Kingdom.*"*

599. Subsections (1) and (2) give effect to Articles 25 and 26 of the Community Patent Convention on direct and indirect infringement, even though that Convention never came into force.

600. Subsection (1) creates three statutory torts of strict liability, whereas subsection (2) requires the presence of a double mental element. The first mental element concerns the state of mind of the supplier, and amounts to either actual ("when he knows") or constructive ("it is obvious to a reasonable person in the circumstances") knowledge. The second mental element concerns the state of mind of the person to whom the means are supplied (or an end user further removed from the supplier), and amounts to a requirement of intention.

601. For there to be infringement under section 60(1)(c), the product must be "obtained directly by means of" the claimed process. No issue arises in the present case with respect to this requirement: Actavis accept that, if Lecaent was manufactured in accordance with the process claimed in claims 1 or 3 of the Patent, then it was obtained directly by means of that process.

Swiss form claims in more detail

602. As explained above, there are two obstacles to the grant of patents for second medical uses of known products, namely that the products themselves lack novelty and that methods of treatment are not patentable. Swiss form claims represent an attempt to overcome these obstacles.

603. The reason why Article 53(c) of the European Patent Convention 2000 (formerly Article 52(4) of the EPC 1973), which is given effect to by section 4A of the 1977 Act (previously section 4), excludes methods of treatment from patentability was stated by the Enlarged Board of Appeal of the European Patent Office in G 2/08 *Abbott Respiratory/Dosage regime* [2010] EPOR 26 at [5.3] to be based on:

> "… socio-ethical and public health considerations. In fact physicians should be free to take all actions they considered suitable to prevent or to cure a disease, and in this exercise they should remain uninhibited by patents."

As the Enlarged Board went on to explain at [5.6]:

> "… any method claim containing even a single step pertaining by nature to a treatment by therapy is not allowable".

604. The consequence of this exclusion from patentability is that it is not possible to overcome the lack of novelty of the product by patenting the new method of treatment, or even by adding a treatment step to a method of manufacture. Instead, the problem of lack of novelty is addressed by making the claims purpose-limited. As noted above, this is achieved by interpreting the word "for" as importing a mental element, rather than merely as meaning "suitable for", which is an objective criterion. Because the process of manufacturing the products is being carried out with a new mental element, it is novel. If "for" meant "suitable for", this would not be the case: pregabalin made before the priority date of the Patent was just as suitable for treating pain as pregabalin made afterwards. What has changed (assuming that the Patent is valid) is that it is now known that pregabalin is effective for the treatment of (neuropathic) pain (or least, has plausibly been predicted to be effective).

605. The issue which arises acutely in this case is as to the nature of this mental element. The reason that it arises so acutely is that Actavis profess to be supplying the product solely for the old purpose of treating epilepsy and GAD, which it is common ground would be entirely lawful, and that there is a substantial market for pregabalin for that old use (whatever the precise size of that market).

The judgment of the Court of Appeal

606. The issue as to the nature of mental element in Swiss form claims was considered in detail by Floyd LJ in *Warner-Lambert CA*. As he said at [99], it is "a very difficult question". For reasons that will appear, it is necessary for me to consider his judgment at some length.

607. Floyd LJ started at [113] by observing that the issue was a question of construction of the claim. Like any such question, the task for the court was to determine what the skilled reader of the patent would understand the patentee to be using the language of the claim to mean. Next, he pointed out at [115]-[117] that it was important to distinguish between the technical subject matter of the claim and the rights which a patent gave the owner of the patent as a matter of national law.

608. He proceeded to analyse the technical subject matter of the claim as follows:

> "118. … The skilled person would understand that the technical features of the present claim extend beyond making pregabalin, yet fall short of including the step of actually using pregabalin for treating pain. Instead it includes a feature concerned with the ultimate purpose of the product manufactured, namely the intentional treatment of pain. I would describe the subject matter of the claim, therefore, as making pregabalin for patients to whom it will be intentionally administered for treating pain. Making pregabalin for patients to whom it is to be administered for the non-patented indications is not within the technical subject matter of the claim. Only the former category of manufacture makes use of the technical contribution of the patentee.
>
> 119. I think the skilled person would understand the technical subject matter of the claim in the way I have indicated because he or she would first understand that it was necessary for the claim to include a manufacturing step to ensure that the claim does not touch the doctor, and fall foul of the method of treatment exclusion. However the skilled person would understand that any manufacturing step is adequate for this purpose, as the doctor does not manufacture the medicament.
>
> 120. The skilled person would understand that the claim in question owes its novelty to the discovery of the new therapeutic use of the medicament. …
>
> 121. Thus the skilled person would understand that the technical subject matter of the claim was concerned with the ultimate

> end use of the medicament, from which it derived its novelty. The therapeutic treatment is of course new because, and only because, it is carried out with the intention of producing the new therapeutic effect. The prior use of the compound may have in fact produced the effect, for example if a patient taking it for GAD or epilepsy was at the time experiencing pain as well. This demonstrates, to my mind, that it is the intention for which the compound is administered which is at the heart of the invention."

609. He then turned to consider the meaning of the word "for", and observed at [122]:

> "Against that background the skilled person would understand the word 'for' in the claim to be providing a link between the act of manufacture using pregabalin and the ultimate intentional use of the drug by the end user to treat pain. The critical issue for me to decide is what is sufficient to constitute that link. An extreme view might be that if the drug is in fact used for the patented indication then it has been made 'for' that indication, whatever the manufacturer's intention might be. [Counsel for Pfizer] did not contend for that construction. I think he was right not to do so. It would mean that a manufacturer could not tell whether he had made use of the subject matter until after, and perhaps a long time after, he had disposed of the product. The realistic candidates are therefore (a) foreseeability that the drug will intentionally be used for the patented indication and (b) a subjective intention to that effect."

610. He rejected Actavis' argument that intention was required for reasons he expressed as follows:

> "123. [Counsel for Actavis] is right that the skilled person would understand the purpose of the Swiss form of claim to be that of avoiding the twin perils of lack of novelty and lack of patentable subject matter. However, as this court made clear in *Actavis v Merck*, the objection of lack of patentable subject matter is overcome by the fact that the claim is a manufacturing process claim. The skilled person would thus appreciate that there is no reason to imply a narrow or strict mental element in order ensure that this peril is avoided.
>
> 124. If [counsel for Actavis] were correct that a subjective mental element on the part of the manufacturer were necessary in order to provide the claim with novelty, there would be powerful reasons for adopting it. However, I do not see how that can in fact be so. If a product is 'for' a particular therapeutic indication if it is reasonably foreseeable that it will be used intentionally for the treatment of pain, then it will not be rendered lacking in novelty by showing that products in the prior art had been manufactured in circumstances when it was not possible to foresee such a result.

> 125. Mr Speck's point is a slightly different one, namely that no-one should be prevented by the grant of a patent from doing that which they did, or could have done, before. He called this the 'golden thread' of English patent law. That principle is not, however, an entirely reliable one. It was relied on in *Merrell Dow* … to suggest that the patent was invalid because it would have the effect of restraining the continuance of the prior use. The principle was ineffective there because the old use itself was 'uninformative'. At pages 86-87 Lord Hoffmann recognised that a gap had opened up under the 1977 Act between anticipation and infringement. The present case is another situation in which one cannot rely on the principle, because the subject matter of the invention is concerned with the purpose of acts which are in themselves no different from those which were done before. In any case it is not correct that the patent can prevent that which was done before. It was not possible before the patent was granted to foresee that the product would intentionally be used for treating pain."

611. Having noted at [126] that the test he had proposed had "structural similarities" to that under section 60(2), and expressed the view that a requirement of intention would "rob Swiss claims of much of their enforceability", he went on:

> "127. I can therefore see no reason why the skilled person would conclude that the word 'for' implied subjective intent. He would understand that the manufacturer who knows (and for this purpose constructive knowledge is enough) or could reasonably foresee that some of his drug will intentionally be used for pain is making use of the patentee's inventive contribution, in the same way as a manufacturer who actively desires that result. In my judgment, therefore, the skilled person would understand that the patentee was using the word 'for' in the claim to require that the manufacturer knows (in the above sense) or can reasonably foresee the ultimate intentional use for pain, not that he have that specific intention or desire himself.
>
> 128. In reaching his conclusion that it was the manufacturer's intention that was determinative, the judge relied on what Jacob LJ said in *Actavis v Merck* at [75], namely that claims in Swiss form were aimed at the manufacturer and did not touch the doctor. I think the judge may have read too much in to this passage. Jacob LJ was there considering whether the claim was a disguised claim to a method of treatment. The inclusion of a manufacturing step ensures that it is not. Jacob LJ was not addressing the nature of the mental element in the claim. It is, I think, important to bear in mind that there are two mental elements involved: the question is what the manufacturer knows or foresees about the intentional use of the drug by the end user which counts."

612. Floyd LJ then turned to the question of the rights conferred on the owner of the patent by national law. Having noted that liability under section 60(1)(b) was strict, he continued at [129]:

> "How does one tell whether a manufacturer is using the manufacturing process of the claim, and therefore rendering himself liable for patent infringement? The answer must be when he manufactures pregabalin when he knows or foresees that users will intentionally administer it for pain."

613. Finally, he considered two "hard cases" which this interpretation gave rise to. The first concerned a manufacturer who had been supplying the medicine in question from before the priority date and whose sales subsequently increased without the manufacturer having done anything to bring that about. Floyd LJ suggested at [130]-[131] that the answer to the "potential unfairness" of the manufacturer being made an infringer was to restrict the scope of the injunction so that it did not prevent sale of the product itself, or even to refuse an injunction altogether, although he acknowledged that the extent of the financial remedy was still "a justifiable concern".

614. The second case he addressed at [132]:

> "Another hard case is that in which a defendant has taken all the steps open to him to avoid his medicine being prescribed for the new use, yet those steps are, due to the structure of the marketplace, insufficient to stop it happening. Actavis' test would provide a defence in those circumstances, because the defendant could credibly say that he did not target those sales which he was striving manfully to prevent. The hard case arises because of the peculiarities of the UK's market place for drugs. Normally a vendor of a product can control by contract the uses to which his product is put and require any intermediary to include similar terms. I do not think we should allow the regulatory environment to dictate the scope of the claim in this way."

615. Accordingly, Floyd LJ concluded at [133] that, applying the law as he had stated it, "it is plain that [Pfizer has] an arguable case of infringement."

Is the Court of Appeal's judgment binding?

616. Counsel for Warner-Lambert submitted that the Court of Appeal's judgment with regard to the mental element in Swiss form claims was part of the *ratio decidendi* of the decision, and therefore binding on this Court. In support of this submission, she relied upon the following passage in Floyd LJ's judgment:

> "110. Both parties are agreed that the issues of law which arise on both types of infringement are ones which are capable of being decided on the materials before us. The Secretary of State for Health … indicated to us … that he would prefer us not to decide those issues, but to leave them over to trial where the

> Secretary of State intended to make a formal application to intervene.
>
> 111. I do not consider that the course advocated by the Secretary of State for Health is a sensible one for us to follow for a number of reasons. Given the parties' agreement that the issue is capable of resolution now, it is plainly desirable that we should decide it so the parties know where they stand. …"

617. Counsel for Actavis and counsel for the Secretary of State both submitted that this part of the Court of Appeal's judgment was *obiter*, and therefore was not binding.

618. In my judgment counsel for Actavis and counsel for the Secretary of State are plainly correct. The Court of Appeal's decision with respect to the appeal against *Warner-Lambert I* was to dismiss Pfizer's appeal against the refusal of an interim injunction. It reached that decision on the ground that it had not been shown that I had made any error in my assessment of the balance of the risk of injustice (see Floyd LJ at [143]-[152] and [156]). Accordingly, the fact that the Court of Appeal took a different view from me as to whether Pfizer had established a serious issue to be tried had no impact on its actual decision.

619. Nevertheless, it is equally plain that, as a considered judgment of a unanimous Court of Appeal reached after full argument on the point, the Court of Appeal's judgment is highly persuasive. Accordingly, I should follow it unless I am entirely convinced that it is wrong.

Is the Court of Appeal's judgment wrong?

620. Counsel for Actavis and counsel for the Secretary of State both submitted that the Court of Appeal's judgment was wrong. Counsel for Warner-Lambert supported it (at least if interpreted and applied in the manner for which she contended).

621. An important point to note before proceeding further is that the construction of the word "for" which Floyd LJ adopted is not one which was contended for by either party in the Court of Appeal. Indeed, as I understand it, it is not one which was canvassed in argument. Furthermore, and perhaps as a consequence of this, the parties disagree as to how this construction is to be interpreted and applied. Although the correctness of Floyd LJ's reasoning may depend on how it is understood, it is convenient to address the two questions separately.

622. Neither Actavis nor the Secretary of State challenge Floyd LJ's preliminary observations at [113]-[117]. Nor do they challenge much of his reasoning at [118]-[121], and in particular his statement that the skilled person would understand that the claim owes its novelty to the new therapeutic use of the medicament or pharmaceutical composition, that is to say, the intention to achieve the new therapeutic effect. Indeed, both Actavis and the Secretary of State say that Floyd LJ was correct to conclude that the claim must include a requirement of intention. Where they differ from him is as to whose intention is material. They contend that it is the manufacturer who must have the intention, rather than someone downstream from the manufacturer.

623. Counsel for the Secretary of State submitted that Floyd LJ started to fall into error when he stated at [119] that "it was necessary for the claim to include a manufacturing step to ensure that the claim does not touch the doctor" and when he stated at [128] that "[t]he inclusion of a manufacturing step ensures that [the claim] is not" "a disguised claim to a method of treatment". He submitted that the correct analysis, as demonstrated by *G2/08* at [5.6], was that it is the exclusion of any step pertaining to treatment which achieves this. I agree with this, but in my view that in itself does not undermine the rest of Floyd LJ's analysis.

624. Counsel for the Secretary of State proceeded to submit that the flaw in Floyd LJ's interpretation of the word "for" was that it made infringement depend on the mental state of the prescriber, which was contrary both to the policy underlying Article 53(c) EPC and the interpretation of that provision adopted by the Enlarged Board of Appeal in *G2/08*.

625. In addition, counsel for the Secretary of State and counsel for Actavis both submitted that Floyd LJ's construction of the word "for" did not accord with its context or purpose. The claim is to a method of manufacture of a pharmaceutical composition which derives its novelty from the mental state of the manufacturer, namely that the manufacturer prepares the pharmaceutical composition "for" treating pain. Counsel argued that this clearly directs attention to the manufacturer's purpose, i.e. intention, rather than mere foreseeability as to the prescriber's intention. As counsel for Actavis put it, on Floyd LJ's construction, there is no technical nexus between the manufacturer's acts and the intention to achieve the new therapeutic effect which gives the claim novelty. Without such a nexus, the manufacturer may infringe as a result of the actions of third parties outside the manufacturer's control.

626. These are powerful arguments, but I am not convinced that they demonstrate that Floyd LJ's interpretation is wrong. It is at least arguable that that interpretation does not infringe the policy underlying Article 53(c) or the interpretation of that provision adopted in *G2/08* because the claimed process is complete when the pharmaceutical composition has been prepared. Thus the claim does not interfere with the prescriber's freedom, any more than a claim for infringement of a conventional product claim pursuant to section 60(2) would do in circumstances where the claimed product came into existence as a result of the prescriber's actions: compare *Actavis UK Ltd v Eli Lilly & Co* [2015] EWCA Civ 555 at [81]-[92] (Floyd LJ). Furthermore, as discussed below, it is not necessarily the case that it is the prescriber's intention which is decisive. Turning to the novelty-conferring effect of the manufacturer's mental state, this is addressed by Floyd LJ at [124]. As for the fact that the manufacturer may infringe as a consequence of the acts of third parties outside his control, Floyd LJ acknowledged this point at [132], but nevertheless was not persuaded by it.

627. This leaves what seems to me to be perhaps the most persuasive argument advanced by counsel for Actavis and counsel for the Secretary of State, which is that Floyd LJ's interpretation does not achieve its intended effect. As they pointed out, Floyd LJ expressly accepted at [118] that "[m]aking pregablin for patients to whom it is to be administered for the non-patented indications is not within the technical subject matter of the claim". Accordingly, this cannot be an infringing act. Counsel submitted that Floyd LJ's construction apparently had the consequence that, if it was foreseeable to an unlicensed manufacturer of pregabalin that "*some* of his drug" (as Floyd LJ put it at [127], emphasis added) would be intentionally administered for the treatment of

pain, then all of that manufacturer's acts of manufacture of pregabalin would be infringing acts even though it was foreseeable that the remainder of its pregabalin would be administered for the treatment of non-patented indications. (In fact, in this case, manufacture of Lecaent could not have infringed the Patent because it was carried out in Bulgaria; but this does not affect the principle involved, nor does it prevent the sale of Lecaent in the UK from being an infringement.) Furthermore, this would be so even if it was foreseeable that the majority (possibly even the vast majority, depending on what was meant by "some") of the pregabalin made by that manufacturer would be administered for the treatment of the non-patented indications and even if the majority (possibly the vast majority) was in fact administered for the treatment of those indications. Still further, all of the pregabalin would be infringing product, and thus anyone who subsequently dealt in it would also infringe on a strict liability basis. Counsel for Actavis submitted that this outcome would be worse for the manufacturer than the "extreme view" which Floyd LJ rejected at [122], because at least the "extreme view" meant that only the proportion of pregabalin which was in fact administered for the treatment of pain would be infringing.

628. I think it is reasonably clear from Floyd LJ's judgment that he did not intend his interpretation to have this consequence. The only indication I can see as to how he thought it was to be avoided, however, comes when he discusses the question of remedies. As noted above, he suggested that any "potential unfairness" of his interpretation in the first of the two "hard cases" he considered could be mitigated by restricting the scope of the injunction so that it did not prevent the sale of the product. This suggests that he considered that the injunction might somehow be tailored so as only to prohibit manufacture of pregabalin which it was foreseeable would be intentionally administered to treat pain, and not pregabalin which it was foreseeable would be administered for non-patented indications, although his statement that it might be unjust to grant an injunction at all indicates that he appreciated that this could be very difficult. Similarly, it appears that he envisaged that the financial remedy would only apply to pregabalin which it was foreseeable would be intentionally administered to treat pain, presumably on a statistical basis.

629. The problem with this is that, on any view, a manufacturer in the position of Actavis cannot foresee which pack of pregabalin will be administered for which indication. (Indeed, as discussed below, it is not merely the manufacturer who cannot foresee this.) Suppose that a manufacturer could foresee that 20% of the pregabalin it manufactured would be intentionally administered to treat pain, and 80% would be administered to treat non-patented indications. The normal rule in patent cases is that each act of manufacture is a fresh potential act of infringement. In the case of any one pack of pregabalin, the statistical chance of it being intentionally administered for treatment of pain would be 20%. Why then should the manufacture of that pack amount to an infringement (particularly bearing in mind that, if one tested the matter on the balance of probabilities, this would fall well short)? And why should all of that manufacturer's pregabalin be treated as infringing product so that any dealer in any of it infringes? The only way to avoid these difficulties would be to apply a statistical approach, i.e. treating 20% of the manufacturer's production as being infringing product, but that approach runs into the difficulty that one cannot divide the packs of pregabalin emanating from that manufacturer into packs which are infringing and packs which are not infringing. The only fair answer would appear to be to say that

20% of the quantity dealt in by every party in the distribution chain should be deemed to be infringing, but on what principled basis can one arrive at that answer?

630. It appears from Floyd LJ's judgment that he may have considered that there was no greater difficulty in such a case than may arise with a claim under section 60(2) in cases like *Actavis v Lilly*. Counsel for Actavis submitted, however, that this was incorrect. As counsel pointed out, under section 60(2), it is only the act of supplying (or offering to supply) the "means, relating to an essential element of an invention, for putting the invention into effect" that is an infringement, not the act of manufacturing the means. Furthermore, the "means" do not become infringing articles any dealing in which will be a strict liability infringement. In those circumstances it is relatively straightforward to confine the effects of a finding of infringement to the proportion of the "means essential" which is foreseeably intended to put the invention into effect. The position here is different, because foreseeability on the part of the manufacturer does not provide a sufficient basis to distinguish between infringing and non-infringing acts of manufacture, particularly when it comes to parties downstream from the manufacturer.

631. I would add to this the observation made by Lord Sumption in *Fish & Fish Ltd v Sea Shepherd UK* [2015] UKSC 10, [2-15] AC 1229 at [44]:

> "Intention in the law of tort is commonly relevant as a control mechanism limiting the ambit of a person's obligation to safeguard the rights of others, where this would constrict his freedom to engage in activities which are otherwise lawful. The economic torts are a classic illustration of this."

This observation has resonance here for two reasons. The first is that, in their leading judgment on the interpretation of section 60(2) of the 1977 Act in *Grimme Machinenfabrik GmbH & Co KG v Scott* [2010] EWCA Civ 1110, [2011] FSR 7 at [106], Jacob and Etherton LJ were guided by the authorities on the interpretation of knowledge and intention in the economic torts. As he made clear at [126], Floyd LJ's interpretation was inspired by section 60(2), and therefore guidance from that field is equally relevant here. The second is that in the present case the manufacturer is lawfully entitled to manufacture pregabalin for the non-patented indications. As discussed in more detail below, the manufacturer is under a duty to respect Pfizer's rights (assuming that the Patent is valid); but it may be thought that this duty is appropriately secured and limited by a requirement of intention on the part of the manufacturer.

632. For the reasons I have indicated above, I have considerable doubts as to the correctness of Floyd LJ's interpretation. Nevertheless, I cannot say that I am entirely convinced that it is wrong. Accordingly, I propose to follow it.

How should the Court of Appeal's judgment be applied?

633. Even on the assumption that the Court of Appeal's judgment is to be followed by this Court, the parties are divided as to how it should be applied. It may be noted in this regard that, although Floyd LJ concluded that Pfizer "plainly has an arguable case" on infringement, understandably he did not attempt to apply his construction of the word

"for" to the specific facts of the case. For reasons that will I explain, applying it is not as straightforward as he appears to have envisaged.

634. There are two main aspects of the dispute. First, counsel for Pfizer submitted that there was no real difference between Floyd LJ's interpretation of the word "for" and a pure test of foreseeability on the part of the manufacturer that its pregabalin would in fact be used for the treatment of pain. I do not accept this submission. Floyd LJ made it clear at [121] that intentional administration was at the heart of the invention, at [122] that the word "for" provided the link between the manufacture of pregabalin and the intentional use of the drug, at [127] that the word "for" required knowledge or foresight of the ultimate intentional use, at [128] that there were two mental states involved and at [129] that a manufacturer infringes when he knows or foresees that users will intentionally administer pregabalin for the treatment of pain. Thus the requirement of intention is central to his interpretation. It is plainly not a pure test of foreseeability. Furthermore, I agree with counsel for Actavis that a pure test of foreseeability would not be enough to confer novelty on the claim. It is the element of intention which ensures novelty.

635. Secondly, if intention is required, counsel for Pfizer advanced three alternative cases as to how that requirement could be fulfilled. The first alternative is predicated on the assumption that the relevant intention is that of the prescribing doctor. On that basis, counsel for Pfizer submitted that it was sufficient if the doctor intends pregabalin from any source to be administered to the patient for the treatment of pain. The second alternative is predicated on the assumption that the relevant intention is that of the dispensing pharmacist, if necessary in combination with the doctor. On that assumption, counsel for Pfizer submitted it was sufficient that the pharmacist knows that the doctor has prescribed pregabalin for pain and dispenses the generic manufacturer's product. The third alternative is predicated on the assumption that the relevant intention was that of the patient, if necessary in combination with the doctor and pharmacist. On that assumption, counsel for Pfizer submitted it was sufficient that the patient knows that the doctor has prescribed pregabalin for pain and that the pharmacist has dispensed the generic manufacturer's product.

636. Counsel for Actavis submitted that the relevant intention was that of the prescribing doctor. I agree that the intention of the doctor is highly relevant, if not exclusively so. Floyd LJ expressly referred to "the doctor" at [119], and at [121] he made the point that the novelty of the claim derives from "the intention of producing the new therapeutic effect". It is the prescribing doctor who intends to produce the new therapeutic effect (here treating pain) because it is the doctor who has the requisite medical knowledge (derived from the SmPC for Lyrica, and hence from the clinical trials carried out by Pfizer to substantiate the claim made in the Patent of efficacy for neuropathic pain, or from the doctor's appreciation that pregabalin may also be effective for treating other kinds of pain if prescribed off-label, as is also claimed in the Patent).

637. Counsel for Actavis also submitted that it was not sufficient that the prescribing doctor intended pregabalin from any source to be administered for the treatment of pain. I agree with this. Floyd LJ expressly referred at [127] to the manufacturer foreseeing that "some of *his* drug will intentionally be used for pain [emphasis added]". Furthermore, it would make no sense for it to be sufficient that the doctor intended pregabalin from any source to be administered for pain. Infringement must

depend on what the manufacturer can foresee happening with the pregabalin it manufactures, not pregabalin made by others. Moreover, statistically, it would be probable that pregabalin from any source would be made by Pfizer and hence non-infringing on any view.

638. What about the pharmacist? Floyd LJ does not expressly refer to the pharmacist in his analysis, but as counsel for Pfizer pointed out, his language in [122]-[129] is quite general, referring, for example, to "intentional use for pain". After considerable hesitation, I have concluded that, on Floyd LJ's reasoning, the intention of the pharmacist is also relevant. In general, of course, the pharmacist will simply intend to dispense the drug which the doctor has prescribed for the purpose of treating whatever indication the doctor has prescribed that drug for. Moreover, in general, the pharmacist will not know what that indication is. In those circumstances the pharmacist's intention adds nothing to that of the doctor. Even if the doctor prescribes generic pregabalin for treating pain and the pharmacist dispenses the generic manufacturer's product, neither the doctor nor the pharmacist nor the two in combination will have *intended* that *that* product be administered for the treatment of pain. But what if the pharmacist knows that the doctor has prescribed generic pregabalin for treating pain and the pharmacist dispenses the generic manufacturer's product? In those circumstances it seems to me that it can be said that the result is intentional administration of the generic manufacturer's product to treat pain.

639. As for the patient, notwithstanding Floyd LJ's reference in [128] to "the end user", I cannot see that the patient's intention is relevant. The patient is the one who is being treated. In general the patient intends to take whatever drug the doctor has prescribed for whatever condition the doctor has prescribed it for. Usually the patient will not have any medical knowledge about the efficacy of that drug for that condition. Moreover, the patient will rely on the pharmacist to dispense the correct drug, and in general the patient will not have any choice as to the source of that drug. Indeed, many patients will be oblivious to the source of the drug.

The position of pharmacists with respect to infringement

640. This leads to consideration of the position of pharmacists with respect to infringement. In the course of her oral opening submissions, counsel for Pfizer conceded that pharmacists who dispensed Lecaent knowing or believing that the patient was being treated for a non-patented indication did not infringe the Patent. In her closing submissions, however, counsel for Pfizer withdrew this concession. The reason for this *volte-face* is not hard to understand. As I have pointed out above, infringement under section 60(1)(c) is a tort of strict liability. It follows that, if the manufacturer had the relevant state of mind at the time of manufacture of some pregabalin, then anyone who deals in any of that manufacturer's pregabalin - including pharmacists - will infringe regardless of their state of mind (and regardless of what use is actually made of the pregabalin). This is what Pfizer and its solicitors meant when they referred in many of their communications with stakeholders to pharmacists infringing the Patent "unwittingly". Counsel for Pfizer initially conceded that pharmacists did not infringe if they dispensed Lecaent for non-patented indications because she appreciated how unattractive this consequence of Pfizer's case appeared. Counsel for Pfizer withdrew the concession because, upon further reflection, she appreciated that it was an inevitable and necessary consequence of Pfizer's case.

What is the relevant date?

641. A question which, as I understand it, was not the subject of argument before the Court of Appeal, and, no doubt for that reason, was not considered by Floyd LJ in his judgment, is the relevant date for the assessment of infringement. This is important not just for the obvious reasons, but also because it sheds light on the nature of the cause of action and the test to be applied. To my surprise, not only was this question not addressed by counsel for Pfizer in her skeleton argument, but also she did not have a ready answer to the question when I raised it during her opening submissions. Indeed, it was not until her closing oral submissions that she was able fully to articulate Pfizer's case. By the end of the parties' closing submissions, however, a considerable measure of common ground had emerged.

642. It is convenient to begin with two points, both of which I understand to be common ground. The first is that, because Swiss form claims are process claims directed at the manufacturer of the medicament or pharmaceutical composition, the mental element must be satisfied as at the date of manufacture: see Floyd LJ at [129]. As noted above, each act of manufacture is a fresh potential act of infringement. Thus acts of manufacture on different dates may differ with respect to the question of infringement if the manufacturer's mental state differs. The second is that the date on which the cause of action for infringement under section 60(1)(c) accrues is the date of sale or other dealing. In principle, each act of dealing is a fresh potential act of infringement committed on that date. Nevertheless, the infringement analysis will not differ depending on the date of sale if all of the product was made on the same date or on dates as at which the manufacturer's mental state was the same.

643. Pfizer's primary case is that infringement should be assessed as at the date of the commencement of Pfizer's claim for infringement, namely, 8 December 2014. Pfizer's secondary case is that infringement should be assessed as at the date when Actavis launched Lecaent, namely 17 February 2015. Pfizer's tertiary case is that infringement should be assessed as at the date when the evidence at trial was completed, namely 15 July 2015. As counsel for Pfizer accepted, however, it is necessary for me to consider the position as at all three dates. Counsel for Actavis did not dissent from this.

644. On the face of it, as at 8 December 2014, Pfizer's claim for infringement was brought *quia timet*. As it turns out, however, by that date Actavis had manufactured and packaged a quantity of Lecaent and imported it into the UK where it was being held in quarantine. The product had been manufactured between June and October 2014 and it was packaged between mid-October and mid-December 2014 (see paragraphs 430 and 437 above).

645. By 17 February 2015, both the circumstances in the UK and Actavis' knowledge of those circumstances had changed considerably since 8 December 2014. For the reasons identified in paragraph 642 above, this is immaterial with regard to the quantities of Lecaent which had been manufactured by 8 December 2014. It is relevant, however, to quantities of Lecaent manufactured after that date.

646. As noted above, I shall assume that Actavis placed a second order for Lecaent in mid-January 2015. I will also assume that this batch of pregabalin was manufactured between mid-February and mid-March 2015.

647. By 15 July 2015, the circumstances in the UK and Actavis' knowledge of those circumstances had changed still further. It is not clear from the present state of the evidence whether Actavis had placed a third order for Lecaent by then. I will assume that Actavis had done so. I will also assume that this batch was manufactured between mid-July and mid-August 2015.

648. In case it is not obvious, the reason why I am making these assumptions in the absence of concrete evidence as to the relevant manufacturing dates is in order to enable me to explore the potential consequences of Actavis' differing states of knowledge as at the three dates postulated by Pfizer.

What relief does Pfizer seek?

649. Again, this question is important not just for the obvious reasons, but also because it sheds light on the nature of the cause of action and the test to be applied. As counsel for Actavis submitted, Pfizer's case in this respect has been a constantly moving target since from before the commencement of these proceedings and it remained so until closing submissions. Again, this was not a matter addressed by counsel in her skeleton argument. Nor did she fully articulate her client's position in her oral opening submissions. By the end of her closing submissions, Pfizer's position was as follows.

650. Pfizer's primary case is that it seeks all the relief ordinarily granted when the court finds that the defendant has infringed a patent. In particular, Pfizer seeks an injunction in the conventional general form i.e. an order that Actavis must not infringe the Patent.

651. In the alternative to an injunction in general form, Pfizer's secondary case is that it seeks an order requiring Actavis to take all steps within its power to prevent Lecaent from being dispensed for the treatment of pain. Counsel for Pfizer accepted, however, that, once Actavis had taken all steps within its power, the proper remedy for any further infringement would be financial rather than injunctive.

652. In the further alternative, Pfizer's tertiary case is it seeks an order requiring Actavis to take the seven steps identified in Pfizer's closing submissions.

653. It is not necessary at this stage for me to consider any of these alternatives in detail. It will be appreciated, however, that the first alternative would be likely to leave Actavis in a state of considerable uncertainty as to what it had to do to comply with the injunction, while the second and third alternatives would require Actavis to take steps to change, or at least try to change, the behaviour of independent third parties (such as NHS England, CCGs, GPs and pharmacists) on pain of being in contempt of court if it failed to do so, but carried on manufacturing pregabalin and marketing it in the UK for the non-patented indications. This naturally prompts questions as to what legal duty Actavis are under which could lead to that result and as to whether any of the other parties are under any relevant legal duties.

What are the relevant legal duties?

654. An important theme of counsel for Pfizer's submissions was that Actavis were under a statutory duty not to infringe the Patent. Counsel for Actavis did not dispute that this

was so, at least in the sense that Actavis were under a duty not to commit acts which constituted infringement of the Patent (assuming for this purpose that it is valid). Counsel for Pfizer further submitted that it followed that it was incumbent on Actavis to take all necessary steps to avoid infringement, and that, if this required Actavis to change the behaviour of independent third parties, then that was what Actavis had to do if it wished to avoid infringement.

655. In support of this submission counsel for Pfizer relied upon what Jacob and Etherton LJJ said in *Grimme v Scott* at [134] about the form of the injunction which should be granted where the defendant has been held liable for infringement under section 60(2):

> "It might be suggested … that the court should modify the injunction so as to try to spell out what it is that the defendant can do. We would not have thought that normally appropriate: it will be up to the defendant to work out how to ensure that there is no ultimate infringement."

656. I accept that, in general, a defendant is under a statutory duty not to infringe a patent. I also accept that, in general, it is up to the defendant to decide what to do to avoid infringement and to take the necessary steps to achieve that. I do not accept that that is the end of the matter, however. For the reasons I discussed in *HTC Corp v Nokia Corp* [2013] EWHC 3778 (Pat), [2014] Bus LR 217 at [3]-[32], I consider that the court is required to ensure that an injunction is proportionate and does not create barriers to legitimate trade. I understood counsel for Pfizer to accept this. In an appropriate case that may require the form of the injunction to be more specific than the conventional general form: see e.g. *Oracle America Inc v M-Tech Data Ltd* [2012] UKSC 27, [2012] 1 WLR 2026 at [10] (Lord Sumption).

657. In the present circumstances it is arguable that the grant of an injunction in general form would be disproportionate and/or create barriers to legitimate trade since it would be likely to force Actavis' withdrawal from the lawful market for the non-patented indications. The same applies to the specific forms of injunction sought by Pfizer in the alternative. As Floyd LJ suggested, it might therefore not be appropriate to grant an injunction at all.

658. I understood counsel for Pfizer also to accept that any financial remedy must equally be proportionate and not create barriers to legitimate trade. But as discussed above, it is not easy to see how to arrive at a financial remedy which is both principled and proportionate and avoids barriers to legitimate trade applying Floyd LJ's test of foreseeability of intentional administration. Taking the example postulated in paragraph 629 above, one might say that dealers in the generic manufacturer's product should only pay damages or account for profits in respect of 20% of the quantities dealt in. That would be a proportionate result, but it would not be a principled one. Rather, it would amount to imposing a restriction on the remedy for infringement in order to achieve a just result when application of the underlying liability principle did not achieve this. It might be said, however, that it is not unknown for courts to prefer practical justice to principle.

659. For his part, counsel for Actavis submitted that Pfizer had deliberately delayed in taking steps to prevent generic pregabalin from being prescribed or dispensed for the

treatment of pain, but he did not contend that (competition law apart) Pfizer was under a legal duty to take steps. Rather, he submitted that Pfizer's failure to do so was relevant to the proportionality of any relief. In this regard, he went so far as to submit that, even if the court concluded that Actavis had infringed the Patent, no relief should be granted to Pfizer. I do not accept this submission. To grant no relief at all for infringement of a patent would itself be disproportionate. On the other hand, I would accept that Pfizer's conduct is a relevant factor to take into account in assessing the proportionality of any relief which may be granted.

660. As for the position of NHS England, counsel for Pfizer maintained that NHS England had come under a duty to issue guidance with regard to the prescribing of pregabalin for the reasons set out in *Warner-Lambert IV*. Counsel for Actavis supported this proposition. Counsel for the Secretary of State took issue with it, but did not advance any arguments to the contrary. NHS England was, of course, unrepresented. That being so, and given that the question was not fully argued and that it is not of decisive relevance to Actavis' liability, I shall not consider this question further. I would nevertheless comment that, if it is correct that NHS England came under such a duty, but NHS England failed to discharge that duty, then that might be something that parties in the position of Actavis could rely upon. As it is, however, in the present case NHS England did issue guidance almost contemporaneously with generic entry into market, albeit as a result of Pfizer's application.

Pfizer's claim under section 60(1)(c): assessment

661. If, as I held in *Warner-Lambert I*, the word "for" in a Swiss form claim should be interpreted as requiring an intention on the part of the manufacturer that the medicament or pharmaceutical composition should be used for the new therapeutic use, then it is clear that Actavis have not infringed claims 1 or 3 of the Patent, since Actavis have never intended Lecaent to be used to treat pain (unless and until claims 1 and 3 of the Patent are held invalid).

662. Applying Floyd LJ's interpretation of the word "for" in the manner explained above, my conclusions are as follows.

As at 8 December 2014

663. As explained above, as at 8 December 2014, Actavis had manufactured a quantity of Lecaent between June and October 2014. Was it foreseeable to Actavis during that period that such Lecaent would be intentionally administered for the treatment of pain? (As noted in *Warner-Lambert II*, it is arguable that manufacturing for the purposes of a Swiss form claim includes packaging with appropriate instructions. At trial neither side pursued this point, however. In any event, it makes little difference given that this batch was packaged between mid-October and mid-December 2014.)

664. As I have explained above, Actavis' intentions crystallised during this period. At the beginning of this period, Actavis had not decided whether to market Lecaent under a full label conditional upon successful revocation of the Patent (or at least claims 1 and 3) or under a skinny label prior to determination of any claim for revocation. By the end of this period, Actavis had decided to market pregabalin under a skinny label. In assessing what was foreseeable to Actavis, it seems to me that I have to consider the

position on the basis of what was foreseeable if Actavis elected, as it did, to market pregabalin under a skinny label.

665. As discussed above, Actavis knew that a skinny label alone would not prevent Lecaent from being dispensed for the treatment of pain. Furthermore, Actavis accept that it was foreseeable that, unless further steps were taken, it was likely that some Lecaent would be dispensed for the treatment of pain as a result of pharmacists being presented with generic prescriptions for pregabalin which did not state the indication for which the drug had been prescribed.

666. Was it foreseeable that Lecaent would be intentionally administered for the treatment of pain? For the reasons explained above, I do not consider that there is intentional administration of Lecaent for the treatment of pain if Lecaent is dispensed in circumstances where the doctor has prescribed generic pregabalin for pain and the pharmacist does not know the indication for which it has been prescribed, but I consider that there is intentional administration of Lecaent for pain if the pharmacist dispenses Lecaent when he or she knows that pregabalin has been prescribed for pain. Thus the question to be resolved is whether it was foreseeable to Actavis that, in the 5% of cases where the prescription indicated that pregabalin had been prescribed for pain, the pharmacist would dispense Lecaent despite the fact that it was not licensed for pain?

667. In considering this question, I consider that it is proper to take into account Actavis' decision to notify superintendent pharmacists specifically that Lecaent was not licensed for the treatment of neuropathic pain. Although Actavis only took this decision towards the end of the period in question, they took the decision soon after electing to launch Lecaent with a skinny label. I consider it probable that, if Actavis had elected to launch Lecaent with a skinny label earlier, they would have made this decision earlier as well. I do not consider that it matters that the intended notification related to neuropathic pain and not all pain: Lyrica is not licensed for pain other than neuropathic pain, and Actavis had no reason to think that pharmacists who refrained from dispensing Lecaent to fulfil prescriptions known to be neuropathic pain would nevertheless dispense it to fulfil prescriptions known to be for other kinds of pain.

668. Furthermore, I do not consider that it can be held against Actavis that they declined to send this notification prior to receipt of the marketing authorisation. That would plainly have been a breach of the Directive. Nor, for the reasons explained in paragraphs 576-584 above, do I consider that Actavis could have sent the alternative form of notification suggested by Pfizer. In any event, Actavis intended to (and did) send the notification immediately upon receipt of the marketing authorisation, and hence at about the same time as the product was launched.

669. It is true that a notice sent to superintendent pharmacists would not necessarily be seen by every pharmacist who was called upon to dispense Lecaent, but sending a notice to every practising pharmacist would have been logistically more difficult. Furthermore, I consider that it was reasonable for Actavis to assume that the message would be disseminated by superintendent pharmacists to those under their supervision (as indeed was specifically requested by the form of notice which was under discussion by the time of the hearing of Pfizer's application for interim relief and by the form of notice which was actually sent by Actavis).

670. As discussed above, Actavis do not say that they foresaw Pfizer taking any of the specific steps which Pfizer took to try to prevent generic pregabalin being prescribed or dispensed for pain. Counsel for Actavis nevertheless submitted that it was objectively foreseeable that NHS England would issue the guidance which it ultimately did issue. Given the way in which that came about, I do not accept this. On the other hand, one thing which Actavis did know, because it is common practice amongst originator companies faced with LOE, is that Pfizer would enter into Brand Equalisation deals with its larger pharmacy customers. Indeed, as noted in paragraph 436 above, in December 2014 Actavis learnt that Pfizer was offering Brand Equalisation deals based on pain being 59% of the pregabalin market. Furthermore, Actavis knew that such deals would be likely to preserve a substantial market share for Lyrica.

671. In all the circumstances, I conclude that it was not foreseeable to Actavis that the Lecaent manufactured between June and October 2014 would be intentionally administered for the treatment of pain save in a small number of exceptional cases which I consider that it is proper to regard as *de minimis*.

As at 17 February 2015

672. By 17 February 2015, the circumstances had changed in a number of respects. First, Actavis had agreed to, and did, notify CCGs (and hence their prescribers) that Lecaent was not licensed for neuropathic pain. Secondly, the form of the notifications to superintendent pharmacists and CCGs had been settled, and these included the information that Pfizer considered that pharmacists who chose to dispense Lecaent for pain risked infringing the Patent. Thirdly, Actavis had became aware of many (but not all) of the steps taken by Pfizer to prevent generic pregabalin being prescribed or dispensed for the treatment of pain. Fourthly, Actavis had become aware of Pfizer's application against NHS England. Moreover, on 18 February 2015 Actavis became aware that this application was likely not to be opposed. Fifthly, this litigation had been extensively covered in the medical and pharmaceutical press.

673. Even if it had been foreseeable to Actavis at the time of manufacturing the first batch of Lecaent in June-October 2014 that a more than *de minimis* proportion of it would be intentionally administered for the treatment of pain, I do not consider that this remained foreseeable as at 17 February 2015, and hence as at the time when I have assumed the second batch was manufactured in mid-February to mid-March 2015.

As at 15 July 2015

674. By 15 July 2015, the circumstances had changed still further. First, NHS England had issued guidance that Lyrica should be prescribed for pain, and NHS Wales and NHS Northern Ireland had followed suit. Secondly, the software providers had modified their systems. Thirdly, Actavis was aware that, as a result of the NHS guidance, the proportion of pregabalin prescribed by reference to Lyrica had risen to 30% by May 2015 and was likely to continue to rise thereafter. Moreover, Actavis knew that there was no possibility of Lecaent being dispensed against prescriptions for Lyrica. Fourthly, Actavis had become aware of all the steps taken by Pfizer to try to prevent generic pregabalin being prescribed or dispensed for pain. Fifthly, Actavis were aware that Pfizer had succeeded in retaining about 80% of the market for pregabalin down to June 2015. Sixthly, Actavis were aware that there was no evidence that Lecaent had in

fact been dispensed to patients who were being treated for pain on a substantial scale (let alone intentionally).

675. A factor which Pfizer relies on as operating in the opposite direction is that by 15 July 2015 Sandoz had launched its generic pregabalin product and it was known that Teva was likely to do so shortly. The relevance of this is that such launches were likely to depress the generic price for pregabalin, and hence the incentive for pharmacists to dispense generic pregabalin rather than Lyrica where possible. On the other hand, to the extent that Actavis' competitors took sales away from Actavis, this would make it less likely that Lecaent would be dispensed. Moreover, the full effect of generic competition on price would only be felt if and when pregabalin was moved from Category C to Category A or M of the Drug Tariff.

676. Even if it had been foreseeable to Actavis at the time of manufacturing the second batch of Lecaent in (I assume) February-March 2015 that a more than *de minimis* proportion of it would be intentionally administered for the treatment of pain, I do not consider that this remained foreseeable as at 15 July 2015, and hence as at the time when I have assumed the third batch was manufactured in mid-July to mid-August 2015.

Conclusion

677. For the reasons given above, I conclude that Actavis have not infringed claims 1 and 3 of the Patent pursuant to section 60(1)(c).

Pfizer's claim under section 60(2)

678. Although she dealt with it in some detail in her opening skeleton argument, and touched on it in her oral opening submissions, counsel for Pfizer did not mention Pfizer's claim under section 60(2) at all in her written or oral closing submissions. In those circumstances, I shall deal with it relatively briefly.

679. In *Warner-Lambert CA* Floyd LJ gave three reasons for allowing Pfizer's appeal against my decision to strike out the section 60(2) claim in *Warner-Lambert III*. The first, at [136], was that the courts of two EPC member states considering this question, namely the Court of Appeal of The Hague in *Novartis v Sun* and the Landgericht Hamburg in *Warner-Lambert v Aliud*, have held that indirect infringement can arise in these circumstances. I am puzzled by his reference to the EPC since, as discussed above, the law with regard to indirect infringement derives from the CPC, not the EPC. Leaving that aside, as discussed in *Warner-Lambert II* at [44]-[57] and *Warner-Lambert III* at [4], the reasoning of the Court of Appeal of The Hague in *Sun v Novartis* simply does not address the difficulties with Pfizer's case on indirect infringement. Much the same is true of the reasoning of the Landgericht Hamburg in *Warner-Lambert v Aliud* considered by Floyd LJ at [82]-[92]. Indeed, as Floyd LJ noted at [89], the Landgericht appears to have treated the Swiss form claims as being the same as EPC 2000 claims i.e. as product rather than process claims. But he himself followed the consistent jurisprudence of the courts of this country and of the EPO Boards of Appeal that they are process claims.

680. Floyd LJ's second reason, at [137], was that:

> "… if, as I have held, there is a case of threatened or actual infringement of the process claim under section 60(1)(b), then it follows that dealings downstream in the direct product of the process are also infringements under section 60(1)(c). Although this may not add anything to the direct infringement case, it is wrong to strike it out as a viable additional cause of action."

681. I have to say that I am baffled by this. Pfizer does not advance any claim against Actavis for infringement under section 60(1)(b), for the very good reason that Lecaent is manufactured by Balkanpharma in Bulgaria. As discussed above, Pfizer's claim for direct infringement against Actavis is made under section 60(1)(c). Furthermore, the mere fact that Pfizer has an arguable case under section 60(1)(c) does not necessarily mean that it has an arguable case under section 60(2).

682. Floyd LJ's third reason, at [138], was that:

> "… it is arguable … that when section 60(2) speaks of 'putting the invention into effect', it may be legitimate to look not just at whether any one person is carrying out the invention in a sense which would give rise to liability of that person for an act of infringement. It may be that the invention is put into effect if pregabalin is manufactured by one person and supplied to another who intentionally uses it for the treatment of pain."

683. I have to say that I do not understand this reasoning either. It seems to assume that the invention is the method of treatment. But section 125 of the 1977 Act provides that the invention is that specified in the claim unless the context otherwise requires. Furthermore, as counsel for Actavis pointed out, the Court of Appeal has previously held that, for the purposes of section 60(2), the invention is indeed what it is claimed: see *Menashe Business Mercantile Ltd v William Hill Organisation Ltd* [2002] EWCA Civ 1702, [2003] 1 WLR 1462 at [24] (Aldous LJ). Thus the invention is the process of manufacture claimed in claims 1 and 3 of the Patent, not the method of treatment. Yet further, for the reasons discussed above, the method of treatment is not a patentable invention anyway, which is precisely why the claims are in the form they are. Finally, this approach is inconsistent with Floyd LJ's interpretation of the mental element in the claims, which requires a mental element on the part of manufacturer, as it must do in order to confer novelty on the claims.

684. The fundamental difficulty with Pfizer's claim under section 60(2) remains, as it has always done, that claims 1 and 3 of the Patent are claims to processes of manufacture, but there is no act of manufacture by any party downstream from Actavis, nor even the prospect of such an act. This is so even if manufacturing (or "preparation", to use the word in the claims) for this purpose includes packaging with appropriate instructions. In particular, there is no act of manufacture by pharmacists, nor any prospect of such an act. It follows that, although there is no difficulty in concluding that Lecaent's active ingredient is "means, relating to an essential element of the invention, for putting the invention into effect", Lecaent is not suitable for putting, or intended to put, the invention into effect: either the invention has already been put into effect by the time that Lecaent leaves Actavis' hands or it is not put into effect at all. Accordingly, I conclude that Actavis have not infringed claims 1 and 3 of the Patent pursuant to section 60(2).

Counterclaim for declaratory relief

685. Independently of their counterclaim for threats, Actavis seek a declaration pursuant to the Court's inherent jurisdiction that neither Actavis nor wholesalers who deal in Lecaent have infringed the Patent. More significantly, Actavis also seek a declaration that none of the following parties have infringed the Patent: (i) doctors who prescribe generic pregabalin for the treatment of pain, (ii) pharmacists who dispense Lecaent and (iii) patients who take Lecaent. I consider that, due to the extensive publicity this litigation has attracted, it would serve a useful purpose for this Court to clarify the position of each of these groups by means of a formal declaration. Given that I have concluded that Actavis have not infringed the Patent, it follows that none of these groups have either. It is nevertheless worth commenting briefly on the position of doctors, pharmacists and patients.

Doctors

686. Although at one stage (see in particular the letter to the Department of Health dated 28 October 2014 quoted in paragraph 696 below) Pfizer asserted that doctors would infringe the Patent if they prescribed generic pregabalin for pain, counsel for Pfizer accepted in her closing submissions at trial that doctors did not infringe. In any event, it is very difficult to see how a doctor could be liable for infringement of the Patent merely by writing a generic prescription for pregabalin for pain, since for all the doctor would know the prescription could well be fulfilled by the pharmacist dispensing Lyrica.

Pharmacists

687. I have discussed the position of pharmacists above. As noted there, it is an inevitable consequence of Pfizer's case that, if Actavis have infringed the Patent, any pharmacist who dispenses Lecaent infringes the Patent even if the pharmacist knows or believes that pregabalin has been prescribed for a non-patented indication.

Patients

688. Counsel for Pfizer accepted in her opening submissions at trial that patients who took Lecaent did not infringe. It is difficult to see how it could be otherwise. To be fair, I do not think Pfizer has ever asserted to the contrary. But, as discussed above, it has relied on the intentions of patients as part of its case against Actavis.

Conclusion

689. I will make a declaration as sought by Actavis in respect of Actavis, wholesalers of Lecaent and each of three groups considered above.

Counterclaim for threats

690. Actavis allege that a large number of communications made by Pfizer to other parties in connection with this dispute amounted to threats. For the purposes of the trial, Actavis identified a sample of 10 communications upon which they relied.

The law

691. Section 70(1) of the 1977 Act provides as follows:

> "Where a person (whether or not the proprietor of, or entitled to any right in, a patent) by circulars, advertisements or otherwise threatens another person with proceedings for any infringement of a patent, a person aggrieved by the threats (whether or not he is person to whom the threats are made) may, subject to subsection (4) below, bring proceedings in the court against the person making the threats, claiming any relief mentioned in subsection (3) below."

692. Subsection (2) provides that the claimant is entitled to relief if he proves the threats were made and that he is a person aggrieved by them, subject to subsection (2A). Subsection (2A) provides that it is defence for the person who made the threats to show that acts in respect of which the threats were made constitute an infringement unless the patent alleged to be infringed is invalid in a relevant respect (and even then if the defendant did not know and has no reason to suspect that the patent was invalid in that respect). Subsection (4) excludes threats in respect of certain types of infringing act from the operation of the section. Subsection (5) provides that certain types of communication do not constitute threats for the purposes of the section, and in particular a communication which "merely (a) provides factual information about the patent".

693. Whether a communication amounts to a threat depends on how it would be understood by an ordinary reasonable person in the position of the actual recipient: see *Terrell on the Law of Patents* (17th ed) at §§22-11 and 22-12 and the cases cited. The ordinary reader will take into account all of the relevant circumstances known to the parties at the date of the communication: see *Best Buy Co Inc v Worldwide Sales Corp Espana SL* [2011] EWCA Civ 618, [2011] FSR 30 at [18] (Lord Neuberger of Abbotsbury MR). A communication may amount to a threat even if it is veiled, covert, conditional or future: see *L'Oreal (UK) Ltd v Johnson & Johnson* [2000] FSR 686 at [12] (Lightman J). A general warning not to infringe a patent is not a threat, but it is otherwise if the warning would be understood to refer to the products of a specific manufacturer, importer or vendor: see *Terrell* at §22-20.

694. In order to be a person aggrieved by a threat, the claimant must show that its commercial interests have been, or are likely to be, adversely affected in a real, as opposed to a fanciful or minimal, way: see *Brain v Ingledew Brown Bennison Garrett (No 3)* [1997] FSR 511 at 520 (Laddie J). Where the threat was made against the claimant, this will normally be inferred: see *Best Buy* at [46], [51].

The alleged threats

695. In chronological order, the sample threats relied upon by Actavis are as follows. In each case, Actavis has identified particular passages in the communications they rely on. The passages are too numerous and lengthy for me to set them all out in this judgment, but I shall quote the key ones.

696. *Letter to Department of Health 28 October 2014*. I have explained the context of this letter in paragraph 464 above. The passages relied on read as follows:

> "As discussed, Pfizer believes that the current prescription, dispensing and reimbursement framework is likely to contribute to infringement of the pain patent. This may occur if generic pregabalin products are prescribed, dispensed and used to treat Neuropathic pain — as opposed to epilepsy or generalised anxiety disorder. Therefore we believe that certain players in the prescription, dispensing and reimbursement chain may albeit potentially unwittingly, be involved in such infringing activities.
>
> Pfizer is ready to work with the relevant stakeholders to achieve the most practical solution to this issue …
>
> You disagreed with Pfizer that an individual prescriber would be infringing Lyrica's pain patent if generic pregabalin were to be prescribed for pain. However, you agreed that it would be inappropriate for CCGs (or other NHS bodies) to instruct as to generic pregabalin usage in pain on the basis of cost, and you confirmed that you would not endorse such guidance."

697. *Communications with PSNC 5 and 13 November 2014*. Two communications are relied upon, namely the letter dated 5 November 2014 and the email dated 13 November 2013. I have explained the context of these communications in paragraph 478 above.

698. The letter dated 5 November 2014 contains the following passage:

> "Pfizer believes that the current prescription, dispensing and reimbursement framework could contribute to infringement of the pain patent This may occur if generic pregabalin products are prescribed, dispensed and used to treat Neuropathic pain — as opposed to epilepsy or generalised anxiety disorder. Therefore certain players in the prescription, dispensing and reimbursement chain may, albeit potentially unwittingly, be involved in such infringing activities."

699. The email dated 13 November 2014 includes the following key passages:

> "First of all let me say that making allegations of infringement against pharmacists (who are in most cases also our customers) is not something that Pfizer would engage in lightly. I also take your point that, as a general matter, patentees have not tended to assert patent infringement against pharmacists for dispensing generic product, although it certainly has happened on occasion.
>
> …
>
> The key issue is whether there is any relevant patent in place — if there is, then subject to the fairly narrow exception in section 60(5)(c) of the Patents Act 1977, it is indeed possible for retail

> pharmacists to be liable for infringement. The facts we are dealing with here are different from the usual generic launch scenario, but the bottom line is that Pfizer has in place a patent that it believes is valid and which it believes could be infringed.
>
> …
>
> … there are various ways in which a retail pharmacist could be said to be liable for infringement, for example if they started taking more than their non-pain demand for pregabalin supplies from generic companies with the inevitable result that neuropathic pain prescriptions were not being filled with Lyrica.
>
> In direct response to your query we do believe that retail pharmacists would be infringing if they receive prescriptions for 'pregabalin' and dispense the generic, knowing it to be for treating neuropathic pain. …"

700. *Letter to NICE 13 November 2014*. This contained the same paragraph as the letter dated 5 November 2014.

701. *Letter to superintendent pharmacists 10 December 2014*. I have explained the context of this letter in paragraph 494 above. It includes the following passage:

> "Whilst Pfizer's pain patent remains in effect, we expect that generic manufacturers will generally only seek authorisation of their pregabalin products for use in epilepsy and generalised anxiety disorder, i.e. the two indications for which Pfizer has no patent protection. It is likely that the generic companies will initiate discussions with you about their products and we therefore think it is important for you to understand that we believe the supply of generic pregabalin for use in the treatment of pain, whilst the pain patent remains in force in the UK, would be infringing Pfizer's patent protection and would constitute an unlawful act."

702. *Letter to CCGs 12 December 2014*. I have explained the context of this letter in paragraph 497 above. It includes the following key passages:

> "In the circumstances described above, Pfizer believes the supply of generic pregabalin for use in the treatment of pain whilst the pain patent remains in force in the UK would infringe Pfizer's patent rights. This would not be the case with supply or dispensing of generic pregabalin for the non-pain indications, but we believe it is incumbent on those involved to ensure that skinny labelled generic products are not dispensed and used for pain.
>
> In this regard, we believe the patent may be infringed, even potentially unwitting, by pharmacists and others in the supply

> chain, if they supply generic pregabalin for the pain indication. Without information, guidance and practical solutions from the authorities, Pfizer believes that multiple stakeholders, possibly without realising, may contribute to patent infringement which would be an unlawful act. This runs contrary to the government's established policy of rewarding additional research by the granting of a second of a second medical use patent.
>
> We also note that, by issuing guidance, your CCG is able to influence patterns of prescribing and dispensing in your area. We believe these powers must be exercised responsibly and a with a view to avoiding the infringement of Pfizer's pain patent.
>
> …
>
> We should also note that, in our view, (i) CCG guidance instructing or encouraging the usage of generic pregabalin in pain would amount to procurement of patent infringement (an unlawful act); and (ii) your CCG is under an obligation to address the risk of wide scale infringement of Pfizer's patent rights. Pfizer therefore formally reserves all of its legal rights in this regard."

703. *Email to PAG 12 December 2014*. Actavis do not complain of anything in the email itself, but rather that it attached a copy of Pfizer's letter to CCGs. Thus this complaint adds nothing to the previous one.

704. *Letter to Department of Health 9 January 2015*. I have explained the context of this letter in paragraph 468 above. It includes the following key passages:

> "<u>Potential liability of pharmacists</u>
>
> The reality is that the majority of pregabalin supplied in the UK is used for the treatment of pain. In relation to the issue of patent infringement by pharmacists, as we explained at our meeting, Pfizer takes its position on this with some reluctance. However, we also explained, the infringement postion arises from the acts of patent infringement that are set out in section 60 of the Patents Act 1977. In this case, we believe infringing acts would include:
>
> * Disposing of or offering to dispose of generic pregabalin for use in the treatment of pain (it is our view that dispensing is the same as 'disposing' for the purposes of the legislation);
>
> …

> It is clear that, in the absence of any specific guidance, prescribers will generally continue to prescribe pregabalin by references to its INN (i.e 'pregabalin'), regardless of indication. Further prescriptions will generally not include details of the indication being treated. Unfortunately, therefore, if pharmacists dispense generic pregabalin without the necessary precautions being put in place, it is clear that, they will be doing so for the treatment of pain. We believe this would amount to infringement by, amongst other things, keeping and disposing of generic pregabalin for the treatment of pain.
>
> …
>
> We would also reiterate that Pfizer has done significant work to consult with pharmacists on the issues presented by the introduction of generic pregabalin. During our discussions with them it is clear that they are concerned about the possibility of being liable for patent infringement, which we understand. Again, it is only because of the regulatory/ prescribing framework which you have explained that you are unwilling to change or clarify, that Pfizer must take a position in relation to pharmacists."

705. *Letter to Murrays Healthcare Ltd 8 February 2015*. The context of this letter appears from the key passages quoted below:

> "We understand that a conversation took place between Neville Fitzgerald of Pfizer and Fiona Murray of Murrays Pharmacy on 4 February 2015 during which Ms Murray made it clear that Murrays Pharmacy would take a position with regard to the dispensing of pregabalin which is one that threatens to infringe Pfizer's Lyrica pain patent, and we are therefore very concerned. We appreciate that the situation is unusual, and so we wanted to write in confidence to you to ensure that you were made aware of the issues, which in turn we hope will allow us to reach an amicable agreement with you on the way forward.
>
> …
>
> Pfizer believes that the current prescription, dispensing and reimbursement framework could contribute to infringement of the pain patent. Patent infringement will occur if generic pregabalin products are dispensed and used to treat pain – as opposed to epilepsy or GAD.
>
> *Potential liability for pharmacists*
>
> In relation to the impact on pharmacists (and pharmacy technicians), the relevant legislation is taken from the acts of patent infringement that are set out in section 60(1)(c) of the

Patents Act 1977. In this case, we believe infringing acts would include:

* Disposing of or offering to dispose of generic pregabalin for use in the treatment of pain (it is our view that dispensing is the same as disposing for the purposes of the legislation);

…

… Pfizer believes that pharmacists (and pharmacy technicians) could be liable for patent infringement under the Patents Act 1977, even potentially unwittingly, if they receive prescriptions for 'pregabalin' and dispense a generic pregabalin for pain. Therefore we believe that the best and simplest solution lies with prescribing doctors ensuring that only Lyrica is prescribed for pain.

…

Our understanding of your position

As we mention at the beginning of this letter, we have become aware of a conversation that took place on 4 February 2015 between Pfizer's Neville Fitzgerald and your Fiona Murray, during this conversation, despite acknowledging the pain patent, Ms Murray stated your view that you do not accept any responsibility for what dispensing practices your pharmacy branches engage in when they are presented with prescriptions from prescribers for either 'Lyrica' or 'pregabalin'. Our understanding is that Ms Murray's current view is that she will not be informing your pharmacists that they should be checking the indication / condition for which the pregabalin has been prescribed. This indicates that you, perhaps unwittingly, would be committing acts which we believe infringe our pain patent if you were to pursue this strategy then you would be threatening to infringe the pain patent.

Next steps

We would like to emphasise again that this matter is a legal one, not a clinical one. …

We request that you agree to change your current position and to ensure until after the trial in June 2015 that:

1. you do <u>not</u> inform pharmacists in your company that generic pregabalin should be dispensed for pain or neuropathic pain or conditions including pain or neuropathic pain or in any other way procure

> pharmacists in your company to dispense generic pregabalin for pain; and
>
> 2. you inform all pharmacists in your company, that until the judgment in the trial referred to above, only Lyrica should be dispensed for the treatment of pain. We request that you provide us with a copy of your advice to your pharmacists in draft form before it is disseminated.
>
> Finally, we recognise that your current position may have resulted from you not being fully appraised of the unusual legal situation concerning Lyrica pain patent.
>
> We would simply ask that you respond to this letter by close of business on Friday 13 February 2015 to confirm that you will agree to the steps set out above and the requested notifications to your pharmacists, to enable us to bring this matter to an amicable conclusion. …"

706. *Letter to BMA 18 February 2015*. I have explained the context of this letter in paragraph 505 above. It includes the following key passages:

> "… we wanted to make you aware of the issues and to discuss how we may work together to ensure that doctors are property informed and that they respect the patent when using Lyrica to treat patients with pain.
>
> …
>
> … Pfizer believes that the current prescription, dispensing and reimbursement framework could contribute to infringement of the pain patent. Patent infringement will occur if generic pregabalin products are prescribed, dispensed and used to treat pain - as opposed to epilepsy or GAD.
>
> For your reference, we received the enclosed letter from NHS England dated 10 February 2015 from Sir Bruce Keogh … The letter specifically refers to BMA (and professional bodies) and its potential role in assisting clinicians to avoid unlawful behaviour.
>
> …
>
> We also would like to emphasise that this matter is different to general off-label prescribing in unlicensed situations where there is no patent in force in respect of the off-label/unlicensed indication. In the patent situation any guidance to encourage prescribing of unlicensed generic pregabalin for pain cannot be for clinical reasons and would infringe the patent.

> We would like to emphasise again that this is a legal matter, not a clinical one. ..."

707. *Letter to superintendent pharmacists 20 February 2015*. I have explained the context of this letter in paragraph 495 above. It includes the following passages:

> "When presented with a generic prescription for pregabalin, you will therefore need to take steps to ensure that the appropriate product is dispensed. This might involve, amongst other things, contacting the prescriber to establish the indication, or making a similar enquiry of the patient.
>
> …
>
> … it is necessary for pharmacists to take steps to avoid dispensing generic pregabalin for pain (as set out above).
>
> We would like to emphasise that this is a legal matter, not a clinical one. However, given the imminent launch of generic pregabalin and the crucial role pharmacists will play, we believe it is important that pharmacists are fully informed of the situation."

708. Enclosed with the letter was an Annex. Appended to the Annex was the guidance which had been issued by the NPA, PSNC and Community Pharmacy Scotland to which I have referred above. Various passages in this guidance, as appended to the Annex, are relied upon by Actavis, but it is sufficient to quote two paragraphs from the NPA guidance:

> "To avoid possible patent infringement by pharmacists, steps will need to be taken to ensure that where generic pregabalin is requested on a prescription the correctly licensed product is supplied. This may mean contacting the prescriber and establishing the indication and requesting that the prescription is amended and ordered by brand as Lyrica if necessary.
>
> …
>
> Using generic pregabalin for neuropathic pain may be deemed by Pfizer to be a patent infringement by all parties concerned, including the prescriber and the supplying pharmacist."

Assessment

709. *Letter to Department of Health 28 October 2014*. As noted above, the recipient of this letter was Ms Howe. She said nothing about this letter in her evidence, and Actavis did not cross-examine her about it. Thus there is no evidence from the actual recipient that it was regarded as a threat of proceedings for patent infringement against any one. That is not conclusive, but in my judgment the ordinary reasonable recipient of this letter in Ms Howe's position would not regard it as a threat to bring proceedings for patent infringement. Rather, it would be understood as an explanation of Pfizer's

concerns to the Government department with responsibility for the English healthcare system. In stating that it considered that certain players would infringe the Patent, Pfizer did not state or imply that it intended to sue those players.

710. *Communications with PSNC 5 and 13 November 2014*. There is no evidence from the actual recipient of these communications, Ms Sharpe. In my judgment the ordinary reasonable reader of the letter dated 5 November 2014 in her position would not have regarded it as a threat for similar reasons to the letter dated 28 October 2014 even though the letter dated 5 November 2014 was addressed to a body representing NHS pharmacy contractors. But in my view the email dated 13 November 2013 would have been understood as a threat of proceedings against pharmacists dispensing generic pregabalin. The email does not simply provide factual information about the Patent. It directly alleges that pharmacists would infringe the Patent in certain circumstances. Moreover, it expressly notes that patentees have occasionally asserted patent infringement against pharmacists. The statement that Pfizer would not lightly make allegations of infringement against pharmacists does not neutralise the threat, but accentuates it. It is immaterial that the threat was made against a potentially large class of persons. The threat plainly related to Actavis' product since the letter dated 5 November 2014 had referred to the prospect of Actavis marketing pregabalin under a skinny label.

711. As to the question of whether Actavis are aggrieved by the email dated 13 November 2014, I consider that they are. Pfizer's purpose in communicating with the PSNC was to ensure that its message was disseminated to those represented by the PSNC, as indeed it was. The background to the email was Actavis' impending launch of a generic pregabalin product. It is immaterial that Actavis was not yet on the market with that product. The email was calculated to have a chilling effect on the willingness of pharmacists to stock and dispense generic pregabalin, and in particular Actavis' product when it was launched. This was harmful to Actavis' commercial interests in a real manner. This is so irrespective of the validity of claims 1 and 3 of the Patent.

712. Given my conclusions with regard to infringement, and regardless of my conclusions with regard to the validity of the Patent, Pfizer cannot justify the threat made in the email dated 13 November 2013.

713. *Letter to NICE 13 November 2014*. There is no evidence from the actual recipient of this letter, Mr Underhill. In my judgment the ordinary reasonable reader of the letter in his position would not have regarded it as a threat for similar reasons to the letter dated 28 October 2014.

714. *Letter to superintendent pharmacists 10 December 2014.* There is no evidence from any of the actual recipients of this letter. According to Ms Tully, Ms Wright would have received a copy, but Ms Wright did not mention it in her evidence and neither counsel asked her about it. Nevertheless, in my judgment the ordinary reasonable reader of the letter would have regarded it as a threat. The letter states that "it is important for you to understand that we believe the supply of generic pregabalin for use in the treatment of pain … would be infringing Pfizer's patent". In my view the reader would think that Pfizer was saying that it was important for them to understand this because Pfizer was warning them that they risked proceedings for infringement if they did this. I do not consider that the fact that the recipients were customers of

Pfizer detracts from this. The letter expressly referred to Actavis' intended launch of generic pregabalin under a skinny label in December 2014/January 2015.

715. As to the question of whether Actavis are aggrieved by the letter, in my judgment they are aggrieved by it for similar reasons to the email dated 13 November 2014. Again, Pfizer cannot justify the threat.

716. *Letter to CCGs 12 December 2014*. Pfizer accepts that this letter was a threat, but disputes that Actavis are aggrieved by it. In my judgment Actavis are aggrieved by it. The letter was designed to try and minimise the prescribing and dispensing of generic pregabalin for pain. The simplest way for doctors and pharmacists to avoid the threat would be to prescribe and dispense Lyrica in all cases. Thus the letter was calculated to have a chilling effect on the sales of Lecaent. Furthermore, if one takes my conclusions as to the validity of claims 1 and 3 into account, it is clear that the effect of the threat was to tend to exclude Lecaent from a part of the market in which it transpires it was lawful for Lecaent to be sold. Again, Pfizer cannot justify the threat.

717. *Letter to Department of Health 9 January 2015*. Again there is no evidence from Ms Howe with respect to this letter. On balance I consider that this letter would have been understood by the ordinary reader in her position as a threat to sue pharmacists. It is very clear and explicit in stating Pfizer's position that pharmacists are infringing the patent. Moreover, it refers to the "potential liability" of pharmacists, which can only mean their liability to Pfizer for patent infringement. Still further, despite noting pharmacists' concern over this possible liability, it states that "Pfizer must take a position in relation to pharmacists". The letter expressly refers to Actavis' product and Pfizer's claim for infringement in respect of it.

718. I am not persuaded, however, that Actavis are aggrieved by this threat. Pfizer did not make the threat with a view to it being disseminated to pharmacists. The purpose of the threat, as with the remainder of the letter, was to try to put pressure on the Department of Health to issue guidance with respect to prescribing Lyrica by brand name for pain. In that respect, Pfizer was aiming at the wrong target, the right target being NHS England. Thus I do not consider that the letter was capable of inflicting any real harm on Actavis' commercial interests.

719. *Letter to Murrays Healthcare Ltd 8 February 2015.* Pfizer accepts that this letter was a threat, but disputes that Actavis are aggrieved by it. In my judgment Actavis are aggrieved by this letter irrespective of my conclusion with respect to the validity of claims 1 and 3 of the Patent. The object of the letter was to try to persuade Murrays only to dispense Lyrica for pain. Indirectly, it was calculated to discourage Murrays from stocking Lecaent, particularly given that it expressly referred to Actavis. Pfizer suggest that, in fact, Murrays were not deterred from doing so. Even if that is correct, I do not regard this as an answer. It should not be forgotten that the requirement to be a person aggrieved is a requirement as to standing. Whether a potentially damaging communication to a customer of the claimant has in fact caused a loss of sales is a matter which goes to remedy. Moreover, given my conclusion as to the validity of the Patent, Actavis are even more clearly aggrieved by the letter. Again, Pfizer cannot justify this threat.

720. *Letter to BMA 18 February 2015*. There is no evidence from the recipient of this letter, Mr Ward. In my judgment this letter would be understood as a threat to bring

proceedings against doctors, pharmacists and possibly even the BMA itself. Not only does the letter set out Pfizer's assertions about infringement, but in addition it emphasises that "this is a legal matter". The letter expressly refers to Actavis' product and Pfizer's claim for infringement in respect of it. In my judgment Actavis are again aggrieved by this letter for similar reasons to those given above. Again, Pfizer cannot justify the threat.

721. *Letter to superintendent pharmacists 20 February 2015*. Ms Wright was one of the recipients of this letter. She explained that the letter was sent by recorded delivery. She gave clear and convincing evidence that she interpreted it as a threat. Furthermore, I consider that the ordinary reasonable reader of the letter in her position would have done the same. Again, the letter emphasises that "this is a legal matter". The Annex makes it plain that Pfizer contends that pharmacists who do not take the steps requested by Pfizer will infringe the Patent. The letter expressly refers to Actavis. I do not accept Pfizer's argument that the letter went no further than the guidance issued to pharmacists by bodies such as the PSNC, particularly since some of this guidance was disseminating other threats made by Pfizer. In my judgment Actavis are again aggrieved by this letter for similar reasons to those given above. Indeed, Ms Wright gave evidence that seven of the ten pharmacies within the John Preddy chain decided not to stock (or if they had stocked it, not to dispense) generic pregabalin as a result of the letter. Again, Pfizer cannot justify the threat.

Afterword: the need for a system

722. I have now lived with this case for nine months. During that time, I have heard and determined the applications which led to the *Warner-Lambert I, II, III and IV* judgments, I have heard and determined a number of other case management applications, I have heard the trial and I have written this judgment. During that time, I have reflected repeatedly and at length on the issues raised by this litigation. At the end of that period of reflection, I remain more convinced than ever that the best solution to the problem of protecting the monopoly conferred by a second medical use patent while allowing lawful generic competition for non-patented indications of the substance in question is to separate the patented market for the substance from the non-patented market by ensuring that prescribers write prescriptions for the patented indication by reference to the patentee's brand name and write prescriptions for non-patented indications by reference to the generic name of the substance (the INN).

723. Prescribers cannot be expected to know when this is required, nor should they be required to take steps to find out. What is needed is for centralised and authoritative guidance to be given to prescribers as to when this practice should be adopted. Such guidance also needs to be conveyed to other relevant stakeholders, and in particular to the software providers. The question is who is to issue such centralised and authoritative guidance. This is a particular challenge for the decentralised (some might say fragmented) English healthcare system since the 2012 Act. As I understand it, the Secretary of State considers that he lacks the power to issue such guidance (see *Warner-Lambert I* at [75]). That being so, the only body in England which appears to have the necessary power and authority is NHS England. In Wales, Scotland and Northern Ireland, the devolved governments appear to have the necessary power and authority.

724. In the present case, NHS England issued guidance as a result of an order made by this Court on an application by Pfizer. Regardless of the legal soundness of that procedure, it had two practical advantages. The first was that it provided a convenient forum to enable the interested parties to negotiate what was to be done, when and by whom. In the end, this was all agreed. The second was that the procedure included the protection for the NHS and for the generic companies of a cross-undertaking in damages. This is particularly important because of the risk that the second medical use patent may prove to be invalid if challenged, as has transpired in the case of claims 1 and 3 of the Patent if I am right.

725. Looking to the future, however, it does not seem to me to be in anyone's interests for these problems to be dealt with in the ad hoc manner in which they were addressed in this case. It is not as if the situation which arose in this case could not have been predicted. On the contrary, as soon as it was known that the SPC had lapsed, the resulting scenario was entirely predictable. (And if I am right that Pfizer planned to allow the SPC to lapse, for whatever reason, then Pfizer was in a position to predict it even before then.) In general, information as to patent expiry dates and loss of data exclusivity dates is in the public domain and can be ascertained in advance. I nevertheless recognise that it is probably too much to expect NHS England to keep track of such dates and to plan for the resulting situations. I consider that it behoves patentees who want their second medical use patents enforced to provide NHS England with all the information and assistance it requires to enable it to issue appropriate guidance as and when required. I also consider that it behoves generic companies who want their interests in obtaining untroubled access to lawful markets protected to cooperate with NHS England as well. I recognise that generic companies are always understandably reluctant to disclose their future commercial plans to anyone, but the potential interest of generic companies in a skinny label launch (whether or not pending a challenge to the validity of the patent) to avoid a second medical use patent will usually be obvious. In short, what is needed is a system for dealing with these situations.

726. The Secretary of State's intervention in this case, and Ms Howe's evidence, demonstrate the seriousness with which the Secretary of State regards these issues. Moreover, Ms Howe's evidence and the closing submissions made by counsel for the Secretary of State make it clear that the Secretary of State accepts the desirability of the solution I have proposed. I therefore trust that the Secretary of State will take steps to ensure that a suitable system is put in place in England. I also trust that he will liaise with his counterparts in the Welsh, Scottish and Northern Irish administrations to try to ensure that the system operates across the whole of the UK.

Summary of principal conclusions

727. For the reasons discussed above, I conclude that:

i) none of the claims of the Patent is obvious over any of the prior art relied upon by Mylan and Actavis;

ii) claims 1, 3, 4, 6, 13 and 14 of the Patent are invalid on the ground of insufficiency;

iii) even if claims 1 and 3 are valid, Actavis have not infringed those claims pursuant to section 60(1)(c) or section 60(2); and

iv) Pfizer is liable for making groundless threats of patent infringement proceedings, albeit not in all the cases alleged by Actavis.