Neutral Citation Number: [2023] EWHC 1836 (Pat)
Case No. HP-2021-000049

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
INTELLECTUAL PROPERTY LIST (ChD)
PATENTS COURT

Rolls Building
Fetter Lane
London, EC4A 1NL
Date: Monday 24 July 2023

Before :
MR JUSTICE MEADE

- -

Between :

TEVA PHARMACEUTICAL INDUSTRIES LIMITED (a company incorporated under the laws of the State of Israel)	**Claimant**
- and –	
TEVA UK LIMITED	**Third Party**
- and -	
GRÜNENTHAL GmbH (a company incorporated under the laws of Germany)	**Defendant**

MISS CHARLOTTE MAY KC and MR. JOE DELANEY (instructed by **Bristows LLP**) for the **Claimant and Third Party**

MR. ANDREW WAUGH KC AND DR. STUART BARAN (instructed by **Simmons & Simmons LLP**) for the **Defendant**

Hearing dates: 11-12,15-18 and 23-24 May 2023

APPROVED JUDGMENT

Remote hand-down: This judgment will be handed down remotely by circulation to the parties or their representatives by email and release to The National Archives. A copy of the judgment in final form as handed down should be available on The National Archives website shortly thereafter but can otherwise be obtained on request by email to the Judicial Office (press.enquiries@judiciary.uk).

Mr Justice Meade:

INTRODUCTION

1. This action concerns European Patent (UK) No. EP 1 457 208 B9 ("the Patent") which relates to a formulation of testosterone undecanoate ("TU") with castor oil and benzyl benzoate for the treatment of low testosterone levels in men, a condition called hypogonadism. Its filing date and unchallenged priority date ("the Priority Date") are respectively 15 March 2004 and 14 March 2003. The Patent expires on 15 March 2024. Testosterone is sometimes just referred to as "T" and similarly reference is sometimes made to "serum T levels" and the like.

2. The Claimant initiated these proceedings by making a claim for revocation against Bayer Intellectual Property GmbH, but the Patent has since been assigned to Grünenthal GmbH ("Grünenthal"), which is now the named defendant. I generally refer just to "Grünenthal" below for simplicity.

3. A formulation of TU covered by the Patent is and has been marketed under the brand name Nebido by Bayer and later Grünenthal. Teva is interested in launching a generic version of Nebido in the UK and as a result there is a counterclaim for infringement.

4. Teva does not contest that its product would fall within the scope of the Patent's claims (in the event that the Patent is valid). In essence therefore this is now a revocation action.

5. There are no EPO opposition proceedings over the Patent but there are proceedings in Germany. A German court found the German designation of the Patent to be invalid on 1 February 2023 with reasons following on 1 June 2023. I return to this below.

6. Charlotte May KC appeared for Teva with Joe Delaney, and Andrew Waugh KC and Stuart Baran appeared for Grünenthal.

7. Grünenthal applied to amend the Patent both conditionally and unconditionally pursuant to section 75 of the Patents Act 1977. There are therefore multiple claim sets in issue.

8. Following developments in correspondence and in discussion at trial, the only material outstanding objection to the amendments is that they do not cure the alleged invalidity of the Patent.

CONDUCT OF THE TRIAL

9. The trial was conducted in person over 8 hearing days. This was an ambitious timetable, with a number of issues to cover which had not been flagged by the parties at the PTR. To accommodate the hearing the court day was extended on several occasions. I would like to thank the court staff and shorthand writers for helping with these longer hours.

10. In addition, one expert (Prof Wu) became Covid positive, and he gave evidence remotely.

11. Although the defendant to the infringement counterclaim, Teva opened the trial because it had become a revocation case in substance.

THE ISSUES

12. The issues narrowed in the run up to trial, and during trial. The remaining issues are:

    i) Identity of the skilled team - the parties agreed that the team would comprise a formulator and a clinician, but did not agree whether the team would also comprise a pharmacokineticist/pharmacologist. As matters developed this proved to be more an issue about how much pharmacokinetic ("PK") expertise the skilled team would have, rather than whether it would have any at all.

    ii) Some issues over the common general knowledge ("CGK").

    iii) Obviousness over a prior art publication referred to as "von Eckardstein" (*"Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study*" by von Eckardstein et al published in the "Journal of Andrology" in May-June 2002) in combination with:

        a) A prior art publication referred to as "Nieschlag" *("Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men*" by Nieschlag et al published in Clinical Endocrinology Volume 51, No. 6 on 10 August 1999); and

        b) A prior art publication referred to as "Behre" (*"Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies"* by Behre et al published in the European Journal of Endocrinology 140.5 (1999): 414-419).

        At the start of trial there appeared to be an issue about combining the three citations (von Eckardstein cites the other two) but by closing submissions this had faded away and Grünenthal did not oppose their being considered together, which would have been my decision in any event.

    iv) Insufficiency:

        a) A "shepherding" squeeze, that the Patent is no more enabling than the prior art.

        b) Two closely related plausibility attacks.

        I describe the insufficiency arguments in more detail below, both in relation to their substantive merits and in relation to a procedural argument over them.

13. There was no dispute between the parties on claim interpretation.

THE WITNESSES

14. Each side called three expert witnesses: a clinician, a formulator and an expert in pharmacokinetics.

Teva's witnesses

15. Teva's clinician was Professor Richard Anderson, Elsie Inglis Professor of Clinical Reproductive Science, and Head of Section of Obstetrics and Gynaecology and Co-Director of the Medical Research Council Centre for Reproductive Health, at the University of Edinburgh. He is also an Honorary Consultant in Reproductive Medicine at the Royal Infirmary of Edinburgh. He has over 30 years' experience treating male patients in need of testosterone replacement and has a continued research interest in testosterone-based male contraception. At the Priority Date, Prof Anderson was treating male patients in the clinic with primary and secondary hypogonadism with male hormone replacement therapy and had been doing so for around 13 years.

16. Prof Anderson prescribed Nebido often from its initial licensing in the UK in 2004. He was asked by Teva's solicitors, Bristows, to put that out of his mind when considering obviousness.

17. Grünenthal criticised Prof Anderson on a number of fronts. The main ones (I will not endeavour to deal with all of them) were:

    i) First, that he was directed by Bristows in relation to what he said about the CGK. While it is important that expert witnesses give their own views about the relevant CGK topics in a case, it is inevitable that they need to be given some flavour of the issues, or otherwise they would have to provide information across a wide range of mostly irrelevant matters. I did not think in general that Prof Anderson's instructions crossed this line. There were a couple of points where specific information was given to Prof Anderson by Bristows (e.g. an SmPC for testosterone enanthate) but these did not undermine his approach materially in my view. Likewise, he accepted a date from Bristows (approval of Testogel) which was inconsistent with his own recollection and turned out to be wrong, but this was a small point.

    ii) Second, that his evidence was affected by his prior knowledge of Nebido, and hindsight generally. I deal with this in context when I assess obviousness. No personal criticism is appropriate though: I am satisfied that Prof Anderson knew he should try to avoid hindsight, and did try.

    iii) Third, that he knew at all times the relevant composition of the Jenapharm TU product used in von Eckardstein (which was within the claims of the Patent). He told Bristows about this, and provided a document in his possession which showed it, only quite close to trial. It seems that Prof Anderson felt that the information was confidential but initially thought it was of low relevance, and then had second thoughts when he realised its greater significance. I think this was a mistake on his part but also conclude that he was acting in a way which he genuinely thought was conscientious. It does go to reinforce Grünenthal's hindsight argument.

iv) Fourth, that his second report, dealing with Prof Larsen's clarified position on obviousness, which I explain when addressing her evidence below, was perfunctory. Prof Anderson explained that he was travelling at the time. I agree that the evidence was lacking in reasoning but I also accept Prof Anderson's explanation. When I weigh up the evidence I will take into account its brevity, but I do not think it supports any attack on Prof Anderson personally.

18. My overall impression of Prof Anderson was that he was both very well qualified and doing his honest best to help the Court. He was a very clear explainer of technical matters and fair and concise in his oral evidence. He answered the questions put to him. As I have already said, I have to take into account the risk of hindsight and the brevity of some of his reports' key sections but neither means that he was not a good witness in general.

19. Teva's formulator was Associate Professor Susan Weng Larsen, who has been an Associate Professor (I refer to her simply as "Prof" below) at the Department of Pharmacy, Faculty of Health and Medical Sciences at the University of Copenhagen since 2008. Before that she was an Assistant Professor in the Department of Pharmaceutics and Analytical Chemistry, also at the University of Copenhagen (that role commenced just after the Priority Date, in June 2003). She completed her PhD thesis in the Department of Pharmaceutics at the (then) Danish University of Pharmaceutical Sciences, titled "*Parenteral oil depots: applicability of the prodrug approach to modify lipophilicity and release rate*", in the same month as the Priority Date.

20. Grünenthal also criticised Prof Larsen on a number of fronts:

i) That she had an unusual depth of knowledge of oily parenteral depot formulations. I agree that she did, but it is not a personal criticism of her. It needs to be borne in mind when assessing hindsight, and I do so.

ii) That she had, in the course of her PhD and as shown in her doctoral thesis, unusual experience of castor oil formulations, the issues of viscosity which they presented, and the possibility of dealing with them by the use of a co-solvent. This is a more detailed facet of point i). Grünenthal suggested that Prof Larsen did not adequately acknowledge this in her written evidence, but I disagree. The information was there in the materials she provided in the annexes to her report.

iii) That she changed her approach to obviousness between her first and second reports materially. In her second report she provided what she termed a "clarification", in which she said (a) that the skilled team following von Eckardstein would not in fact do animal experiments and (b) that the skilled team following von Eckardstein would test their progress by trying to emulate the plot of the single dose curve of Behre reproduced in Fig 2 of von Eckardstein. I explain in more detail below what this concerns. I agree that it was not a clarification at all but a major change in Prof Larsen's approach which presented a significant risk of hindsight because it came about only after she had seen the Patent and Grünenthal's defence of it.

iv) That she gave a different reason in cross-examination for choosing the maximum amount of benzyl benzoate (solubility) than she had in her reports (viscosity). In oral evidence, Prof Larsen was asked why she had not mentioned this before given that she had provided the earlier "clarification" to which I have referred. She accepted that she could provide no excuse. Counsel for Teva said in oral closing submissions that the point was not in Prof Larsen's written evidence because it was in response to Prof Østergaard's reply evidence but I think that was an artificial and unreal explanation which I note Prof Larsen herself did not advance. I think this is further evidence of hindsight creeping in. It may also be down to the fact that Prof Larsen was involved in the German proceedings where viscosity and solubility were deployed differently by Teva, as I go into below.

v) That she did not give enough attention to the relative amounts of benzyl benzoate and castor oil in the prior art/CGK. This point is better considered in context.

21. Points iii) and iv) together lead me to conclude that Prof Larsen's overall approach to the case carried with it significant hindsight. I touch on this in more detail below. This does not mean that I question her integrity. She was honest and direct in her answers, and was well-qualified to give her evidence. I agree that she knew more about the very specific formulations in issue in this case than the ordinary skilled formulator would have, but no expert corresponds perfectly to the notional ideal and on its own it does not lead me to discount her evidence.

22. Teva's pharmacokineticist was Professor Hannah Batchelor, who is a Professor in Pharmaceutics at the University of Strathclyde's Institute of Pharmacy and Biomedical Sciences, a role she has held since 2020. In 2000 she completed her PhD in Drug Delivery at the School of Pharmacy, University of London. From 2000 to 2007 (covering the Priority Date), she was a Lecturer in Pharmaceutics at Aston University, where she taught pharmacokinetics to first year undergraduate pharmacy students and undertook research on the design of new medicines for oral administration. She worked in industry for AstraZeneca from 2008 to 2011 before becoming a Research Fellow and then a Senior Lecturer at the University of Birmingham.

23. Grünenthal criticised Prof Batchelor for having "no more hands-on experience (indeed, perhaps less) of relevant PK than did Prof Anderson". I disagree and thought Prof Batchelor was a model witness, extremely lucid and very fair. It has to be recalled that she was engaged to provide a direct response to Dr Peeters' evidence and to support Teva's case that both the prior art and the Patent contain a similar kind of clinical data, in particular that neither has data for individual patients. Her understanding of the kind of modelling that could and could not be done in this context was more than sufficient.

Grünenthal's witnesses

24. The Defendant's clinician was Professor Frederick Wu, who is Emeritus Professor of Medicine and Endocrinology, Division of Endocrinology, Diabetes & Gastroenterology, School of Medical Sciences, Faculty of Biology, Medicine

and Health, University of Manchester. He qualified in Medical Sciences in 1970 before going on to complete specialty training in endocrinology, diabetes and general medicine. In 1983 he was appointed Clinical Scientist and Consultant Andrologist at the MRC Reproductive Biology Unit where he developed a research programme on hormonal male contraception, male infertility and neuroendocrine control of male pubertal transition. He was appointed Senior Lecturer in Medicine (Endocrinology), Department of Medicine, University of Manchester, Honorary Consultant Endocrinologist, Salford Royal Hospital and Manchester Royal Infirmary in 1992 and subsequently promoted to a Chair of Professor of Medicine and Endocrinology in 2003.

25. Teva made only modest criticisms of Prof Wu:

    i) That he "stuck unnecessarily to the party line on the Saad paper" because he was aware of the arguments and "invested in the case". I do not accept the criticism. I do not think Prof Wu understood what was being driven at in the passage of cross-examination relied on and anyway the Saad paper was peripheral to his evidence.

    ii) That he did not adequately understand the concept of the notional skilled person. He did indeed use the expression "non-expert skilled clinician" but I did not think it denoted the kind of lack of understanding Teva implied.

26. Overall I thought Prof Wu was an excellent witness. I find, as Teva accepted, that he was very well qualified and doing his best to assist the Court.

27. Grünenthal's formulator was Professor Jesper Østergaard. Following his PhD, he was appointed Assistant Professor (2003), then Associate Professor (2006) in the Department of Pharmaceutics and Analytical Chemistry at the University of Copenhagen. Since 2019, he has been a Professor in the Department of Pharmacy, Faculty of Health and Medical Sciences at the University of Copenhagen. This is the same department as Prof Larsen; they have been colleagues from before the Priority Date.

28. Teva pointed out that Prof Østergaard had not, prior to the Priority Date, worked on oil based parenteral formulations, and nor did his PhD cover them, so he was dependent on reading into aspects of this litigation. I agree with this, but it is no more than the flip side of Prof Larsen being more qualified than the notional skilled person. I consider that he did a good job of putting himself in the position of the ordinary skilled person.

29. Teva also said that Prof Østergaard was unrealistic in saying that a peer-reviewed publication should always contain enough information to allow the reproduction of the work it describes. I consider that Prof Østergaard was correct in what he said in a general sense; it may not have been truly applicable to the statement in von Eckardstein - essentially a clinical paper - of a formulation matter, the composition of the TU given, and I deal with that below. But in any event there was no lack of sincerity in what he said and this was a very small point on any view.

30. Overall I found Prof Østergaard an excellent witness, well qualified, fair and with the goal of assisting the Court in an independent way.

31. Grünenthal's pharmacokineticist was Dr Peeters, who is a consultant clinical pharmacologist at Curare Consulting, having been a registered clinical pharmacologist since 1998. He has spent almost all of his 35 years in the pharmaceutical industry in early clinical drug development, having been involved in or responsible for several hundred clinical trials. From 1998 to 2007 he was at Organon becoming Executive Director of Clinical Pharmacology and Kinetics having been Departmental Head of Clinical Pharmacology. Organon was responsible for different testosterone formulations. He is also an author of over 60 peer-reviewed publications and taught Early Clinical Drug Development at the University of Utrecht for 10 years from 2006.

32. Teva criticised Dr Peeters for wrongly saying in his first report that Organon was not interested in oil-based products for parenteral administration between 1998 and 2003; in fact it was, and that fact might have assisted Teva. Teva fairly said that if that had just been a mistake or misrecollection then it would not amount to anything, but that Dr Peeters' explanation in his third report (that he was distinguishing between contraception and hypogonadism) was unacceptable because he said in oral evidence that he was not differentiating in that way. I agree with this, and Dr Peeters' further explanations made matters still worse.

33. I do not think that Dr Peeters did himself any credit in this context, but it was a relatively minor issue and in general his evidence was fair. I think however he was very focused on the extremely detailed and cogent individual patient-level data needed for regulatory approval and was not really on the wavelength of what would be appropriate to early-stage development. I return to this point in relation to the skilled team, and in relation to obviousness.

THE SKILLED TEAM

34. There were four issues over the skilled team:

    i) As to the skilled clinician, there was a minor dispute on terminology as to whether that clinical member of the team is specifically an endocrinologist (Prof Wu's view) or whether that person could come from a background in endocrinology, reproductive medicine or urology (Prof Anderson's view). Following cross-examination of the clinical experts, this point did not go anywhere as Prof Wu accepted that some urologists specialised in reproductive medicine, whilst Prof Anderson noted that the skilled clinician would require training in reproductive endocrinology. I need say no more about this point.

    ii) As to the skilled formulator, the parties were in dispute as to whether or not the skilled formulator would have existing experience of formulating lipid-based/oily depots, or whether they would be more of a 'general formulator'.

    iii) The parties disagreed whether the team would also necessarily comprise a pharmacokineticist or clinical pharmacologist.

iv) Grünenthal said that Teva's experts had been unduly "siloed" from one another and prevented from sharing their views as a real skilled team would; by contrast, Grünenthal's experts attended a three-way meeting at the instigation of Prof Wu.

35. The last of those points is process-related; it concerns the conduct of litigation rather than the correct conceptual identification of the notional skilled person or team as a standard against which to assess validity. So I will deal with it separately.

The skilled team – applicable law

36. The parties were in agreement regarding the basic notion of the skilled addressee as being a person with a practical interest in the subject matter of the patent under consideration, possessed of the common general knowledge, and diligent but uninventive. Nor was it in dispute that the addressee may be a team, and would be in the present case.

37. The parties cited a number of authorities on the correct approach to this issue and I have dealt with this in a number of recent cases, by reference to my decision in *Alcon v. Actavis* [2021] EWHC 1026 (Pat) drawing on the decision of Birss J, as he then was, in *Illumina v. Latvia* [2021] EWHC 57 (Pat). I will proceed by reference to the three questions posed by Birss J in *Illumina* at [68].

The skilled team - analysis

38. First, what problem does the Patent seek to solve? In my view the problem it seeks to solve is the provision of an injectable formulation of TU allowing prolonged maintenance of physiological levels of testosterone in patients with hypogonadism. Proposed amended claim 7 is more specific than the product claims, of course, and all the claims have details of the formulation used, but this level of generality is the right one for identifying the skilled team.

39. Second, what was the established field in which the problem was located? This includes consideration of real teams. In a broad sense the answer is drug development, but rather than try to describe the field from scratch in my own words, it is simpler to say what the real bone of contention was, which seemed to be the familiarity of the skilled team with injectable oily depot formulations. Teva said that the way the Patent described the underlying technology indicated that the skilled team must be familiar with such matters, but that is not the same as the question of what real teams existed. There was no evidence that there was any real number of teams concentrating on anything so narrow as oily depot formulations, although there were no doubt a few workers such as Prof Larsen with highly specialist knowledge. So in this respect the real teams were more general formulators, who might be in academia or in industry.

40. Relatedly, pharmacokinetic ("PK") knowledge was, on the evidence I heard, provided in a number of different ways. Some clinicians had adequate PK knowledge for some tasks and in academic research settings that is what would be relied on if it was thought that it would be good enough. In industry and especially for drug development aimed at regulatory approval the expertise would

be provided by a separate individual. In academic research, teams would not turn down specialist PK knowledge if it was on offer, and they might seek out a specialist with deeper knowledge if it was thought needed. So this is a situation where the skilled team varied in the real world depending whether the setting was academia or industry.

41. The true bone of contention on the PK side was how much PK knowledge was needed in the circumstances of this case. Teva's case was that to understand the PK information in the prior art and in the Patent, the level of knowledge possessed by someone like Prof Anderson was enough, and in that sense the skilled team might have two members: a formulator, and a clinician who would provide both clinical input and adequate PK understanding.

42. Grünenthal's case fluctuated rather, but at its highest seemed to be, as I drew from Dr Peeters' evidence, that without complex PK analysis of individual patient data the skilled team would not have the confidence to take the prior art forward. The prior art does not contain any such individual patient data. This would imply, it seemed to be argued, that there would be three members of the skilled team: a formulator, a clinician, and a PK expert with the level of skill and knowledge possessed by Dr Peeters.

43. It was these two different conceptions of the skilled team that led to Grünenthal calling Dr Peeters from the outset and Teva deploying Prof Batchelor only in reply.

44. Each side overstated the other's position. In particular, Grünenthal presented Teva's position as being that the skilled team would not have any PK expertise despite the Patent describing "an invention borne out of a pharmacokinetic problem". It plainly was not Teva's position that the skilled team would not have PK expertise; Teva's position was that it would have PK expertise at the sort of level that Prof Anderson was comfortable with.

45. Teva submitted at one stage that Grünenthal's case had echoes of the point that arose in *Schlumberger* ([2010] EWCA Civ 819) but in reverse. What it meant was that it perceived that Grünenthal was arguing that the Patent was not obvious because the prior art lacked data for individual patients of the kind that the high-level PK expert would demand, but was sufficient because it could be put into practice across the scope of the claims without such expertise. I found that somewhat contorted and anyway Grünenthal did not argue the case that way. There are rare cases where the skilled team is different for inventive step and for insufficiency, where the invention is transformative, but this is not such a case.

46. I therefore answer the third question as follows: the skilled team would include a general formulator, a clinician with appropriate knowledge (whether that be called an endocrinologist or not being unimportant) and a person with PK expertise and understanding at the level of the disclosure of the prior art and of the Patent. The team might in real life number two or three depending on whether the PK expertise was possessed by the clinician or not, and/or on whether the team was in academia or industry.

47. While on this topic I mention two more points:

i) The dispute over the skilled formulator is unimportant to the result since it ultimately went to whether the skilled team reading von Eckardstein would think that the vehicle was not pure castor oil. It is clear and indeed not really disputed that they would be bound to work that out early on, even if they were not previously experienced with oily injectable depots or castor oil.

ii) I agree with Teva that if Grünenthal had been arguing that a high-level PK expert such as Dr Peeters had to be part of the skilled team and would then advise that the prior art could not be progressed because of a lack of any confidence in the absence of individual patient data, then Grünenthal would be in a squeeze when it came to insufficiency, since the Patent lacks individual patient data. But if Grünenthal had ever been arguing that, it faded away.

48. In what follows I sometimes refer to the skilled team and sometimes to its individual members, including when I quote the agreed statement of CGK or the evidence, both of which used e.g. the term "Skilled Formulator". These references should be understood in context. Overall, the relevant addressee is the team, and that team will communicate. But sometimes the focus of what I am saying is on one team member on a particular point.

The process point - "siloed" experts

49. This point was addressed in *Alcon v. AMO* [2022] EWHC 955 (Pat) by Mellor J. at [233]-[235]:

> 233. One of the curiosities in this case was that, despite the agreement that the SO and SE would collaborate, on Alcon's side their two experts were kept firmly separate. This emerged in the course of cross-examination on particular passages in the expert reports which were either identical or very nearly so. Although each expert was given a final or near final draft of the other's report to read, they were not allowed to communicate at all. The result was that any 'communication' between the two experts took place via what the solicitors chose to tell them. This had the further consequence that certain important passages in the respective reports were identified in cross-examination as being identical. Thus some of the critical words with which each expert gave his ultimate conclusions on obviousness were effectively the same. I have no doubt that each expert firmly believed what was set out in his report. Thus, I conclude that the identity in the language used was the result of the solicitors summarising discussions using the same words.
>
> 234. When solicitors are endeavouring to develop expert evidence in accordance with the Medimmune guidance, it is understandable that they seek to exert tight control over the process. However, that control ought not, in my view, to be allowed to interfere with the development of a necessary part of the expert evidence. Real life teams in this field, when developing systems of this nature, would have been engaged in a potentially lengthy and complex project which would have proceeded through a number of stages, including: initial concepts and outline design

> and (if the concept and design were considered to be worth taking forward) development of prototype sub-systems (e.g. laser system, control, measurement/imaging) and testing, more detailed system design, development and testing, assembly and testing of overall system. The level of collaboration would vary considerably though the stages but I have no doubt that the collaboration would be intense when initial concepts and outline design were under consideration. In view of the obviousness issues in the particular circumstances of this case, it is that stage which is critical.
>
> 235. Accordingly, the fact that Professor Mrochen had to develop his views without the benefit of face-to-face discussion with Professor Lawless (and vice-versa) interfered with the presentation of the expert evidence in this case. I will have to assess the impact of this but, from my viewpoint, I think the primary effect was to create difficulties for each of them in cross-examination.

50. Grünenthal said that this guidance had been contravened in the present case. I agree, but to a more limited extent than Grünenthal said.

51. I respectfully agree with Mellor J that members of real teams will communicate, and often they will do so frequently and in detail (not always, though: it must be a spectrum and in some instances a very self-contained task might be delegated with a one-off communication). A process of evidence preparation in patent cases ought to allow this to be reflected. One way to do that might be for the experts to hold an in-person meeting, as happened in the present case at Prof Wu's request. But I do not think that is essential, and in many cases it might be impractical; for many years it has been the practice in patent actions for experts in different disciplines on the same side of a case to learn and understand their colleague's views by reading and reflecting on draft reports. What went wrong in the situation Mellor J was dealing with was, as I understand it, that process being used in a controlling and restricting fashion that was particularly ill-suited to the kind of case under consideration. The use of identical language by the experts was a symptom of the problem. It is important that experts have a genuine opportunity to consider their colleagues' draft reports to raise queries and concerns and to modify their own evidence if required; it must not be a merely mechanical rubber stamp exercise.

52. In the present case, I see no reason to think that the exchange of draft reports in the first round on Teva's side was not adequate in giving time for review and reflection. But in the second round of evidence it does not seem to have been well done. Prof Anderson had only a fleeting opportunity to consider Prof Larsen's "clarification" and that means that a very important plank in Teva's case was not put to the test of how a real team would think about it in consultation with all its members.

THE COMMON GENERAL KNOWLEDGE

53. There was no dispute as to the applicable legal principles: to form part of the CGK, information must be generally known in the art, and regarded as a good basis for future action. Material that would be found by routine research in the

course of developing the cited prior art may be taken into account in assessing obviousness, but it is not CGK as such.

Agreed common general knowledge

54. The parties agreed a Statement of Agreed Common General Knowledge (the "SACGK"). What follows is an edited-down version from which I have removed material which has turned out to be of low, or no relevance. I have also removed diagrams to save space where the explanation in the text is enough on its own. My removing material does not change the parties' agreement that it was CGK. It just means that I do not think reference to it is necessary for my judgment.

55. What follows is not all of the agreed CGK; there were other matters such as Spiegel and Noseworthy, covered below, which were agreed in the course of the trial to be CGK but did not appear in the SACGK.

56. The SACGK made clear that the references to the expert evidence (in square brackets, which I have retained) were for information only; they did not indicate that the entire content of the underlying source paragraph was agreed to be CGK; nor that the references covered all relevant comments on the topic in the expert reports.

57. The SACGK was (mostly) written in the present tense despite identifying the position at the Priority Date. Although stylistically I find this awkward, I have not changed it in view of the effort that would be involved. I have also left unchanged those few instances where the past tense is used.

58. The SACGK contained a section on pharmacokinetics/pharmacodynamics. It reflected what was agreed to be the CGK of the PK expert, *if* one was on the skilled team at all, which was a matter of dispute that I have covered above. I have held that the skilled team would have PK/PD expertise but not at the level argued for by Grünenthal, as to advanced modelling of patient-level data. The relevant section below should be read in that light and represents my decision as to what would be CGK given the nature of the skilled team as I have identified it.

CGK of the clinical member of the skilled team

Testosterone

59. Testosterone is the primary male steroid hormone within the group of steroid hormones known as "androgens".

60. Testosterone promotes, regulates and maintains male characteristics such as larynx development (voice deepening), bone growth/mineralisation, hair growth, muscular development, physical function/strength, prostate growth, sperm/semen production and male sexual function and potency.

Male hypogonadism

61. Male hypogonadism is a clinical syndrome complex defined by low testosterone and low sperm production. Male hypogonadism may be caused by hypothalamic, pituitary or testicular disorders, which can be congenital or acquired in origin. It

is categorized according to whether pathology occurs at the testicular (primary hypogonadism) or pituitary/hypothalamic (secondary hypogonadism) level. [Wu 1/5.18; Anderson 1/47-49]

62. Male hypogonadism manifests as a multitude of clinical symptoms, reflecting the many physiological functions of testosterone in males. The age of onset is a critical influence in the manifestation of hypogonadism because of the central role of testosterone in sexual maturation at puberty. In pre-pubertal patients, testosterone deficiency gives rise to sexual infantilism and delayed puberty. In post-pubertal patients, hypogonadism is commonly associated with decreased libido, erectile dysfunction, oligo- or azoospermia, loss of facial/pubic/body hair, low moods, poor concentration, decreased strength/physical stamina, decreased muscle mass, osteoporosis, anaemia and decreased testicular and prostate size. It should be noted that most of these clinical features are not exclusively specific to androgen-deficiency. [Wu 1/5.21; Anderson; 1/50]

63. A combinatorial approach needs to be taken for accurate diagnosis of hypogonadism, i.e. an approach based on evaluating medical history, physical examination and laboratory testing. [Wu 1/5.23; Anderson; 1/51] The laboratory diagnosis of male hypogonadism is typically done by taking a blood sample from the patient early in the day and measuring their serum testosterone concentration, amongst other factors. While a testosterone level of less than 10 nmol/l is usually considered hypogonadal (with some variation in precise cut-off value depending on how the local laboratory defined normal range), the patient's clinical symptoms will also be taken into account in considering whether a prescription for testosterone substitution is appropriate. For example, in "classical" cases of hypogonadism, such as Klinefelter and Kallmann syndromes, the patient's clinical presentation often clearly indicates testosterone deficiency and the need for replacement therapy. Conversely, in borderline cases (e.g. older men – see next paragraph) where a patient's serum testosterone is slightly low but otherwise they present only with vague symptoms (e.g. lethargy, relatively lower libido than previously), the prescribing of testosterone therapy would be more hesitant, given uncertainties over long-term safety, and lifestyle changes, such as weight loss, might be more appropriate. [Anderson 1/51]

64. In older men, many symptoms associated with ageing, obesity and co-morbidities may mimic some of the less specific features of adult-onset hypogonadism. Serum T levels in men declines progressively after the age of 30-40 years. Serum T levels might drop towards or even into the range compatible with hypogonadism (e.g. approximately 12 – 8nmol/L, discussed below) in a sizeable proportion of men over the age of 50 years. Age-related low testosterone may co-exist with some of the clinical features of hypogonadism, but without identifiable pathologies in the hypothalamus, pituitary and testes. [Wu 1/5.22]

Treatment of hypogonadism

65. The goal of testosterone replacement therapy ("TRT") is to restore testosterone levels in the hypogonadal patient back to the normal range for young healthy adults to reproduce the physiologic target tissue actions of endogenous testosterone. Treatment is generally life-long as the pathological basis of hypogonadism is usually an irreversible disorder of the hypothalamus, pituitary

or testis. [Wu 1/5.38; Anderson 1/54, 55] The choice of therapy depends on multiple factors, including age of the patient, their own preference, arrangements for administration of injections (given that self-administration is not advised for i.m. injections), convenience, cost, available experience (e.g. for subcutaneous implants), adverse effects and availability (as some preparations are available only in some countries or vary significantly in the date they came to market). [Wu 1/5.40; Anderson 1/55.]

66. Normal or physiological serum testosterone levels are described as being in the range 10-35 or 12-35nmol/L, i.e. with a lower limit of 10-12 nmol/L. Levels of 10-35 or 12-35 nmol/L would be viewed as typical and acceptable, in particular in relation to suitable measurements achieved during testosterone replacement therapy – i.e. that when testosterone levels drop to 12 nmol/L, it is acceptable to re-administer therapy. [Wu 1/5.36; Anderson 1/54]

67. Free testosterone in circulation has a short half-life (10 min) and low oral bioavailability due to rapid degradation by the liver to biologically inactive metabolites. To avoid hepatic first-pass metabolism, prolong half-life and improve systemic bioavailability into the general circulation, testosterone needs to be administered in a modified form (with the exception of testosterone pellets). Common modifications to the testosterone molecule include esterification of the 17-beta hydroxyl group with fatty acid esters of different aliphatic or other chain length, which increase the hydrophobicity or fat solubility for prolonged release after parenteral administration by deep i.m. injection as a depot. [Wu 1/5.57 and 5.59]

Licensed treatments for hypogonadism on the UK market

Testosterone implants

68. Implants are the oldest form of testosterone replacement therapy, available since the 1930s/1940s and still marketed and popular in the UK in 2003. They are not available in many other countries, either in Europe or globally. [Wu 1/5.63; Anderson 1/68]

69. Implants provide relatively stable, physiologic testosterone levels for up to 6 months after a single implantation of six 100 mg or four 200mg pellets, which are inserted under the skin of the abdominal wall or hip. This requires minor surgery under local anaesthesia [Anderson 1/69].

70. Testosterone implants are a long-term, cost-effective form of TRT mainly used for maintenance therapy in patients who have already shown satisfactory response and tolerance to androgens (i.e. using shorter-acting preparations initially). Due to the higher likelihood of adverse effects, this mode of treatment is not the most appropriate for older patients. [Wu 1/5.65]

Testosterone oral capsules

71. Oral TU is sold under the brand name Restandol in the UK.

72. The efficacy of oral TU is limited due to unreliable oral bioavailability resulting in fluctuating serum T levels, and a short half-life, which necessitates multiple daily dosing (usually 40 or 80g (1 or 2 x 40mg capsules), three times daily with meals to aid absorption). Nonetheless, oral TU has some useful applications, for example, to induce puberty in adolescents (where lower doses are preferred) or, less commonly, as second line treatment in adults who are intolerant of injections (or implants). [Wu 1/5.67; Anderson 1/71]

Testosterone intramuscular injections

73. At the Priority Date, male hypogonadism is generally treated in the UK with testosterone substitution by i.m. injection. The treatment approach is the same for patients with either primary or secondary hypogonadism. [Wu 1/5.68; Anderson 1/52]

74. The reason why i.m. injections are generally given to men in need of treatment for hypogonadism is that i.m. injections have proven to be reasonably effective in keeping levels of testosterone within normal ranges whilst achieving acceptable levels of patient compliance. Testosterone medicines for administration by other routes such as oral, transdermal and subcutaneous implantation are not as widely prescribed as i.m. injections. [Anderson 1/53]

75. It is understood that, for any medicine that is delivered by injection (including testosterone medicines), the level of discomfort and pain experienced by the patient is related to, among other things, the width of the bore of the needle used to administer the injection – the wider the bore of the needle, the more pain that a patient will likely experience. [Anderson 1/56; Wu 2/5.10(A)]. It is also understood that highly viscous liquid formulations will be required to be administered with wider bore needles than formulations of lower viscosity. [Anderson 1/56; Wu 2/5.10(B)]

76. It is common practice to refer to needles by colour rather than size or gauge number. [Anderson 1/57; Wu 2/5.10(D)] Sustanon and testosterone enanthate are commonly administered using a 21G (green) needle [Anderson 1/63-64; Wu 2/5.10(D)].

77. It is understood that pain and discomfort are also associated with the volume to be injected; the greater the volume, the more likely the patient will experience pain and discomfort [Anderson 1/58; Wu 2./5.10(E)]. In practice, very few medicines require a volume of over 3 ml. Giving i.m. injections more slowly is also known to reduce the pain of injection. Ideally only one injection site is used. [Wu 1/7.20; Anderson 1/58]

78. The following testosterone i.m. injections are available for treating hypogonadism at the Priority Date:

Sustanon

79. Sustanon 250, a mixture of four different testosterone esters (30 mg propionate, 60 mg phenylpropionate, 60 mg isocaproate, and 100 mg decanoate) in an oily

solution is the most commonly prescribed i.m. TRT therapy. It is administered at doses of 250mg (in 1ml). Sustanon 250 is marketed alongside Sustanon 100 which has a lower dose (20mg testosterone propionate, 40mg testosterone phenylpropionate, and 40mg testosterone isocaproate). [Wu 1/5.68; Anderson 1/61]

80. Sustanon 250 is usually administered every 3 weeks and Sustanon 100 is usually administered every two weeks. Sustanon cannot generally be used in patients with nut allergies because of the presence of peanut oil. [Anderson 1/63]

Testosterone enanthate

81. Testosterone enanthate, another commonly available preparation in an oily solution, is shorter acting than Sustanon 250 and administered at doses of 200-250mg (0.8 or 1ml). [Wu 1/5.69; Anderson 1/65]

82. In comparison to Sustanon, testosterone enanthate contains only one testosterone ester. [Anderson 1/67]

Testosterone propionate (Virormone)

83. Testosterone propionate (Virormone) is a licensed i.m. injection containing 100 mg of the ester testosterone propionate in a 2 ml ampoule (with the recommended dose being 50 mg i.e. 1 ml i.m. injection) 2-3 times weekly. However, testosterone propionate, whilst being one of the esters in Sustanon is not viewed favourably on its own given its very short half-life. It was no longer widely used by the Priority Date in the UK, although it still remained an approved drug. [Wu 1/5.72; Anderson 1/72]

84. All marketed preparations of testosterone esters for i.m. injection are known to give rise to high supraphysiological peak T levels within the first week which then fall sharply to the lower limits of normal before the next dose. The supraphysiological peaks of testosterone cause side effects (e.g. acne, high haematocrit). Some patients are disturbed by fluctuations in libido, mood, and stamina associated with the repeated rise and fall of T levels as well as the frequent painful, deep, intramuscular injections. [Wu 1/5.73]

Transdermal patches

85. Testosterone patches, (known as Andropatch) are available in the UK at the Priority Date. These are convenient in that they can be applied directly to the skin by the patients themselves and do not require injections or surgery to administer. However, they require daily re-application. Additionally, to enhance transdermal delivery over the thicker, less vascular and less permeable non-scrotal skin (preferred locations are back, abdomen, upper arm or thigh), alcohol or enhancers are used which cause an unacceptable degree of irritation in a significant number of patients. The concomitant use of steroid cream is suggested to minimise skin reaction to these patches. As a result, testosterone patches are not widely used. [Wu 1/5.76; Anderson 1/70]

Gels

86. Testosterone gels (such as Testogel) are being developed by a number of companies at the Priority Date and are known to be close to obtaining marketing approval in the UK. These are positively viewed for use in elderly men. Gels have obvious downsides (not fully realised at the Priority Date) including the need for daily administration, the relatively large skin area of gel application and the timing of application versus the activities of bathing/showering/swimming. Precautions also need to be taken to avoid potential transference of testosterone to partners and children via skin contact. [Wu 1/5.77; Anderson 1/77]

Testosterone preparations under development at 2003 – intramuscular injections

Testosterone undecanoate

87. Amongst the products being developed at the Priority Date (not including the gels, which came to market at the Priority Date), the long-acting i.m. preparations were the most prominent products under development given the popularity of the existing i.m. preparations and as they address the downside of frequent visits to the clinic for injections. [Wu 1/5.83(D); Wu 2/5.24]

88. Developments (including clinical trials) into oily formulations of i.m. TU led by Professor Nieschlag's group would likely have been known of, although the details of such publications were not. [Wu1/5.1 and Wu 2/5.21; Anderson 1/75]

Testosterone decanoate

89. Testosterone decanoate is one of the esters present in Sustanon 250 but is also a novel preparation under investigation for male hormonal contraception by 2003 [Wu 1/5.83(D); Anderson 1/76]. Testosterone decanoate might have a longer duration of action than testosterone enanthate due to the increased length of the alkyl side chain. At the Priority Date however, testosterone decanoate is less well known than testosterone undecanoate. [Anderson 1/76]

Testosterone buciclate

90. Testosterone buciclate is another long-acting ester [Wu 1/5.83(D); Anderson 1/78], which had been identified as one of the potential drug candidates in a WHO steroid synthesis programme initiated in the 1980s for male hormonal contraception. [Anderson 1/78; Wu 1/6.61(D)]. Testosterone buciclate had shown some promise in the 1990s but by the Priority Date progress of its development had stalled. [Wu 2/5.23; Anderson 1/78]

CGK of the Skilled Formulator

Routes of parenteral administration

91. Parenteral administration means administration via routes that do not involve the digestive tract. The term is often used to refer to administration by injection or infusion, and includes intramuscular (i.m.), subcutaneous (s.c.), intravenous (i.v.) and intra-articular (i.a.) injections. [Larsen 1/37]

Intramuscular (i.m.) administration

92. Intramuscular injectable drug products have been around since the late nineteenth century. I.m. is one of the most common routes of parenteral administration. It provides a means for sustained release of drugs (referred to as the "depot effect") formulated as aqueous or oily solutions and suspensions. This route of administration is often used for drugs which are intended to have effect over an extended period of time. [Larsen 1/42]

93. At the Priority Date, the most commonly used formulation for i.m. depot injectables were oily solutions and aqueous suspensions, as drug substances administrated as aqueous solutions are absorbed more rapidly. [Larsen 1/43; Østergaard 2/5.6]

94. Suspensions: Water insoluble drug complexes may be administered i.m. (or sometimes s.c.) as a suspension. In a suspension, solid particles of the drug or a prodrug thereof are dispersed/suspended in the dispersion medium. At the Priority Date, suspensions included formulations of corticosteroids, insulins, steroid hormones (in oil vehicles) and drugs for the treatment of mental disorders. Suspensions may be used when a drug or prodrug is insoluble in the vehicle. In some instances, there may be circumstances where formulating a suspension may be preferred, for example due to a slower rate of drug absorption compared to oily solutions.

95. Oily solutions: In an oily solution, the drug compound or a prodrug thereof is dissolved in the oily vehicle. Oily solutions have certain benefits over suspensions because manufacturing and stabilisation of suspensions is more challenging.

96. If an oil solution was desired and a drug compound (known as the "active pharmaceutical ingredient" or "API") was insoluble in a particular oil, or a particularly high drug loading was needed (without commensurate solubility in that oil), there would be various options. Firstly, to enhance the oil solubility of the drug compound, for example by changing the oil or adding co-solvents (as solubility will likely differ depending on the composition of the oily vehicle used), and/or secondly, by changing the properties of the drug substance e.g. by prodrug derivatization.

97. The i.m. administration route is limited (*inter alia*) by the maximum volume which can tolerably be injected into the patient. In terms of volume, the i.m. route is usually around 2 - 4 ml if administration is into the gluteus medius, whereas

the maximum volume that can be injected into the arm without too much discomfort is less, at around 0.5 ml. [Larsen 1/44]

Commercially available oily depot injections

98. By the Priority Date, there were several commercially marketed parenteral oily depot injections available on the market [Østergaard 1/5.9; Larsen 1/116].

99. On a general level, the clinical indications for which these sorts of preparations had been developed would be known, including hypogonadism using testosterone products and others such as neuroleptics, slow-release hormone preparations for contraception and hormone replacement. [Østergaard 1/5.11]

100. These commercially marketed parenteral oily depot injections were developed to prolong the action of the administered compound, often in combination with a prodrug approach (for instance in the form of ester derivatives). The recommended injection intervals would be a primarily clinician-led issue. However, the injection intervals (typically around 2-4 weeks) reflect the duration of action, which is achieved by a combination of the properties of the drug/prodrug itself and the formulation factors (as well as the physiological factors). [Østergaard 1/5.13]

101. It is easier to obtain approval of a formulation comprising known components that are, or previously have been, used in approved injectable products. To adopt a formulation with more of a component than had previously been approved may require further safety testing. [Østergaard 2/5.5; Larsen 1/40; Larsen 2/50.2]

The oil vehicle

102. "Vehicle" is a term used by formulators to refer to the medium, e.g. the solvent, in which the API is administered. The vehicle (or carrier), composed of inactive components (ideally) and the API constitute the formulation (drug product); thus, the vehicle does not refer to the formulation but only the part of the formulation without the API.

103. At the Priority Date, non-aqueous solvents available for use as oily vehicles for parenteral administration were well established. Such oils include fixed (non-volatile) oils of vegetable origin such as olive oil, corn oil, sesame oil, almond oil, peanut (arachis) oil, soya oil, cottonseed oil and castor oil, as well as medium chain triglycerides such as Viscoleo (fractionated coconut oil). [Østergaard 1/5.14; Larsen 1/54]

104. Certain synthetic alternative vehicles would also be considered to be suitable including isopropyl myristate, ethyl oleate, benzyl benzoate. [Østergaard 1/5.15; Larsen 1/54].

105. Fixed and synthetic oils are both considered "oil". They are described alongside each other as they act in a similar way. [Østergaard 1/5.18; Larsen 1/54-55].

106. Oils differ in their fatty acid composition [Østergaard 2/5.22; Larsen 1/71], and there were resources setting out their relevant properties, including The

Handbook of Pharmaceutical Excipients [JO-6/ SW-13], the European Pharmacopeia [SWL-24/ SWL-32], the Merck Index [SWL-18] and Martindale [JO-7]. [Larsen 1/56; Østergaard 1/5.19-5.20]

107. In the preparation of an oily depot injectable formulation, the vehicle has to be chosen with care, considering the drug to be dissolved (including its solubility), the desired release profile (or depot effect), the condition to be treated and the possible side-effects of the drug/oil formulation. These criteria would be established as part of the objectives for any particular drug development project. [Østergaard 1/5.21; Larsen 1/58-74].

108. Further criteria include: [Østergaard 1/5.22]

    i) Chemically, the oil should be stable and should not react with the medication to form toxic products. Fixed oils must be free from rancidity and must not contain mineral oils or solid paraffins, as these are not metabolised by the body and might eventually cause tissue reaction and even tumours.

    ii) Biologically, the oil should be inert, non-toxic, nonantigenic, non-irritant, biocompatible, pyrogen free, and it should be absorbed from tissues after administration, leaving no residues. Any breakdown products should also be non-toxic and be absorbed from the injection site. The vehicle should have no pharmacological action of its own nor potentiate the activity of the medicament.

    iii) Physically, the oil should be a good solvent or dispersing medium for the drug. A high loading capacity is desired such that sufficient drug can be administered without the injection of excessive volumes of oil. The vehicle should also remain fluid over a fairly wide range of temperatures and should not have a high viscosity for good syringeability and injectability.

Solubility

109. Solubility is the maximum concentration of a solute that can dissolve in a solvent at equilibrium at a given temperature. It is a property of the solute in the given solvent. [Larsen 1/59]

110. The solubility of the drug or prodrug in the selected oil is important, and the solubility of a particular drug or prodrug will vary depending on the composition of the oily vehicle. In an oily solution, the oily vehicle needs to be capable of solubilizing a sufficient amount of the drug or prodrug in question to enable a formulation with the required dose. [Larsen 1/60]

111. In general terms, it is expected that "like dissolves like" (e.g. non-polar dissolves non-polar, polar dissolves polar etc). Generally therefore, the more lipophilic the drug or prodrug molecule, the more soluble it will be in any given oil. [Larsen 1/61]

112. The solubility of a drug (or prodrug) in a given oil (or oils) may be determined by carrying out routine experiments. [Larsen 1/62; Østergaard 2/5.10]

113. The solubility of a drug or prodrug in a given oil may be further enhanced by the addition of one or more suitable solvents (preferably one) to the oil, which should be miscible with the oil in question. [Larsen 1/63; Østergaard 1/5.42; Østergaard 2/5.13]

Drug absorption from oil solutions

114. Oily solutions can give rise to a depot effect because, upon i.m. administration of an oily solution into an aqueous environment, the oil forms a depot at the injection site. The oil essentially acts as a drug reservoir, with the drug being slowly released from the oil formulation, transported through the surrounding tissue and absorbed into the blood circulation before it becomes bioavailable. [Østergaard 1/5.23 and 2/5.24; Larsen 1/75]

115. Following i.m. injection, an oily parenteral formulation forms a localised depot at the injection site, whose spread depends on the formulation, its viscosity and surface tension, the needle size and the force used during injection. Firstly, following i.m. administration, the drug (which is dissolved in the oil) needs to diffuse within the oil depot to the interface between the oil and the tissue. The dissolved drug molecules partition from the oil formulation (the "oil phase") into the aqueous interstitial fluid (the "aqueous medium") and are then subsequently absorbed into the bloodstream for transport to the target site before the drug substance becomes bioavailable. [Østergaard 1/5.24 and 2/5.24; Larsen 1/75-76]

116. Drug partitioning from the oil phase to the aqueous medium is believed to be the rate-limiting step controlling release of drug molecules from oil solutions. It follows that the absorption rate and, hence, the depot characteristics can be altered by manipulating the factors affecting the partition coefficient, for example, the nature of the vehicle or the lipophilicity of the drug (e.g. through the use of prodrugs). [Østergaard 1/5.25]

117. The persistence of the oil depot is important in determining the period over which the drug is released from the formulation. The oil itself is very slowly cleared from the injection site and this enables it to act as a drug reservoir. Clearance of the oil, and thus *in vivo* absorption, was thought to occur via absorption through the capillary blood vessels, by lymphatic absorption, by phagocytosis and by metabolism in situ followed by absorption. The contribution of each of these pathways is expected to depend on the nature of the oil itself and the formulation and could well depend on the volume and frequency of dosing, and the administration site due to the anatomical difference in the nature and distribution of capillary and lymph vessels. [Østergaard 1/5.26].

Factors that influence the depot effect

118. The rate of drug release from oily solutions is dependent on a number of factors, including the lipophilicity of the vehicle, lipophilicity of the drug, the viscosity of the vehicle, and the volume of the injected formulation. In some instances, clearance of the oil vehicle from the injection site can also play a role. [Østergaard 1/5.27; Larsen 1/78]

119. These factors all play a role in the overall rate of drug release and the resulting depot effect, the mechanism of drug release has not been fully elucidated by the Priority Date. [Østergaard 1/5.24-5.25; Larsen 1/79]

Lipophilicity of the vehicle / lipophilicity of the drug / partition coefficient

120. The partition coefficient of a drug substance is the ratio between the concentrations of the drug in two immiscible solvents (e.g. oil and water) at equilibrium. The partition coefficient of a drug reflects the tendency of the drug to stay in the oil compared to its tendency to move into the aqueous phase. The higher the partition coefficient, the longer the drug will remain in the oil. [Østergaard 1/5.24, 5.32-5.33; Larsen 1/80]

121. Drug partitioning from the oil to the aqueous tissue fluid was suggested to be the rate-limiting step in drug release from oil solutions. Therefore, depot characteristics may be controlled by modifying the partition coefficient or the factors relevant to it, including the lipophilicity of the vehicle and/or the drug. [Østergaard 1/5.2, 5.27-5.33; Larsen 1/81]

122. Therefore, drug partitioning and/or the partition coefficient can be changed by, e.g. (i) altering the composition of the oil vehicle or (ii) altering the lipophilicity of the drug substance (e.g. by the use of prodrugs). [Larsen 1/82]

123. In relation to (i), using an oil vehicle in which the drug was more soluble would generally be expected to increase its tendency to stay in the oil phase. The choice of the vehicle can exert an effect on the absorption of lipophilic drugs from oil solutions, particularly where partitioning of a drug from the formulation (such as oily depot formulations) may be the rate-limiting step. Usually, the more lipophilic the vehicle, the slower the release rate of the drug. A high affinity of the drug for the oil will result in a slower rate of release of the drug from the formulation into the aqueous interstitial fluid at the injection site and, therefore a slower absorption rate and a longer depot effect. [Østergaard 1/5.28; Larsen 1/82]

124. In relation to (ii), increasing the lipophilicity of drugs by chemical modification is another means of reducing the rate of partitioning of drugs from oil solutions into the local interstitial media and enabling sustained biological activity. It was known that esterification of a drug substance containing a carboxylic acid or hydroxyl group (including testosterone) to obtain water-insoluble oil-soluble (lipophilic) prodrugs (e.g. prodrugs with long alkyl chain length) would prolong the duration of action. This prodrug approach was also known to be widely used for injectable formulations in antipsychotic and hormone replacement therapy. As such, it was understood that preparing a lipophilic prodrug, and also increasing the lipophilicity by increasing the alkyl chain length of the ester, would result in slower release due to the increased oil-water partition coefficient. When the ester prodrugs are present in the oil vehicle, they are protected against degradation. Once the ester prodrugs are released from the oil and transported into the aqueous environment in the body, they are subjected to enzymatic cleavage by esterases and converted into its active form (the parent drug). [Østergaard 1/5.30; Larsen 1/82]

125. When testosterone is injected as a solution in oil, only a small and transient androgenic (i.e. therapeutic) effect is observed due to rapid metabolism and excretion of the steroid. Improved plasma levels of testosterone were achieved with testosterone esters, with the duration increasing with the chain length of the fatty acid pro-moiety (of the ester). This is also accompanied by a decrease in the aqueous solubilities of the esters, a corresponding increase in the oil/water partition coefficient and a longer depot effect. [Østergaard 1/5.31]

Vehicle viscosity

126. The viscosity of the formulation can influence the shape of the depot formed and the extent of spreading. Viscous oils are thought to spread less (i.e. to maintain a coherent oil depot). [Østergaard 1/5.24; Larsen 1/84]

127. The vehicle viscosity also changes the diffusion rate of the drug/prodrug inside the oil. Increasing viscosity lowers the diffusion rate of the drug within the oil to the edge of the depot. [Østergaard 1/5.24; Larsen 1/85]

128. Increasing the viscosity of a formulation in an attempt to enhance the depot effect, is subject to practical considerations such as the syringeability and injectability of the formulation. [Østergaard 1/5.35]

Volume of administration

129. The volume of injection may also affect the absorption rate. Although the impact of altering the injection volume on the depot effect is not fully understood, increasing the injection volume has been observed to result in a longer duration of action. [Larsen 1/86]

130. This can most likely be explained by a decrease in surface area to volume ratio. The volume of an injection will affect the size of the oil depot formed. A small volume may provide a large surface area:volume ratio; thereby providing a relatively larger surface area across which dissolved drug can be released into the interstitial fluid, resulting in higher absorption rates. Conversely, if the volume is increased, while the surface area increases, the surface area:volume ratio will decrease, resulting in lower absorption rates. Such a correlation is thought to arise as a result of the spheroidal shape assumed by an oily formulation after a single injection. Similarly, a large volume split up into multiple injections of smaller volumes may result in higher absorption rates due to higher surface area compared to a single injection. [Larsen 1/86; Østergaard 1/5.36]

131. Therefore, a single, large volume for an injection may result in lower absorption rates and be preferred, for example, for a more sustained release of the drug. [Østergaard 1/5.36]

Clearance from the injection site

132. For very lipophilic compounds, with strong affinity to the oil, the depot effect may not solely be explained by the partitioning process. In this case, the release of compound from the oil may follow the fate of the oil in the body i.e. the

compound would be released when the oil is broken down by metabolic degradation. [Østergaard 1/5.26; Larsen 1/88]

133. Exactly how the oil is cleared from the injection site was not elucidated at the Priority Date, although various processes such as absorption through the capillary blood vessels, by lymphatic absorption, by phagocytosis and by metabolism in situ followed by absorption are suggested to contribute. [Østergaard 1/5.26; Larsen 1/89]

Syringeability

134. Syringeability is the ability of the formulation to be drawn up into the needle prior to administration. The syringeability of oil formulations is inversely related to the viscosity of the formulation. [Larsen 1/64; Østergaard 2/5.11]

135. Oils are Newtonian fluids, which means that their viscosity is generally straightforward to measure. [Larsen 1/65; Østergaard 2/5.11]

136. The viscosity of oils is temperature dependent. When considering syringeability, the viscosity of the formulation at the temperature at which a formulation is likely to be drawn up is of most relevance. Where possible, storage and injection at room temperature is preferable from a clinical and practical perspective. [Larsen 1/66; Østergaard 2/5.11]

Injectability

137. Injectability refers to the ease with which a formulation can be injected. It is influenced by a variety of factors including the viscosity of the formulation, (which in turn affects the gauge of the needle, the injection time and the forces required to administer the injection), and the injection volume. Factors related to the injectability have a direct effect on patient comfort during injection. Obviously, it is desirable to minimise discomfort where possible. This can be more important where injections are administered more frequently. [Larsen 1/68; Østergaard 2/5.11].

138. Adding excipients, such as oil miscible co-solvents, or mixtures of different oils (including synthetic oils) possessing differing viscosities, may impact or likely reduce the viscosity of the oily vehicle [Larsen 1/63; Østergaard 2/5.13; Larsen 1/72]

CGK of the pharmacokinetic expert

Pharmacokinetics/pharmacodynamics

139. The term "pharmacokinetics" describes the study of the time course of a drug in the body including the absorption, distribution, metabolism and excretion ("ADME") of a drug and the relationship of these processes to the intensity and time courses of pharmacologic (therapeutic / desired and toxicologic / unwanted) effects of drugs. "Pharmacodynamics" ("PD") deals with the time course of drug

action and is intimately linked to PK. Understanding ADME and the relationship between PK and PD is fundamental to develop drugs effectively. [Peeters 1/5.4]

140. In general, PK may be broadly defined as the study of what a subject does to a drug (e.g. impact of dose on plasma concentration) whereas PD is the study of what the drug does to the subject. [Peeters 1/5.5]

141. In preclinical development, PK/PD is applied to establish the relationship between the plasma concentration range for which the relevant pharmacological effect can be measured in the appropriate animal species. Through physiological-based pharmacokinetic (PBPK) modelling, this animal data can be extrapolated to man. In clinical studies, PK/PD is used to support dose-escalation in First into Human studies and dose finding in subsequent patient studies. [Peeters 1/5.7]

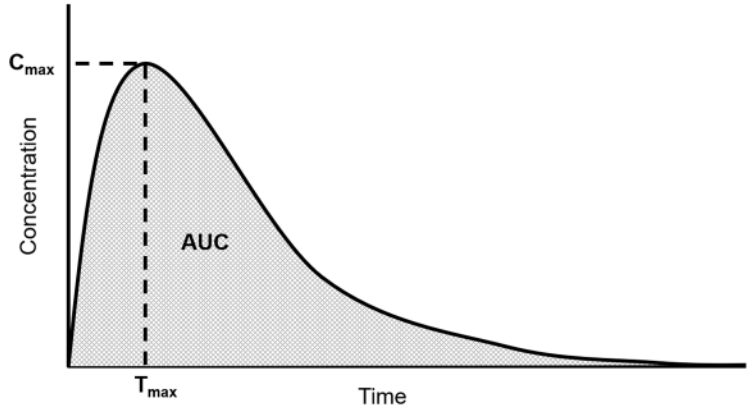
PK parameters

142. "C_{max}" is the term used to describe the highest (peak) concentration of a drug in, for example, the bloodstream or another part of the body following drug administration. [Peeters 1/5.8]

143. "T_{max}" is the time when C_{max} is reached. [Peeters 1/5.9]

144. The Area Under the Curve ("AUC") reflects the exposure of the body to a drug after administration of a dose and is expressed as the concentration of a drug as a function of time. It is dependent on the dose administered and the rate of elimination of the drug from the body. To calculate the total amount of drug eliminated by the body the amounts eliminated can be added up in each time interval, from time zero (the time of administration) to infinite time. This total amount is representative of the fraction of the dose administered that reaches the systemic circulation. Relative bioavailability (the rate and extent to which the drug is absorbed and reaches the circulation) can be determined by comparing the AUC of a drug delivered intravenously to the AUC of the same drug delivered by another means (e.g. orally or intramuscularly) as the absolute bioavailability of any drug delivered intravenously is theoretically 100%. [Peeters 1/5.10]

145. Below is a sample of a plasma concentration-time curve following extravascular administration to illustrate the parameters referred to above:



[Peeters 1/5.11]

146. The half-life ("$t_{1/2}$") is the length of time it takes for the concentration of a drug in the body to fall by half. [Peeters 1/5.12]

147. "Clearance" is the measure of elimination of the drug from the body. As clearance decreases, the half-life would be expected to increase unless impacted by the volume of distribution. [Peeters 1/5.14]

Steady state

148. Steady-state describes a situation where the minimum (or trough) plasma concentration of the drug (C_{min}) does not change upon multiple dosing. As a "rule of thumb" plasma concentrations should be measured 3-4 times before a subsequent dose is given to demonstrate that steady-state has in fact been reached for a particular dose or dosing regimen. [Peeters 1/5.21]

149. There is a lag period before the drug concentration exceeds the minimum effective concentration ("MEC"). The duration of a drug's effect is reflected by the time the drug level is above the MEC and its intensity relates to its concentration above the MEC. [Peeters 1/5.26]

150. However, undesired drug effects may result above a certain concentration. Unless the drug is not toxic, increasing the dose is not a useful strategy for extending a drug's action but rather another dose of a drug should be given to maintain concentrations within what is known as the "therapeutic window". This is the concentration range at which there is efficacy without unacceptable adverse events. The upper and lower limits of the therapeutic window of different drugs can be highly variable. [Peeters 1/5.27]

151. The typical objective is to maintain steady-state concentrations of a drug within a therapeutic window, particularly avoiding peak concentration levels rising above the MEC for adverse response. The therapeutic window associated with therapeutic efficacy and minimum of adverse events is based primarily on clinical input on what the preferred range would be. [Peeters 1/5.28]

Multi-dosing

152. It is common to administer drugs in a series of repetitive doses or as continuous infusions to maintain a steady-state drug concentration within the therapeutic window. The objective is therefore to calculate the appropriate maintenance dosage (dose amount and interval between doses) to achieve this steady-state concentration. In order to maintain the target concentration, the rate of drug administration is adjusted such that the rate of input equals the rate of elimination. [Peeters 1/5.29]

153. The average concentration of a drug in the plasma in multiple dosing at steady state can be predicted using a single-dose study. In a multi-dosing regimen, at steady state, the plasma concentration of drug at any time during any dosing interval should be identical to the concentration at the same time during any other dosing interval. [Peeters 1/5.30]

154. When a multiple dosing regimen is initiated, during each interdose interval plasma concentrations will increase, reach a maximum (C_{max}) and then decline. For drugs administered in a fixed dose at a constant interval, a second dose is administered before the first dose is completely eliminated and therefore the plasma concentrations will be higher than those from the first dose. This accumulation will continue to occur at a decreasing rate with the number of doses until steady-state is reached. The rate and extent of accumulation of a drug is a function of the relative magnitudes of the half- life of the drug and the dosing interval. [Peeters 1/5.31]

Loading Dose

155. A dose, or multiple doses, administered at the beginning of a therapy with the target of reaching the therapeutic window quickly are referred to as "loading doses". It can be beneficial to give a loading dose where, relative to the temporal demands of the condition being treated, the time required to achieve steady-state by the administration of a drug at the same interval is long. [Peeters 1/5.32]

156. To calculate the appropriate magnitude for the loading dose, it would be necessary to consider the target plasma concentration of the drug, the PK parameters after single and multiple dose (at steady-state) and the relative bioavailability of the dose. [Peeters 1/5.33]

157. There can be significant disadvantages to using a loading dose. The high concentration abruptly administered in a loading dose could lead to unwanted (severe) adverse events in certain individuals. [Peeters 1/5.34]

158. In relation to intravenous administration, it was generally advisable to divide the loading dose into a number of smaller doses, administered over a period of time. [Peeters 1/5.35] However, regardless of the route of administration, loading dose could be administered as a series of doses rather than just a single dose, depending on the characteristics of the drug. [Batchelor 1/39; Peeters 3/4.21]

PK study design

159. In the first instance, it would be desirable to collect samples to plot the full profile, with as frequent as possible sampling around the expected C_{max} of a single dose of the drug. Samples will be taken for a minimum period of four to five half-lives, as estimated using an animal model. [Peeters 1/5.36] In cases where four to five half-lives would be too long a period from a clinical perspective, shorter periods may be considered. [Batchelor 1/40 and Peeters 2/6.16] Once this data has been obtained, a multi-dosing study will be carried out. With a constant dose regimen, steady-state is usually reached after around four to five half-lives. In order to determine whether steady-state has been reached during the multi-dosing regimen, samples will be taken just before the next dose of the drug (the "trough" concentration). Any increase in the trough concentration from one dose to the next is indicative of accumulation. Where the trough concentration does not change after 3-4 doses, it can be comfortable to conclude that steady-state has been reached in the multi-dose regimen. Data should then be collected to plot a full profile of the next dose within the multi-dose regimen. [Peeters 1/5.36]

Disputed CGK

160. With their agreed statement of CGK, the parties identified the areas of disagreement on the CGK as lying in the following areas:

    i) On clinical CGK:

        a) The posology of testosterone enanthate ("TE").

    ii) On formulation CGK:

        a) The extent to which viscosity, syringeability and injectability are relevant factors in the preparation of an oily depot formulation; and

        b) Whether it was CGK that castor oil (alone) would be too viscous to be acceptable for i.m. injection in humans.

    iii) On PK CGK:

        a) Whether PK modelling would be used in most if not all circumstances when considering dosing regimens and regardless of the stage of drug development from preclinical to Phase IV trials.

<u>The clinical CGK dispute.</u>

161. The issue about the posology of TE arose from the fact that there was published guidance in the British National Formulary ("BNF") to give TE with a loading dose (250mg every 2-3 weeks) and later a maintenance dose (250mg every 3-6 weeks), referred to as a "mixed posology". The significance to the issues of this point was for Teva to be able to show some CGK use of loading doses in testosterone replacement therapy.

162. Normally, the BNF would be regarded as a reliable source of CGK information, and the complication in the present case arose because the evidence of Profs Anderson and Wu was that neither of them normally gave TE in a loading dose. Prof Wu was slightly more emphatic about this. In addition, there were other well-known texts that referred only to maintenance doses.

163. I find that the skilled clinician would be aware that general practice was to give TE at 2-3 week intervals and not to use a loading dose. If they went to look up the BNF rather than any other source they would be surprised at its contents in this regard and would not regard it as sound advice (so not a "good basis for further action" in the terms of the law of CGK). They would not know why the BNF was out of step with real practice on this point, although a possible reason could be that it was out of date, but would not think they needed to know why for practical purposes.

164. I should make it clear that this was quite a minor point: since the general concept of a loading dose was accepted to be CGK the point could only serve to improve Teva's case by additionally showing its use in the context of testosterone

replacement therapy and I agree with Grünenthal that the skilled clinician would not unthinkingly accept that even if a loading dose was in use for TE it was therefore appropriate for TU.

165. Teva sought to downplay the importance of this point by arguing that Grünenthal's witnesses accepted that a loading dose was an obvious thing to do from von Eckardstein based on the broader CGK of loading doses generally. That is a different question and I address it below.

Negative attitude to testosterone replacement therapy?

166. This was a point run by Grünenthal which was not on the parties' list of CGK disputes but which I think most naturally fits here; its impact comes in at the first stage of the obviousness case over von Eckardstein.

167. Grünenthal said that the field was "a Cinderella of hormone therapy: somewhat underrated and overlooked", with only a few people working on it, little R&D and only a modest array of long-established treatments. Grünenthal also said that insofar as there was any interest it was in more accessible user-friendly options such as gels.

168. I do not agree with Grünenthal on this. Work was being done to produce better treatments and so there was clearly a commercial incentive sufficient to motivate development. The fact that the field was a relatively narrow one does not mean that there was no sufficient interest to improve things. The fact that von Eckardstein was working on injectables itself shows that there was enough interest, and the existence of that sort of work, if not the details of the papers, was accepted to be CGK – see above.

The formulation CGK disputes

169. In addition to the two points identified by the parties as set out above, there was a disagreement about what the CGK was (and/or what would be found in the course of routine development work) as to the proportions of castor oil and co-solvent(s) in formulations in the literature. I am going to deal with that point when I come to obviousness, conscious that aspects of it concern CGK and other aspects concern what was obvious to find or to reason.

170. In relation to the first of the two points identified by the parties, it was clear that viscosity, syringeability and injectability were relevant factors in the preparation of oily depots, in the sense that there would come a point at which a depot injection could not practically be administered at all, or only with severe pain. Prof Østergaard accepted that viscosity (in particular) would be important and just qualified that by saying that solubility was a more crucial factor, which I accept.

171. Thus the focus of the argument was about whether castor oil would be recognised as a matter of CGK to be too viscous for use as a vehicle on its own. If it were, the reader of von Eckardstein would know as soon as they read the document that there must be something in the TU formulation used as well as castor oil.

172. In my view the skilled formulator would know as a matter of CGK that castor oil was highly viscous, and significantly more viscous than the other oils typically used in injectable i.m. formulation. However, they would not be aware of any injectable formulations which they would know had castor oil alone as the vehicle; Counsel for Grünenthal accepted that there were none. They would not have any experience of injecting castor oil alone. Prof Larsen did, in an experimental setting, but she was unusual in this respect.

173. Since hands-on experience would not be part of the CGK, attention focused on what would be in the literature. It was accepted that the viscosity of castor oil could be looked up readily; it is 986 mPas at 20°C (lower at higher temperatures). While this is a high value, it would not tell the skilled formulator that castor oil could not be injected unless the skilled formulator also knew as a matter of CGK some maximum viscosity for injectability. The Patent at [0030] gives a value of 100 mPas, but Grünenthal did not accept that that was an accurate statement of CGK and Teva accepted that a statement in the Patent is not binding as to the CGK. Teva's only literature source for such a maximum value was a textbook in Danish which was only introduced into the case at trial after Prof Larsen mentioned it in her oral evidence. I was not satisfied that it was a CGK source, and certainly not in the UK (which I mention because it was common ground that it is CGK in the UK that matters, albeit that international publications may contribute to CGK in the UK).

174. Grünenthal pointed to various products which were known to have castor oil in their formulations and in relation to which there were (it said) no reports in the literature of problems with injectability. However, this does not mean much at all unless the skilled formulator believed they were formulations where the vehicle was *only* castor oil, and that was not the case.

175. My conclusion is that it was not shown by Teva that it was CGK that the viscosity of castor oil was so high that it was *impossible* to use it as a vehicle on its own. The skilled formulator would think that it was highly viscous and that it would be very likely to be desirable to use an additional ingredient in a formulation, to reduce the overall viscosity.

176. This point ultimately does not matter, though, because working from von Eckardstein the skilled formulator would inevitably find when they tried to dissolve TU in castor oil alone that there must have been another component in the formulation.

The PK CGK dispute

177. The issue here is whether complex and sophisticated PK modelling based on data at the individual patient level was necessary in order to undertake formulation development. I have dealt with the substance of this point in relation to the skilled team, above.

THE PATENT

178. The Patent begins with the following introductory paragraph:

> [0001] The present invention relates to the field of pharmaceutical formulation science as well as the field of therapeutic applications of hormones in hormone replacement therapy in men and in male contraception. In particular, the invention relates to compositions of testosterone esters in castor oil that upon intramuscular injection provides reliable physiological acceptable serum testosterone levels for a prolonged period.

179. And at [0006]-[0007] it describes the general and developing situation in relation to i.m. injections of testosterone esters; it describes the problem of variations in patient well-being due to short-term fluctuations of serum testosterone levels resulting from the pharmacokinetic profile after intramuscular injection:

> [0006] Current standard therapies aims at restoring physiologically relevant levels of testosterone in serum, which applies to concentrations of about 12 nmol to about 36 nmol. Intramuscular injection of testosterone esters, such as testosterone enanthate or testosterone cypionate, administered every two to three weeks, still represents the standard of testosterone replacement therapy in most countries of the world. Apart from the inconvenience of frequent visits to the doctor's office, the patients complain about variations in well-being due to short-term fluctuations of serum testosterone levels resulting from the pharmacokinetic profile after intramuscular injection of for example testosterone enanthate.
>
> [0007] Recently, the use of testosterone esters with longer aliphatic chain length and/or higher hydrophobicity, such as testosterone undecanoate, has become interesting in terms of prolonging the interval between injections. Longer intervals between injections are advantageous from a patient's point of view.

180. The Patent records prior art attempts to address these issues (including work from the Behre/Nieschlag/von Eckardstein group), but notes at [0015]:

> [0015] However, it is well known that therapies with testosterone esters, such as testosterone undecanoate, still need to be improved in terms of achieving reliable serum testosterone levels in the physiologically acceptable range for a prolonged period of time. There is a need of providing reliable standard regimens acceptable for a broad population of men in need thereof, preferably regimens without the need of occasional control of serum testosterone levels, and regimens wherein steady state conditions are achieved within a shorter time period.

181. The invention is then summarised from [0016] to [0020], I note the relevant provisions below:

> [0016] The present invention relates to injectable compositions comprising long-term acting testosterone esters for use in testosterone replacement therapy. Upon injecting the compositions, physiologically normal levels of testosterone in serum are reached within a short time period. Furthermore, the physiologically normal serum levels of testosterone are maintained for an extended period of time, without showing fluctuations

> in the hypogonadal range. The compositions are chemically stable with respect to the testosterone ester as well as physically stable with respect to the vehicle for a prolonged time.
>
> [0017] … in a first aspect the present invention relates to a composition intended for injectable administration, such as by intramuscular injections, the composition comprises a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, … preferably testosterone undecanoate; and a vehicle, which comprises castor oil and a co-solvent.
>
> [0018] … The method comprises administering by injection a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates, such as testosterone undecanoate, according to a particular scheme comprising:
>
> > i) an initial phase of 2 to 4 injecting a dose of said testosterone ester with an interval of 4 to 8 weeks between each administration, each dose is in an amount therapeutically equivalent to a dose of testosterone undecanoate of between 500 mg and 2000 mg; followed by
> >
> > ii) a maintenance phase of subsequent injecting a dose of said testosterone ester with an interval of at least 9 weeks between each subsequent administration, each dose is in an amount therapeutically equivalent to a dose of testosterone undecanoate of between 500 mg and 2000 mg
>
> [0020] … further aspects relate to the use of a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates… for the preparation of medicaments that are in a form for parenteral administration, such as in a form for intramuscular injection and further comprises a vehicle comprising castor oil and a co-solvent.

182. [0021] contains a similar statement to [0015] and I will not set it out in full but bear it in mind.

183. [0023]-[0024] discuss the depot effect, factors affecting its achievement and the potential difficulty in predicting what kind of vehicles will be suitable:

> [0023] Without being adapted to a particular theory, a number of parameters will influence the pharmacokinetic profile of a testosterone ester that is injected intramuscularly, in particularly if a depot effect is desirable. A depot effect can in general be achieved by selecting a testosterone ester that slowly degrades into free testosterone once it has entered the blood circulation. An additional factor contributing to the depot effect is the diffusion rate of the testosterone ester from the site of injection to the circulating blood system. The diffusion rate may depend on the dose and the volume injected in that the concentration gradient of the testosterone ester at the site of administration is thought to affect the

> diffusion rate. Furthermore, the type of vehicle injected together with the testosterone esters will influence the rate of diffusion of testosterone esters from the vehicle into the surrounding tissues and the rate of absorption into the blood circulation. Therefore, the partition coefficient (n-octanol-water partition coefficient) of the testosterone ester in the vehicle as well as the viscosity of the vehicle should be considered in order for adapting a depot effect following intramuscular injection of testosterone esters.
>
> [0024] Moreover, for safety reasons and ease of handling, the testosterone ester should be proper dissolved in a vehicle. Often it is impossible to predict which kind of vehicles that both can dissolve the testosterone ester and provide the needed depot effect. Therefore, mixtures of various solvents may be required, although undesirable from a manufacturing point of view.

184. Paragraph [0030] refers to issues with injecting very viscous vehicles:

> [0030] Injection of high viscous vehicles, such as castor oil, is associated with technical limitations to the size of cannula due to the resistance of the vehicle when passing the cannula. It is commonly recommended that the viscosity of an injection solution should be kept below 100 mPas. In certain instances, the viscosity of a final product, ready to be injected, such as a re-constituted product may be, e.g., less than 100 mPas, such as 90 mPas, 80 mPas, 70 mPas at room temperature. In some embodiments, the viscosity of the vehicle is less than 60 mPas, 50 mPas, 40 mPas or 30 mPas at room temperature.

185. As I note when dealing with CGK, the fact that the Patent contains the statement as to what is "commonly recommended" does not mean that it is necessarily CGK, but it is some evidence that it may be.

186. Paragraphs [0032] to [0041] give various ranges for the parameters of the ingredients of the vehicle and discuss choices of co-solvent. Benzyl benzoate is particularly mentioned at [0037] along with the possibility of using ethanol or benzyl alcohol. [0038] refers to the possibility of TU being in suspension rather than in solution. [0044] explains the significance of volume to release rate and the practical limitations applying to it:

> [0044] The volume that can be injected intramuscularly is known to affect the release rate of an active principle from a vehicle. An injection volume of 5 ml is generally considered as the maximum volume that can be administrated by one single intramuscular injection to one injection site. When intramuscular injection of volumes greater than 5 mL is required, the injection volume needs to be divided into two or more separate injections to different injection sites. However, multiple injections for the administering of one dose are generally not preferred because of the inconvenience conferred to the patient.

187. [0054] refers to other excipients which may be present in the vehicle:

> [0054] It is submitted that the vehicle, wherein the testosterone ester is dissolved, may further comprise one or more excipients, such as preservatives, stabilising agents, other co-solvents and antioxidants. Suitable vehicles are sterile, pyrogen-free and free of particles.

188. From [0055] the specification turns to the posology of the invention and it is in these paragraphs that the basis for the relevant features of the use claims appears.

The Examples

189. The Examples start at [0076]. I will narrate them and identify Teva's criticisms of them, but I make clear at the outset that the overall position is that while the experts agreed that the description is confusing and rather scrappy, Teva accepted that the deficiencies it alleged do not amount to a discrete attack on the Patent's validity as such. There is an adequate disclosure that the single preparation described did achieve a long-lasting depot effect according to the posologies described. The presentation of the methods and data falls well short of what would be required in a peer-reviewed publication but is adequate to support the high-level conclusions stated.

Example 1

190. Example 1 refers to methods of making testosterone formulations according to the Patent, noting that compositions are in general prepared by incorporating a therapeutically effective amount of any of testosterone ester of the invention, such as the testosterone undecanoate, in an appropriate vehicle comprising castor oil and a co-solvent, such as benzyl benzoate, with the possibility of adding further excipients.

191. It refers to a specific example as at [0080]:

> [0080] In one specific example of the invention the testosterone undecanoate is dissolved in benzyl benzoate, the testosterone undecanoate/co-solvent solution is then combined with the castor oil, which is then filtrated through a 0,2 µm filter, filled into amber-glass bottles, and finally sterilised at 180°C for 3 hours.

Example 2

192. Example 2 concerns the use of a particular composition in a one-arm clinical study in which ([0081]) the "therapeutic efficacy and safety of a formulation containing testosterone undecanoate 1000 mg in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume". It is agreed between the parties that this ratio would be understood as a vol% of 37% castor oil and 63% benzyl benzoate. This formulation was investigated in hypogonadal men according to the following scheme:

> a) an initial phase comprising 4 injections of the formulation with intervals of 6 weeks between the injections.

b) a maintenance phase comprising injecting the formulation in intervals of 10 or 12 weeks between injections.

193. Paragraph [0082] says that the patients received four TU injections. The first three times of injections with an interval of 6 weeks, the 4th injection and subsequent injections with 12-week intervals. This is inconsistent with the earlier reference in paragraph [0081] of the intervals being every 10-12 weeks in the maintenance phase.

194. The protocol for this investigation is provided as a table in [0083] as follows:

Name of active ingredient:	Testosterone Undecanoate (TU)
Objectives:	To obtain further information on efficacy and safety of the TU preparation after long-term administration over a period of more than 18 months at prolonged (12-week) intervals between the injections of 1000 mg TU in 4 ml oily solution
Methodology:	Open, one-arm, multiple-dose study
Total number of subjects:	planned: 36
Diagnosis and main criteria for inclusion:	Hypogonadal men aged 18 to 65 years and with serum T (testosterone) levels without androgen treatment lower than 5 nmol/L, who orderly completed the main study with a final examination, did not exhibit any relevant pathological findings, and gave their written informed consent to either extend the TU treatment from the main study or switch over from TE (testosterone enanthate) to TU
Test product:	Testosterone Undecanoate (TU)
dose:	in patients on TU : 8 x 1000 mg at 12-week intervals
mode of administration:	Intramuscular injections (*gluteus medius* muscle)
Duration of treatment:	80 weeks 84 weeks
Efficacy end points: -	Primary variables: erythropoiesis (hemoglobin, hematocrit), grip
	strength; Secondary variables: serum levels of testosterone (T),
	dihydrotestosterone (DHT), estradiol (E2), luteinizing hormone (LH), follicle stimulating hormone (FSH), leptin and sex hormone-binding globulin (SHBG); bone density; parameters of bone metabolism; body composition; lipids (total cholesterol, triglycerides, low-density , high-density and very low-density lipoproteins, apolipoprotein A1 and B, lipoprotein (a))
Safety end points:	Adverse events (AEs); serum level of prostate-specific antigen (PSA); ultrasonographic findings in prostate; hematological and liver (ASAT, ALAT, gamma-GT, total bilirubin) parameters, ferritin, iron;

195. Teva submitted that the protocol set out in the table under paragraph [0083] raises inconsistencies as to the details of the study that was actually performed, including:

i) There is no mention of using 10-week intervals in this part of the protocol, although the "Duration of treatment" entry further down the table says "80 weeks 84 weeks" which would be consistent with 8 maintenance doses at either 10 week or 12 week intervals.

ii) The protocol does not refer to the initial study at all and the "Diagnosis and main criteria for inclusion" entry suggests that some patients recruited to the study were already being treated with TU.

196. Both Prof Wu and Prof Anderson observed that it is quite difficult to understand exactly what the protocol is in this example. Prof Wu's evidence was [0082] and [0083] relate to the same study, because both paragraphs describe an initial phase of four-loading doses, six weeks apart. Prof Anderson however suggested an alternative explanation is that Example 2 could be describing two separate studies, one that uses 4x injections for the initial phase and one that uses 3x injections for the initial phase. Prof Wu highlighted that this protocol exemplifies the problems with a mixed posology; that it is very easy to confuse how many initiation doses, how many maintenance doses and when you move from one phase to another, and that clinicians prefer a fixed regime.

197. Although with some scepticism about its conclusions, Prof Wu viewed Example 2 as a long term clinical investigation (in 36 patients for over 1.5 years) which suggests that physiological serum T levels, with satisfactory efficacy and safety profiles, can be achieved with the use of the same composition in a 12 weekly maintenance regime.

198. Prof Anderson agreed that whilst data are not provided for the studies, [0084] provides that the results demonstrate that in the maintenance phase, a period of 12 weeks between injections was adequate for most of the patients i.e. treatment with only 4 TU injections was sufficient to restore serum T levels to the normal range for a prolonged period.

Example 3

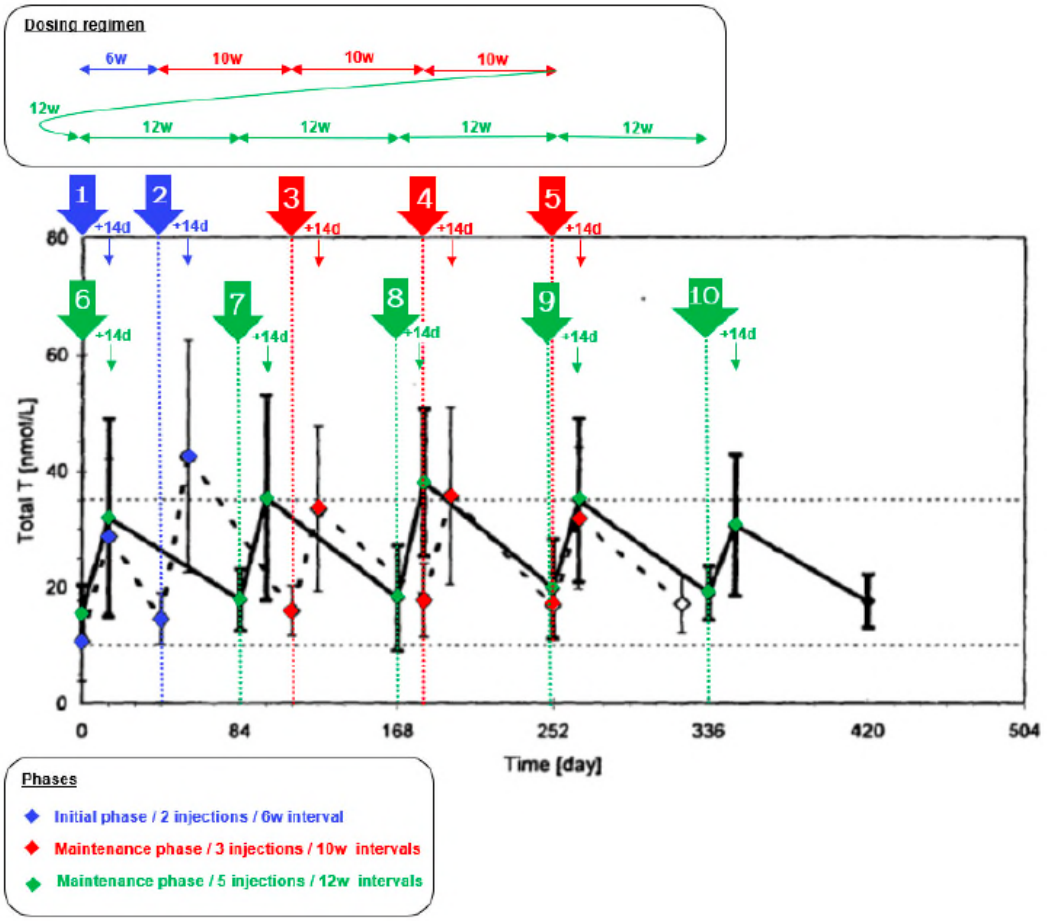
199. Example 3 is described at [0085]-[0086]. It describes testing of the PK profile of a TU formulation as in Example 2. It is a long-term study on hypogonadal patients. The administration scheme uses the same dose of TU, but with the following phases:

    i) an initial phase of 2 i.m. injections with a 6-week interval;

    ii) a maintenance phase of 3 further injections separated by a 10-week interval; and

    iii) injections every 12 weeks (for 5 treatment periods).

200. The results are presented in Figure 1. Reproduced below is a copy of Figure 1 annotated by Prof Wu, with which the parties are in agreement. The below marks each injection with an arrow and colouring the three phases of the clinical study:



201. Teva noted the following about the data shown in Figure 1:

i) The mean serum T level before the first injection is just above 10 nmol/l, which is difficult to reconcile with the statement in paragraph [0085] that the subjects were hypogonadal men having serum T levels "less than 10 nmol/l".

ii) Prof Anderson noted that explanation might be that the participants had been receiving TRT treatment before the start of the study without an adequate washout period. Prof Wu agreed with this, noting this is not unusual and that it is highly unlikely that the patients would have been on treatment for testosterone and had to wash-out, unless they had been diagnosed to have hypogonadism. In any event, it makes the data harder to interpret. In particular, to the extent these data are compared to that in the prior art, account needs to be taken of this elevated baseline level (in the prior art the baseline T level at day=0 was around 5 nmol/l).

iii) The mean serum T levels following the 7th, 8th and 9th injections are either at or above the upper physiological limit of 30 nmol/l.

iv) The size of some of the error bars is striking. The Patent does not state whether they show standard deviation (SD) or standard error of the mean (SEM), but even assuming the former (which tend to be smaller than the latter), the data show that some patients reached serum T levels

substantially exceeding the physiological range two weeks after each injection (e.g. two weeks after the second injection, at least some patients reached serum testosterone levels of over 60 nmol/l i.e. double the upper limit of normal.)

202. With regards to Figure 1, relating to the starting serum T level of the patients in Example 3 being approximately 10 nmol/L, Prof Anderson stated that "This makes the data in Example 3/Figure 1 more difficult to interpret and further undermines the credibility of the data in the Patent". Prof Wu did not agree that the skilled clinician would consider this to be material; they would appreciate that the statement in paragraph [0085] that "hypogonadal men (having testosterone levels in serum of less than 10 nmol/l)'' refers to the diagnostic criteria for hypogonadism (at the time of initial diagnosis), and that (as Prof Anderson also noted) one or more of the patients in this study may have started with a serum T level higher than the pre-treatment baseline (likely from incomplete washout of prior testosterone therapy), bringing up the average. However, this would not be considered unusual in a study of this kind (with previously treated hypogonadal patients) and does not undermine the credibility of the data.

203. Teva had the following further criticisms of Example 3 [0086]:

    i) The maximal values for serum T level (both average and individual) plainly exceed 30 nmol/l in places over the course of the experiment.

    ii) Although the data do suggest that the average values for serum T level did not drop below 10 nmol/l over the course of the experiment, they started above that value.

    iii) The patentee did not carry out another study using 14 week intervals, they just 'extrapolated' the 12-week serum T levels from Example 3 out to 14 weeks. No further details of this 'extrapolation' are given, but the sparsity of serum measurements taken in this study suggests that it likely just involved extending the straight line of the graph by 14 days.

204. Prof Wu considered that Example 3 is a long-term investigation which provides pharmacokinetic data confirming that 1000 mg of TU in the composition described, administered, following an initial phase of two injections 6 weeks apart, at 10 week or 12 week intervals (that could be extrapolated up to 14 weeks), can achieve and maintain serum T levels within the physiological range for over 2 years.

205. Prof Anderson agreed that it is reasonable to think that the injection interval in the maintenance phase could be extended up to 14 weeks given that 12 weeks after the final injection of the study, the average testosterone concentration is well within the normal range.

Example 4

206. Example 4 is described at [0087] as being a "Comparison of initial phases with 6 weeks between injections and 10 weeks between injections." The same

testosterone preparation as used in Examples 2 and 3, is used again in hypogonadal men.

207. Serum T levels are compared for two initial injection intervals where the only variable is the interval between the 1st and 2nd injection: in Regimen A the interval is (on average) 9.2 weeks and in Regime B the interval is (on average) 6.1 weeks.

208. [0092] shows the mean serum levels of testosterone for the two regimens based on data for 6 men as follows:

Mean Testosterone levels (total) in serum according to the number of weeks between injections.

	↓ 1st injection			↓ 2nd injection	
Regime	Base value; mean testosterone level (nmol/1) before 1st injection	Mean weeks after 1st injection	Mean testosterone level (nmol/l) after weeks	Mean weeks after 2nd injection	Mean testosterone level (nmol/l) after weeks
A	7.9	9.2	7.0	10.8	8.8
B	6.8	6.1	12.2	10.1	12.5

209. These data provide some support for the suggestion in paragraph [0093] that a 6-week interval between first and second injection provides a more reliable regimen than a 9 week interval.

210. However, once again, Teva submitted that the data need to be treated with some caution:

    i) Given the variation in the mean intervals that are described, this seems to be a retrospective analysis of data that was collected in other studies.

    ii) Paragraph [0092] refers to "data for 6 men" although it is not clear if this is the total number of subjects or the number per group.

    iii) No indication of the variation between patients is provided.

    iv) The data seem suspect in places, for example: the average serum T level has decreased following the first injection (baseline of 7.9 nmol/l drops to 7.0 nmol/l 9 weeks after the first injection) which does not make any sense.

211. Prof Anderson's view was that the Skilled Clinician would consider the utility of the data presented in Example 4 to be limited, given the use of mean testosterone levels only, data from only the first 2 injections of a longer series being presented, and the lack of information regarding the protocol followed.

212. Prof Wu viewed Example 4 as a final study using the same TU composition, which provides evidence that by shortening the injection interval to 6 weeks, serum T levels can be quickly raised above hypogonadal levels and maintained

in the target therapeutic range using a subsequent injection of approximately 10 weeks.

213. Again, there are problems with the data which the skilled team would note, but there is fair support for the overall proposition as to the comparison between 6 and 10 week intervals.

CLAIMS IN ISSUE

214. The Defendant relies on Claims 1 and 4 (as proposed to be unconditionally amended) and Claims 7 and 16 (as proposed to be conditionally amended) as having independent validity. During the trial the Defendant indicated that it would not pursue proposed amended claim 15 on the basis that it could add nothing to proposed amended claim 16 (see below).

215. Claim 1 of the Patent as proposed to be unconditionally amended is set out below with the amendments marked up:

> A composition formulated for intramuscular injection comprising testosterone undecanoate ~~a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates;~~ and a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent, wherein the co-solvent is benzyl benzoate.

216. Claim 4 (as proposed to be unconditionally amended) adds the requirement that the concentration of benzyl benzoate in the vehicle is between 55 to 65%.

217. Claim 7 (as proposed to be conditionally amended) is a Swiss form claim as set out below with the amendments in mark up:

> Use of testosterone undecanoate ~~a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates~~ for the preparation of a medicament for treating primary and secondary hypogonadism in a man, said medicament is in a form for intramuscular injection and comprises a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent, wherein the co-solvent is benzyl benzoate [in an amount ranging from 55 to 65 vol% of the vehicle]1, and wherein said ~~use~~ treating is characterized by i) an initial phase comprising 2 injections of a single dose of testosterone undecanoate with an interval of 6 weeks between each injection, each dose in an amount of ~~between 500 mg and 2000~~ 1000 mg testosterone undecanoate; followed by ii) a maintenance phase comprising subsequent injections of a single dose of testosterone undecanoate with an interval of at least 9 weeks between each subsequent injection, each dose in an amount of ~~between 500 mg and 2000~~ 1000 mg testosterone undecanoate.

218. Claims 16 (as proposed to be conditionally amended) is also a Swiss form claim as set out below with the amendments in mark up:

> 16. The use according to any of claims 7 to 9 or claim~~s~~ 11 ~~to~~ or claim 15, wherein the maintenance phase comprises subsequent injections of a single dose of testosterone undecanoate with an interval of 10 weeks or 12 weeks between each subsequent injection.

219. Claim 15 was also in issue at the start of trial and required an interval of 10 to 14 weeks between maintenance doses. Helpful discussion during closing submissions identified that it had no separate importance, so it was dropped by

Grünenthal for independent validity, and that has the result that it is unnecessary for me to rule on Teva's objection that it added matter.

220. In broad terms, the importance of the various claims is:

i) Claims 1 and 4 are product claims; if successful Teva's obviousness case would knock them both out and there is no need to distinguish between them.

ii) The use claims specify the posology and to knock them out requires further steps to be found obvious on top of those required to knock out claims 1 and 4.

iii) The changes to claim 7 to introduce the posology is only advanced by way of conditional amendment in the event that the product claims are invalid.

iv) Claim 7 has an interval of "at least 9 weeks" between maintenance doses and this raises two particular points on plausibility, namely (a) is it possible to make a prediction about a 9 week interval from the use in the examples of the longer periods of 10 or 12 weeks, and (b) what is the effect of the fact that the time interval in claim 7 has no upper bound?

v) Neither of those last two points runs against claim 16 which stipulates specifically 10 or 12 weeks, so they cannot win the case for Teva.

VALIDITY

221. I will deal with obviousness and then insufficiency.

Obviousness - Legal principles

222. There was no significant dispute about the high-level applicable principles. Both parties referred to the decision of the Supreme Court in *Actavis v. ICOS* [2019] UKSC 15, per Lord Hodge at [52]-[73]. Thus:

a) There is a single statutory question: whether the invention is obvious, having regard to the state of the art at the priority date.

b) In some cases the *Pozzoli* [2007] EWCA Civ 588 approach is helpful.

c) The Supreme Court endorsed the statement of Kitchin J (as he then was) in *Generics (UK) Ltd v H Lundbeck A/S* [2007] EWHC 1040 (Pat) at [72]:

> The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success.

d) Whether at the priority date something was "obvious to try". This was considered by Lord Hodge at [65] where he said:

> First, it is relevant to consider whether at the priority date something was "obvious to try", in other words whether it was obvious to undertake a specific piece of research which had a reasonable or fair prospect of success: *Conor v Angiotech* (above) para 42 per Lord Hoffmann; *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2012] EWCA Civ 1234; [2013] RPC 27, paras 90 and 91 per Kitchin LJ. In many cases the consideration that there is a likelihood of success which is sufficient to warrant an actual trial is an important pointer to obviousness. But as Kitchin LJ said in *Novartis AG v Generics (UK) Ltd* [2012] EWCA Civ 1623, para 55, there is no requirement that it is manifest that a test ought to work; that would impose a straightjacket which would preclude a finding of obviousness in a case where the results of an entirely routine test are unpredictable. As Birss J observed in this case (para 276), some experiments which are undertaken without any particular expectation as to result are obvious. The relevance of the "obvious to try" consideration and its weight when balanced against other relevant considerations depend on the particular facts of the case.

e) The routine nature of the research and any established practice of following such research through to a particular point may be a relevant consideration on the facts of the case. Weighed against this is the burden and cost of the research programme, which may be relevant. The court should also have regard to the necessity for and the nature of value judgments which the skilled team will have to make in the course of any research.

f) There can be multiple obvious avenues or routes and an obvious route is not rendered less obvious for this reason.

g) the motive of the skilled person is a relevant consideration.

h) the fact that the results of research which the inventor actually carried out are unexpected or surprising is a relevant consideration as it may point to an inventive step, at least in so far as it suggests that a test was not obvious to try or otherwise the absence of a known target of the research which would make it less likely that the skilled person would conduct a test.

i) the courts have repeatedly emphasised that one must not use hindsight, which includes knowledge of the invention, in addressing the statutory question of obviousness.

j) It is necessary to consider whether a feature of a claimed invention is an added benefit in a context in which the claimed innovation is obvious for another purpose.

223. Not all of these principles turned out to be relevant as the arguments progressed.

224. As to hindsight, an obvious danger of a step-by-step analysis is that the combination of steps by which the inventor arrived at his invention is ascertained

by hindsight knowledge of a successful invention. Lord Diplock warned against this in *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] RPC 346, 362. I agree with Birss J's analysis in *Hospira UK Ltd v Genentech Inc* [2014] EWHC 3857 (Pat), para 240, where he stated:

> The particular point made in *Technograph* was that it was wrong to find an invention was obvious if it was only arrived at after a series of steps which involve the cumulative application of hindsight. In some circumstances success at each step in a chain is a necessary predicate for the next one and it is only the hindsight knowledge of the invention as the target which could motivate a skilled person to take each step without knowledge about the next one. In a situation like that, *Technograph* is important.

225. It may be legitimate to take a step-by-step analysis where the pattern of the research programme which the notional skilled person would undertake can clearly be foreseen. In *Gedeon Richter plc v Bayer Schering Pharma AG* [2011] EWHC 583 (Pat), Floyd J stated (para 114):

> I think that the guiding principle must be that one has to look at each putative step which the skilled person is required to take and decide whether it was obvious. Even then one has to step back and ask an overall question as to whether the step-by-step analysis, performed after the event, may not in fact prove to be unrealistic or driven by hindsight.

Obviousness over von Eckardstein in conjunction with Behre and Nieschlag

226. I will deal with von Eckardstein first since that is the primary basis of Teva's case; it argues that the skilled team would read von Eckardstein and then be led to look up Behre and Nieschlag. Grünenthal does not oppose their being read together. I deal with Behre next and Nieschlag last (i.e. in chronological order as between the two, although nothing turns on the sequence).

Teaching of von Eckardstein

227. von Eckardstein is an article with the title "*Treatment of Male Hypogonadism with Testosterone Undecanoate Injected at Extended Intervals of 12 Weeks: A Phase II Study*". It was authored by Sigrid von Eckardstein and Eberhard Nieschlag, two of the leaders in this field. It was published in the May/June 2002 issue of the Journal of Andrology.

228. The findings of von Eckardstein are summarised in its abstract as follows:

> **ABSTRACT:** This paper reports the result of an open-label, nonrandomized clinical trial investigating the efficacy and safety of an injectable preparation of testosterone undecanoate (TU) dissolved in castor oil and given over a 3.2-year period. In a previous study we demonstrated that injections of TU every 6 weeks resulted in satisfactory substitution but a tendency toward testosterone accumulation. Here we investigate prolonged TU treatment at extended injection intervals in hypogonadal men. Injections were given at gradually increasing intervals between the fifth and 10th injection, and from then on every 12 weeks. Steady state kinetics were obtained after the 13th injection. Well-being, sexual activity, clinical chemistry, prostate volume, and prostate-specific antigen (PSA) and serum hormone levels were monitored.

> Patients were clinically well adjusted throughout the study. Before the next injection, testosterone, dihydrotestosterone, and estradiol levels were mostly within the normal range and showed a tendency to decrease with increasing injection intervals. Body weight, hemoglobin, serum lipids, PSA, and prostate volume did not change significantly during the 3.2 years of treatment. PSA levels were always within the normal limit. Maximal testosterone levels during steady state kinetics were measured after 1 week with 32.0 ± 11.7 nmol/L (mean ± SD). Before the last injection, mean testosterone concentrations were 12.6 ± 3.7 nmol/L. Compared with conventional testosterone enanthate or cypionate treatment requiring injection intervals of 2–3 weeks and resulting in supraphysiological serum testosterone levels, injections of TU at intervals of up to 3 months offer an excellent alternative for substitution therapy of male hypogonadism.

229. In the opening paragraphs of the article, there is a cross reference to the Nieschlag prior art in the second paragraph, and a comment that after 4 injections of TU with a 6-weekly injection schedule "a tendency toward a gradual increase in testosterone levels was observed, suggesting that prolongation of application intervals should be possible".

230. A footnote on the first page says that Jenapharm GmbH supplied the TU injections, noting in particular "Prof Dr M. Oettel, Dr D. Hübler, and Dr Saad". I digress to say that I find that the material used in von Eckardstein, Nieschlag and Behre was the same as in the commercial Nebido product. Teva proved that via a 1999 Investigator's Brochure. That means that if the skilled team did successfully reverse engineer the formulation from the cited prior art the result would be within the product claims of the Patent.

231. Under the "Patients" subheading in the Materials and Methods section the authors say that the 7 men with primary or secondary hypogonadism involved in the study had already participated in "the first trial" i.e., the Nieschlag trial that used 6-week injection intervals. There is also a reference to 2 of the 7 men having previously also participated in the Behre trial that compared the pharmacokinetics of TU dissolved in castor oil to TU dissolved in tea seed oil (the latter referred to as the "Chinese preparation"). Table 1 provided the diagnosis and previous treatment modality as follows:

Table 1. *Clinical characteristics of patients entering the follow-up phase of substitution therapy with 1000 mg TU*

Patient	Diagnosis	Age (y)†	Treatment (before TU)†
1	Bilateral orchidectomy due to seminoma	37	TE 250 mg/4 weeks
2	Bilateral testicular atrophy due to cryptorchidism	19	None
3	Bilateral orchidectomy due to seminoma	49	TE 250 mg/2.5 weeks
4	Bilateral orchidectomy due to seminoma	37	None
5	Hypopituitarism (postcraniopharyngeoma)	57	TE 250 mg/3 to 4 weeks
6	Bilateral orchidectomy due to seminoma	31	TE 250 mg/2 to 4 weeks
7	Hypogonadotropic hypogonadism (ectopic neurohypophysis)	29	TE 250 mg/4 weeks

* Patients who had already participated in the study on comparative pharmacokinetics with TU in castor oil or tea seed oil.
† Age and previous treatment modalities refer to the date before the first TU application. TE indicates testosterone enanthate.

232. There is then the following:

> Testosterone Preparation
> TU was obtained from Jenapharm GmbH & Co. KG, Jena, Germany. Each ampule contained 1000 mg TU dissolved in 4 ml castor oil. Single injections were administered with the total volume at one site intramuscularly into the musculus gluteus medius, taking care to perform injections slowly to avoid pain

233. I will return to this below, as there was a potentially important dispute about what it means.

234. Then the article has a "Study Design" section, describing that there was a washout phase of at least 4 weeks prior to the first injection of TU as part of the study. There follows the explanation that:

> After 4 injections had been given at 6-week intervals, the intervals were gradually extended between the 5th and 10th injections. Intervals were extended by 1 to 2 weeks if serum testosterone levels were above 12 nmol/L before the next injection, and if subjective impairment of well-being was absent. From the 10th injection onward, TU was applied every 12 weeks. After the 13th application, steady state kinetics were obtained as evidenced by weekly determinations of testosterone serum concentrations for 12 weeks.

235. An overview of the studies evaluating TU is given in Table 2, which refers to Behre as "Study I", Nieschlag as "Study II" and the current study as "Study III". The Behre design is described as 'pharmacokinetics after a single injection' and Nieschlag's as 'Four injections at 6-week intervals'.

Table 2. *Overview of studies evaluating pharmacology and effectiveness of injectable TU dissolved in castor oil*

Study	Design	Patients	Publication
I	Pharmacokinetics after a single injection	*n* = 14	Behre et al, 1999a
II	Four injections at 6-week intervals	*n* = 14 (*n* = 2 continued from study I)	Nieschlag et al, 1999
III	a) Nine injections at increasing intervals from 6 to 12 weeks b) Steady state pharmacokinetics c) Five injections at 12-week intervals	*n* = 7 (*n* = 2 continued from studies I and II) (*n* = 5 continued from study II)	

236. The "Results" section begins on page 421 of the paper:

> **Results**
>
> General Effects, Well-Being, and Sexual Function
>
> During TU applications, patients reported stable values for all parameters of well-being and sexual function (numbers of erections and ejaculations per week and satisfaction with sex life). At the end of the injection interval, when questionnaires were compared with those at half-time, no statistically significant differences were found.
>
> Injections were well tolerated by all men except one, who requested extremely slow injections to avoid discomfort. No local side effects or impaired well-being occurred, except for one occasion when, during prostate sonography, a patient had short-term circulatory problems after the injection. One patient complained initially of mild acne within 2 weeks following injection. However, these problems disappeared during the 12-week intervals.
>
> Testosterone and Free Testosterone
>
> …
>
> Maximum steady state kinetics for levels of testosterone and free testosterone were reached after 1 week. The mean maximum concentration for testosterone was 32 nmol/L, ranging from a minimum of 15.6 to a maximum of 44.3 nmol/L. A comparable pattern was observed for free testosterone levels, with a mean of 787 pmol/L (Table 3). Initial kinetics obtained in 14 subjects after the first injection of TU and steady state kinetics in the current trial are shown in Figure 2.

237. The serum T levels obtained before each injection are plotted in Figure 1.

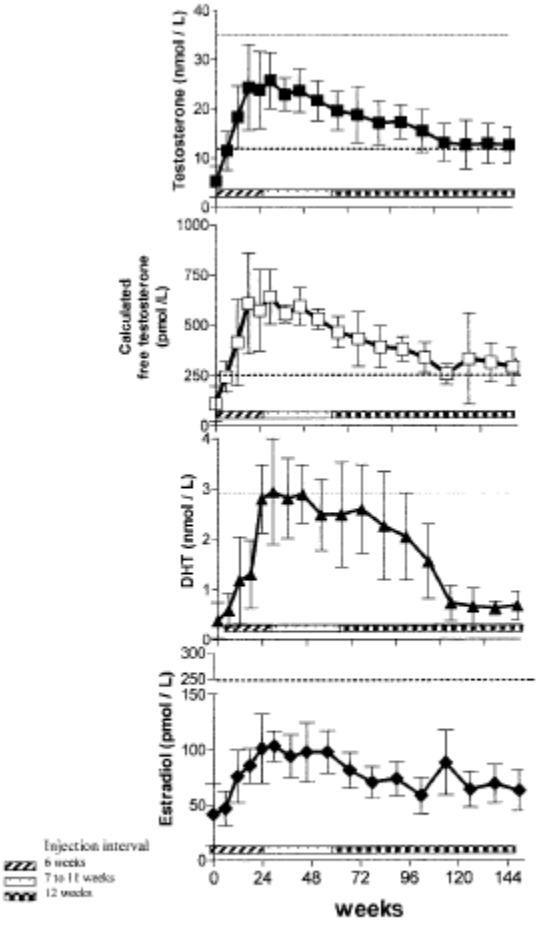
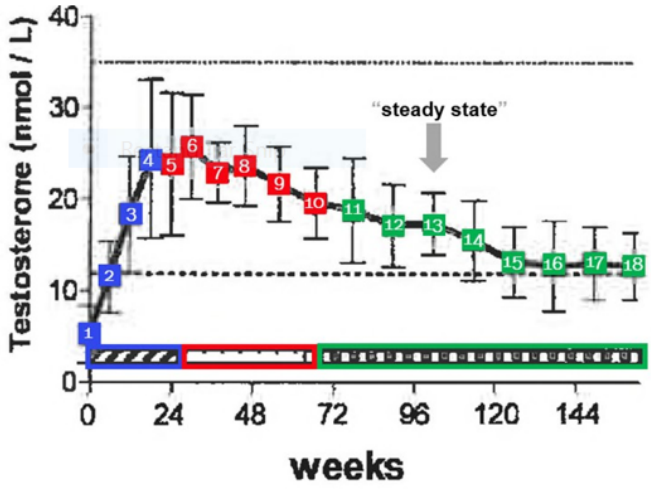


Figure 1. Serum testosterone, free testosterone, DHT, and estradiol in 7 hypogonadal men treated with 1000 mg TU in increasing injection intervals. Values were obtained before injections and are given as means ± SD. Dotted lines indicate normal limits.

238. Figure 1 shows the measured serum values just before each injection i.e. the "troughs". Peak concentrations that would have been obtained following each injection are not shown.

239. Dr Peeters usefully annotated the top part of Figure 1 to show the numbering of the serum T measurements, which is reproduced below (numbered data point 'n' is the serum T level just prior to the 'nth' injection)



Injection interval 6 weeks 7 to 11 weeks 12 weeks	
	Injections 1-4 (6 weekly) / Nieschlag 1999
	Injections 5-10 (6/7–11/12 weeks)
	Injections 11-18 (12 weekly)

240. This shows visually the accumulation in trough serum T levels that occurred during the Nieschlag study using 6-weekly injection intervals to which von Eckardstein refers, and that by extending the intervals up to 12-weeks the trough serum T levels decreased and levelled out just above the lower limit of normal. The text of the article, quoted above, says that steady state was achieved after the 13th injection but in fact Figure 1 is inconsistent with that and one can see visually steady state from the 15th injection onwards. Nothing material turns on this, however.

241. Figure 2 shows the more granular (weekly) serum T data that was obtained over 12 weeks following the 13th injection. The data in Figure 2 has been overlaid on top of the equivalent data from the Behre study that was obtained after the 1st injection.

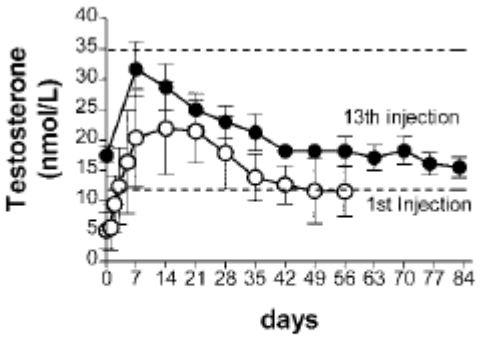


Figure 2. Serum testosterone after a single injection of 1000 mg TU in 14 untreated hypogonadal men (Behre et al, 1999) (open circles) and during treatment with TU for 102 weeks (closed circles). Values are given as means ± SD. Dotted lines indicate normal limits.

242. This figure shows visually that:

i) after a single injection (Behre), serum T levels on average rose to normal levels within 7 days of the injection, and gradually tapered down to just within the lower normal range after 6 weeks before hovering at the lower limit of the normal level by around the 7-to-8-week mark.

ii) by the time of the 13th injection (of the combined regimen of Nieschlag and von Eckardstein) the baseline serum T level was in the normal range (with the 12th dose having been administered 12 weeks prior).

iii) following the 13th injection (of the combined regimen of Nieschlag and von Eckardstein), the average serum testosterone rose and peaked at just under the upper limit of the normal range after 7 days, and gradually tapered back down to a little below the initial level by the 12-week mark.

243. There follows the Discussion which starts on p.423.

> Discussion
> …
> Based on our initial pharmacokinetic study we postulated that injections will maintain normal testosterone levels for 6 to 10 weeks (Behre et al, 1999a). Choosing the shortest injection interval, it turned out that TU had a tendency to accumulate when given at 6-week periods (Nieschlag et al, 1999). The current trial confirmed that the schedule of application can be extended up to 12 weeks once normal testosterone levels have been achieved. It is difficult to speculate on testosterone profiles if treatment would have been based on 12-week intervals from the beginning, because all men participating in this trial had already participated in the earlier 6-week schedule. Withdrawal of therapy is accompanied by severe disturbances in well-being and, as a result, it is disliked by patients. For this reason we did not include a second washout phase.

244. I will return to what the skilled reader would make of this below.

245. At the last paragraph of the left-hand column of p424, the authors observe that:

> Improvement and stabilization of mood is one of the prime effects of testosterone substitution in male hypogonadism (Wang et al, 1996). In this connection, the fluctuations in serum testosterone levels arising during treatment with TE or testosterone cypionate (TC) are not well tolerated by patients. Even though TU injections initially result in slightly supraphysiological levels, depending on the injection intervals and decrease steadily thereafter, no clinically apparent changes in mood occurred.
> …
> Direct comparisons between short-acting and long-acting testosterone preparations or the larger phase III trials may be better suited for evaluating such physiological effects.

246. The conclusion is that:

> In summary, results of this trial show that in an injectable form, TU is a highly interesting alternative to the currently most widely used injectable preparations, TE and TC. When applied at appropriate intervals of 10 to 12 weeks, TU injections by and large avoid supraphysiological testosterone levels, and their unwanted side effects. In addition, the study is one of the few trials reporting long-term treatment extending over more than three years with a single preparation. As recent advances in hormonal male contraception (Kamischke et al, 2000 and 2001) and

> substitution of male senescence indicate an increased demand for testosterone preparations, such information on the long-term safety of testosterone application is timely and crucial.

Teaching of Behre

247. Behre is an article which was published in the European Journal of Endocrinology in 1999. It is headed "*Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies*". It is authored by H M Behre, K Abshagen, M Oettel, D Hübler and E Nieschlag.

248. The Abstract explains that the objective of the paper is to investigate TU dissolved in either tea seed oil or castor oil. "Study I" investigates the preparation in tea seed oil, and "Study II" investigates the preparation in castor oil.

> **Abstract**
> *Objective*: In the search for long-acting testosterone preparations suited for substitution therapy of hypogonadal men, testosterone undecanoate (TU) dissolved in either tea seed oil or castor oil was investigated.
> *Design:* In study I, 1000 mg TU in tea seed oil (125 mg/ml) were injected in equal parts into the gluteal muscles of seven hypogonadal men. In study II, 1000mg TU in castor oil (250 mg/ml) were injected into one gluteal muscle of 14 patients.
> *Results*: In comparison with published data on testosterone enanthate, most widely used for i.m. injections, the kinetic profiles of both TU preparations showed extended half-lives and serum levels not exceeding the upper limit of normal. The castor oil preparation had a longer half-life than TU in tea seed oil (33.9 ± 4.9 *vs* 20.9 ± 6.0 days (mean ± S.E.M.)).
> *Conclusion*: The longer half-life and the smaller injection volume make TU in castor oil a strong candidate for further applications in substitution therapy and in trials for male contraception.

249. The Introduction explains, by way of background, that:

> **Introduction**
> Testosterone has been used for substitution therapy for almost six decades. Since the number of patients suffering from hypogonadism and requiring such therapy is relatively small there has not been much drive to develop new testosterone preparations beyond subdermal implants developed in the 1940 s, enanthate and cypionate esters for i.m. injections developed in the 1950 s and oral testosterone undecanoate (TU) developed in the 1970 s. Although still in use, these preparations are not ideal because of their kinetics, resulting in either supraphysiological or fluctuating serum testosterone levels, and because of the inconvenience of frequent application (for review see reference 1). Only the possibility of new and more widespread indications stimulated a search for alternative application modalities. One result was transdermal systems well suited for long-term substitution because of almost physiological serum testosterone levels (2–4) and because of the possibility for immediate interruption of the treatment if required (e.g. when substituting hypogonadism in senescence) (5). For younger patients and for hormonal male contraception, however, long-acting testosterone preparations continue to be required.

250. The Subjects & Methods section explains that the tea seed preparation was provided and manufactured by a Chinese company, and that Jenapharm provided the TU dissolved in castor oil.

> **Subjects and methods**
> *Testosterone preparations*
> The TU preparation (3-oxoandrost-4-ene-17β-yl-undecanoate) used in study I was provided and manufactured by Zhejiang Xian Ju Pharmaceutical Corp. (Zhejiang, People's Republic of China). The steroid was dissolved in tea seed oil at a concentration of 125 mg/ml. TU used in study II was prepared by Jenapharm GmbH & Co. KG (Jena, Germany). The batch used for all injections had a concentration of 250 mg TU dissolved in 1 ml castor oil.

251. The Study Design and Patients section notes:

> ***Study design and patients***
> Study I was performed as a therapeutic trial in agreement with German Drug Law. The protocol of study II was approved by the Ethics Committee of the University of Munster and the State Medical Board. Both studies were conducted at the Institute of Reproductive Medicine in Munster, in agreement with the Declaration of Helsinki and in accordance with Good Clinical Practice. All subjects gave written informed consent.

252. Study I (tea seed oil) was performed on 7 hypogonadal patients and Study II (castor oil) on 14 hypogonadal patients. The patients in Study I received a single dose of 1000mg TU via 2x4ml injections, and the patients in Study II received a single dose of 1000mg TU via 1x4ml injection. The schedule of blood sampling included pre-injection samples, followed by samples drawn at days 1, 2, 3, 5, and 7 post-injection, followed by weekly samples up to week 8. The data was provided in Table 1 as follows:

Table 1 Anthropomorphic and clinical data of patients.

	Age (years)	Height (cm)	Weight (kg)	BMI* (kg/m^2)	Type of hypogonadism	Previous testosterone treatment
Study I						
1	51	175	80.0	26.1	Primary	TU p.o.
2	37	187	74.6	21.3	Secondary	TE i.m.
3	26	182	66.0	19.9	Secondary	Without
4	29	178	62.5	19.7	Secondary	TE i.m.
5	25	172	61.5	20.8	Primary	Without
6	35	184	85.0	25.1	Primary	Without
7	40	179	93.5	29.2	Primary	TE i.m.
Study II						
1	42	179	99.1	30.9	Primary	TE i.m.
2	20	161	55.2	21.3	Primary	TE i.m.
3	21	179	96.0	30.0	Primary	Without
4	34	191	82.2	22.5	Primary	TE i.m.
5	19	178	94.7	29.9	Primary	TE i.m.
6	36	182	73.0	22.0	Primary	TE i.m.
7	31	198	84.6	21.6	Primary	TE i.m.
8	39	188	79.5	22.5	Secondary	TE i.m.
9	38	176	95.1	30.7	Secondary	TE i.m.
10	22	171	67.0	22.9	Secondary	TE i.m.
11	26	176	102.0	32.9	Primary	TU p.o.
12	19	186	72.1	20.8	Primary	Without
13	35	190	114.4	31.7	Secondary	TE i.m.
14	45	182	70.0	21.1	Secondary	Without

* BMI = body mass index.

253. The Results reported that the injections were all well-tolerated and "No patient reported the injections to be more painful or inconvenient than former i.m. injections". Under the "Testosterone and DHT" subheading it was also reported as follows:

> In study I, injections of TU in tea seed oil increased testosterone serum levels in a time-dependent pattern (Fig. 1, upper panel) ($P < 0.001$). One day after injection serum levels of testosterone rose from basal levels of 4.8 ± 0.9 to levels of 14.9 ± 1.4 nmol/l in the normal range.

254. The upper part of Figure 1 (reproduced below) is a plot of the serum T concentrations for both the tea seed oil (filled in squares) and castor oil (open circles) preparations.

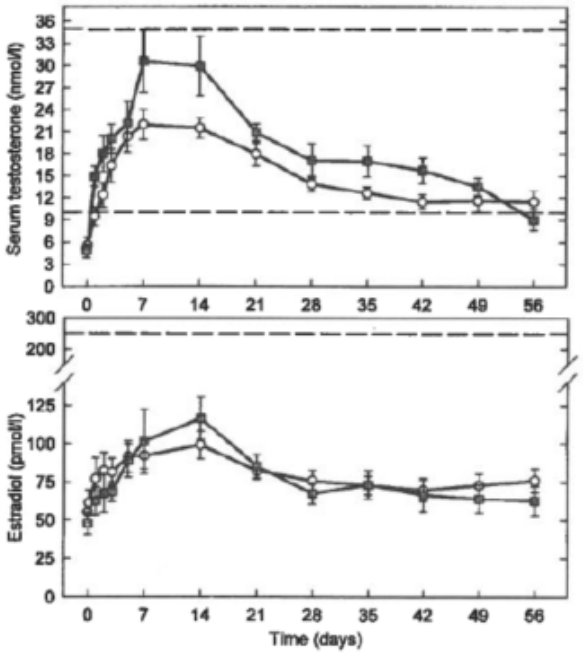


Figure 1 Serum concentrations (mean ± S.E.M.) of testosterone (upper panel) and estradiol (lower panel) after single dose i.m. injections of 1000 mg TU in tea seed oil in 7 hypogonadal men (study I, squares) or castor oil in 14 hypogonadal men (study II, circles). Broken lines indicate normal range of testosterone and upper normal limit of estradiol.

255. The skilled addressee would note that the castor oil profile in the upper panel (testosterone) is that attributed to Behre in Figure 2 of von Eckardstein. However, the lower limit of normal is marked on Figure 1 of Behre as 10 nmol/l, whereas in von Eckardstein it was marked as 12 nmol/l. Nothing turns on this; both values were accepted to being within the CGK notion of the lower level of normal.

256. There is then pharmacokinetic data set out in Table 2:

Table 2 Pharmacokinetic data (mean ± S.E.M.) of the two TU preparations after i.m. injection of 1000 mg TU in comparison with previously published kinetic data from TE and testosterone buciclate (TB).

Preparation/concentration	Total dose injected (mg)	AUC (nmol × days/l)	C_{max} (nmol/l)	t_{max} (days)	$t_{½}$ (days)
TU 125 mg/ml (tea seed oil)	1000	$AUC_{(0–8\ weeks)}$ 825 ± 93	30.1 ± 5.5	13.0 ± 3.7	20.9 ± 6.0
TU 250 mg/ml (castor oil)	1000	$AUC_{(0–8\ weeks)}$ 534 ± 49	19.3 ± 2.1	11.4 ± 1.5	33.9 ± 4.9
TB 200 mg/ml (aqueous suspension)*	600	$AUC_{(0–16\ weeks)}$ 377 ± 68	6.7 ± 1.2	25.8 ± 8.2	29.5 ± 3.9
TE 250 mg/ml (castor oil)†	250	$AUC_{(0–3\ weeks)}$ 376	39.4	10	4.5

* Data from reference (6).
† Data from reference (11) as re-analysed from reference (18).

257. The Discussion section includes the following:

> **Discussion**
> …
> Although the current study deals with a much higher dose of testosterone than administered in previous studies, TU does not result in supranormal serum testosterone levels, but in much prolonged action. Extrapolating from single-dose kinetics it appears that upon repeated injections of 1000 mg, injection intervals of 6–10 weeks will be possible. The prolonged intervals and the normal serum testosterone levels throughout the injection-free period would be welcomed by the hypogonadal patient requiring substitution as well as by the eugonadal male seeking contraceptive protection.
> …

> Recently, it was shown in Chinese men that i.m. injection of 1000 mg TU dissolved in tea seed oil at a concentration of 125 mg/ml has a similar pharmacokinetic profile with a t½ β of 23.7 ± 2.7 days compared with our study with the tea seed oil preparation in Caucasian men (15). The longer duration of action of TU in castor oil compared with TU in tea seed oil could be due to the properties of the oils, the different concentrations (125 *vs* 250 mg/ml) and injection volumes (4 *vs* 8 ml), as well as unilateral vs bilateral gluteal application. It is conceivable that the larger surface of the depot produced by 2x4 ml injections leads to a slightly faster release of the testosterone ester, resulting in higher Cmax values and a slightly shorter half-life than the single 4 ml depot with more concentrated TU.
> --

258. And the concluding paragraph summarises the study as showing that "i.m. TU in castor oil has a considerably longer half-life than conventional TE, producing serum levels in the normal range over 6 weeks".

259. The Acknowledgements include the following:

> **Acknowledgements**
>
> …
>
> We thank Dr Fricke, Jenapharm GmbH & Co. KG for the supply of the TU ampoules.

Teaching of Nieschlag

260. Nieschlag is an article which was published in Clinical Endocrinology in 1999. It is headed "*Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men*". The authors include Eberhard Nieschlag, Dorothee Buechter, Sigrid von Eckardstein, Katrin Abshagen, Manuela Simoni and Hermann M. Behre.

261. Nieschlag provides a convenient summary:

> Summary
>
> OBJECTIVE To investigate the suitability of intramuscular testosterone undecanoate (TU) injections for substitution therapy in hypogonadal men.
>
> STUDY DESIGN Clinical, open-label, non-randomized trial of 13 hypogonadal men receiving 4 intramuscular, injections of 1000 mg TU in 4-ml castor oil at 6-week intervals. General wellbeing, sexual parameters, clinical chemistry, hormone levels, prostate size and prostate-specific antigen (PSA) were evaluated over 24 weeks and compared with baseline values.
>
> RESULTS Testosterone serum levels were never found below the lower limit of normal and only briefly after the 3rd and 4th injection above the upper limit of normal, while peak and trough values increased over the 24-week observation period. Oestradiol and dihydrotestosterone followed this pattern, not exceeding the normal limits. No serious side effects were noted. Slight increases in body weight, haemoglobin, haematocrit, prostate volume and PSA, suppression of gonadotrophins as well as increased ejaculation frequency occurred as signs of adequate testosterone substitution.
>
> CONCLUSION Testosterone undecanoate is well tolerated by the patients. The injection intervals can be extended even beyond the 6-week periods chosen in the present study. Altogether, intramuscular testosterone undecanoate appears to be well suited for long-term substitution therapy in hypogonadism and hormonal male contraception.

262. The formulation information bridges the left hand and right-hand columns on page 758:

> Testosterone preparation
>
> TU was administered in castor oil at a concentration of 250 mg/ml. Each injection of 1000mg (4ml) was administered intramuscularly. The preparation was provided by Jenapharm GmbH & Co. KG, Jena, Germany (Behre et al., 1999a)

263. The results for serum T levels are shown in the top part of Figure 1, below is a copy of Figure 1 as annotated by Teva to show the time point of each of the 4 injections:

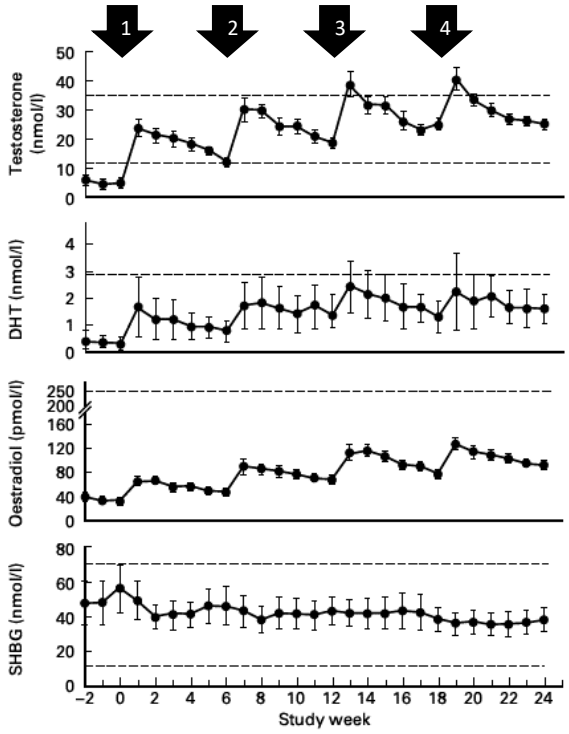


Fig. 1 Serum testosterone, dihydrotestosterone (DHT), oestradiol and SHBG serum levels in 13 hypogonadal men before and during substitution therapy with intramuscular testosterone undecanoate. Injections of 1000 mg were given at weeks 0, 6, 12 and 18. Values are given as mean ± SEM.

264. Each of the 6-weekly injections caused a rapid increase in serum T level. The levels of testosterone detected were within the normal range except that, after the 3rd and 4th injection, the detected levels were in the supraphysiological range at 7 days following each of those injections.

265. The Discussion section refers to the Behre study and notes that:

> In a previous phase-I pharmacokinetic study we found a terminal half-life for serum testosterone of 33.9 ± 4.9 days (mean ± SEM) following the intramuscular injection of 1000 mg TU (Behre et al., 1999a). Extrapolating from these single TU injections we estimated that 6-week injection intervals would be required to substitute hypogonadal patients sufficiently with 1000 mg intramuscular TU injections. The results of the present study show that this dosage scheme provides serum T levels always above the lower limit of normal. In fact, the slowly increasing serum

T levels at the end of the injection intervals and just following the next injection indicate that the intervals can be extended even further, probably up to 10 weeks and more.

266. As explained by Prof Anderson, this latter point is also the point made in von Eckardstein, namely that 6-weekly intervals lead to accumulation.

Interpretation of von Eckardstein

267. It is convenient at this stage to deal with two points about the interpretation of what von Eckardstein teaches.

268. The first is what is meant by the TU preparation being "1000mg TU dissolved in 4 ml castor oil".

269. Grünenthal argued that this meant that this was a complete description; that the TU was in castor oil and nothing else. Teva argued that it meant that the preparation comprised castor oil, but that the words did not preclude something else being present.

270. The skilled team would also have in mind what Behre and Nieschlag say about the preparations, but while those documents are expressed slightly differently, they do not make a difference one way or another on this issue.

271. Grünenthal relied, through Prof Østergaard, on the fact that scientific papers are expected to give enough information to reproduce them, and that von Eckardstein would be read in that light. Accordingly, Grünenthal said, castor oil must have been the only excipient since if other unnamed ones had been present the paper could not be reproduced. Teva retorted that von Eckardstein is a clinical paper not a formulation paper so the reader would not expect all the formulation details to be there, and that it would not be surprising in any event for details of a drug still in development and not on the market to be withheld. Teva also pointed to other situations such as Murdan and Florence, discussed below, where formulated drugs were referred to by reference to the active and the main excipient even where it was known that other ingredients were present too. I agree with Teva on this sub-point.

272. Teva also relied on the skilled formulator knowing from their CGK that castor oil was too viscous ever to be used on its own in this way. I have rejected that as being CGK but I do agree that the skilled formulator would think that castor oil was very viscous and that would be enough for them to be led to think that it was somewhat unlikely that castor oil was being used on its own. Both sides relied on what von Eckardstein said about avoiding pain on injection and the single patient who had an issue with it, but I do not think those statements help one way or another on this point of interpretation.

273. I conclude that the description is ambiguous: it might mean castor oil only or it might mean that there was something else in the preparation as well. A skilled formulator with an interest in progressing von Eckardstein would think about these issues sufficiently closely to realise the ambiguity and to know they had to take it into account. At the risk of repeating myself, this does not in the end matter very much because of the common ground between the parties that testing the

solubility of TU in castor oil would rapidly make clear that there was something else present.

274. The second point is more one of attitude than interpretation of the words used and relates to the relationship between von Eckardstein, Behre and Nieschlag.

275. Part of Teva's case is that the concatenation of the work in Nieschlag (6 week intervals) and von Eckardstein (10 or 12) amounts to four loading doses followed by a number of maintenance doses and that all that was necessary to get to the features of the use claims of the Patent would be to reduce the number of loading doses to two. Teva particularly brought this argument to bear on the passage in the discussion section in von Eckardstein on page 423 quoted above which relates to what Behre had done, the reasoning behind Nieschlag, and the progression to the posology in von Eckardstein.

276. I do not agree that the skilled team would look at von Eckardstein in the way Teva says. It is artificial and hindsight-driven to see Nieschlag followed by von Eckardstein as loading doses followed by maintenance doses. The progression, which the skilled team would quite readily understand, was that the Nieschlag/von Eckardstein team had initially made a mistake in their choice of a fixed dosing interval and had "agilely" (as Prof Anderson put it) changed their trial protocol in the middle to a longer dosing interval. They may understandably have been a bit defensive about this and hence the way they explained it – Prof Anderson described them as being "a bit economical with their conclusions."

Pozzoli analysis

277. The structured approach to the assessment of obviousness was set out by the Court of Appeal *Pozzoli v BDMO* [2007] EWCA Civ 588, [2007] FSR 37. It is:

    i) (a) Identify the notional person skilled in the art;

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

    ii) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

    iii) 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;

    iv) 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?

278. I have identified the skilled team and the common general knowledge above.

279. As to the inventive concept I do not think there is anything to be gained by paraphrasing the claims.

280. As to *Pozzoli* question 3, the differences between von Eckardstein (read in the light of Behre and Nieschlag) and the claims of the Patent are following:

i) von Eckardstein does not disclose castor oil in a concentration of 25-45%.

ii) von Eckardstein does not expressly disclose a co-solvent, nor that the co-solvent is benzyl benzoate.

iii) von Eckardstein does not disclose the precise amount of any co-solvent.

iv) In relation to the use claims, Von Eckardstein does not disclose two loading doses at 6 week intervals.

Teva's case

281. Teva's case was that it was obvious that the injectable preparation of TU in castor oil investigated by von Eckardstein was a promising treatment option and there was every reason to want to follow up that work by replicating the formulation and using it to investigate suitable dosing regimens. As to the formulation, it would immediately become apparent that a co-solvent would be needed to solubilise the 1000mg dose of TU in a volume of 4ml, and the benefit of using one with castor oil would be apparent in any event given castor oil's viscosity. It was plainly not inventive to choose a ratio of castor oil:benzyl benzoate that had been used in commercial preparations before, which is what the claims cover.

282. In particular, Teva said the following were the four necessary steps to reach the product claims:

i) Ascertaining the solubility of TU in castor oil.

ii) Choosing the co-solvent: benzyl benzoate would be at least an obvious option.

iii) Identifying the ratio(s) of castor oil to benzyl benzoate that would provide the desired solubility.

iv) Select the formulation(s) to take forward into a single dose study.

283. As to the use claims, Teva then said that the only further step necessary would be to change from 4 loading doses 6 weeks apart, to 2 loading doses six weeks apart. Teva said this was clear from the face of the results in Nieschlag because at doses 3 and 4 the peak TU concentration was too high.

284. Breaking the argument down in this way oversimplifies it, and also does not give an adequate flavour of the reasoning said to underlie the skilled team taking this course. To assess the obviousness case, I need to explain more about that.

285. Teva's case was that the skilled clinician would be the primary mover; that he or she would find von Eckardstein and the earlier work in Behre and Nieschlag interesting and worth progressing (I agree with this, despite Grünenthal's argument to the contrary, which I address below); and that he or she would give the following instructions to the Skilled Formulator (from Anderson 1 paragraph 135):

i) Recreate as closely as possible the formulation of TU in castor oil used in Behre, Nieschlag and von Eckardstein;

ii) The aim of testosterone replacement therapy is to keep patients' levels of testosterone within the normal range for as long as possible. Testosterone replacement therapy is typically given life-long and so reducing the burden on patients and Healthcare Professionals by having infrequent intervals between doses is a goal;

iii) The formulation must be of sufficient viscosity such that it can be administered to patients using a needle which is suitable for long-term i.m. injection (i.e. the pain and discomfort level must be low enough to be acceptable for long-term use);

iv) The formulations are stored and injected at room temperature.

286. Grünenthal picked away at some details of this, for example "as long as possible" in the second point cannot be taken too literally, and one would expect the third and fourth points to follow inevitably if the first were achieved. What I think is important, however, is that the overall goal is very definitely set as being the *closest possible recreation* of the TU formulation of the prior art.

287. If the detailed composition with amounts or percentages had been given in the prior art (of course it was not) then its recreation would be easy. It might also have been easy if a sample had been available to the skilled team so that it could be analysed, but that was not the case, although oddly some questions were put to Grünenthal's witnesses on the unwarranted assumption that a sample was available, and the responses cannot be given weight as a result.

288. Therefore Teva had to make a case that the skilled team would proceed by logic and inference to arrive at a formulation thought likely to replicate von Eckardstein, and then assess whether or not it did so by testing it in the clinic and seeing if its PK properties matched the results in the prior art.

289. Teva's case being of that nature, it is not enough simply to ask about the individual steps on the path listed above; it is necessary also to ask whether this *kind* of exercise would be obvious.

290. It is also worth noting that Teva's case was not really based, either in its main thrust or as an alternative, around the skilled team taking the pointers from von Eckardstein as to volume, dose and castor oil and then with the assistance of the CGK choosing co-solvent(s) that were simply sensible and likely to work. That would be a more conventional obviousness case, and from what I can tell it is what Teva successfully argued for in Germany – see below. Teva's first round evidence in this action was more along those lines, also discussed below. But it is different from an argument based on close recreation of what von Eckardstein's formulation actually and specifically was. The difference has an impact on my assessment of the evidence, and in particular I think that the cross-examination of Grünenthal's witnesses was a mixture of the reverse-engineering type case and the more conventional approach.

291. The structure of Teva's case in terms of its experts was that Prof Anderson provided the clinician's notional instructions to the skilled formulator, and then Prof Larsen explained how the skilled formulator would implement them.

292. Prof Larsen explained this in her first report at paragraphs 160ff. It involved certain tests of solubility and viscosity with varying mixtures of castor oil and benzyl benzoate as the vehicle to choose formulations that would dissolve 1000mg of TU in 4ml and would be of a viscosity suitable for injection, and then trying one or more candidate formulations in animals and humans to assess the depot effect. Out of a desire to keep things simple, the skilled team would, she said, not add any more excipients than necessary.

293. In her second report, in the last section, Prof Larsen provided the "clarification" of this scheme which I have mentioned above in my assessment of her as a witness. There were two aspects to the clarification. The first and more minor was to say that on reflection she did not think animal experiments were necessary.

294. The second was to explain the human experiments that she had in mind. She explained that this would involve taking candidate formulations and doing a single dose study, with the idea of seeking a formulation that gave the same profile as Behre, as reproduced in von Eckardstein figure 2. She envisaged using two different formulations, with the better taken forward into later phases of the trial, with another loading dose and the maintenance doses.

295. As to choosing the candidate formulations, Prof Larsen said this:

> 50. An obvious approach for the Skilled Formulator to take in identifying the formulations to test in this way would be to choose a formulation at either end of the range within which the formulation used in von Eckardstein was most likely to fall. They would do this by:
>
> > 50.1. choosing a formulation with a viscosity towards the upper limit of injectability (i.e. around 100 mPa s). Assuming the relationship between viscosity and amount of castor oil set out in the patent as explained in paragraph 144 of my First Report is correct, this would give a formulation with a ratio of approximately 50 vol% castor oil: 50 vol% benzyl benzoate in the vehicle.
> >
> > 50.2. choosing a formulation with a similar amount of benzyl benzoate as recorded as having been used in the Handbook of Pharmaceutical Excipients supported by reference to Spiegel and Noseworthy (as discussed at paragraphs 18-19 above). This reflects the highest level of benzyl benzoate used in commercially available i.m. injected formulations (i.e. 46% benzyl benzoate by volume of the formulation as a whole) and is therefore towards the lower end of the likely acceptable viscosity range. (The Skilled Formulator would appreciate that to adopt a formulation with more benzyl benzoate than this may require further safety testing prior to obtaining regulatory approval. I set out in Confidential Annex 1, the percentage by volume of benzyl benzoate in the Teva Product as a whole. It can be seen from my calculations that the Teva Product

> contains 45 vol% benzyl benzoate by volume of the total formulation; and 59 vol% by volume of the vehicle. This suggests that the Skilled Formulator would likely choose a formulation with a ratio of approximately 40 vol% castor oil : 60 vol % benzyl benzoate in the vehicle. Assuming the relationship between viscosity and amount of castor oil set out in the Patent, this would give a viscosity of roughly 56 mPa s.

296. As I have already said, I do not consider this was a clarification at all. It changed Teva's case materially and filled in some major gaps. It made clear that the exercise being proposed was a distinct sort of reverse engineering where success in recreating von Eckardstein would be judged by comparing results from human trials with results from the prior art.

Motivation to pursue von Eckardstein?

297. I will return to analyse Teva's case in more detail below, but first it makes sense to assess the logically prior matter of Grünenthal's argument that the skilled team would not pursue von Eckardstein at all.

298. This argument is based on Grünenthal's "Cinderella" point, and its contentions that this was a small field in which there had been little progress, with there being other, better, newer options such as gels.

299. I have explained my findings about the attitudes of the art when dealing with the CGK above, and based on them I reject this argument. I.m. injections were a very important part of the clinical picture for hypogonadism but the frequency of injections was a significant limitation on their desirability and usefulness. Von Eckardstein offered a major improvement that could significantly reduce the number of injections needed.

Obvious steps

300. In dealing with the CGK and the interpretation of von Eckardstein I have commented on the skilled formulator's attitude to castor oil and its viscosity. But whatever the precise position on that, and whatever the instructions given by the skilled clinician, it was common ground that if a skilled formulator was seeking to take von Eckardstein forward, a necessary and very early step would be to test the solubility of TU in castor oil. This would reveal that 1000mg did not dissolve in 4ml of pure castor oil; it would also necessarily give the skilled formulator some first-hand experience of castor oil so as to emphasise its very high viscosity. The formulator would conclude that a co-solvent would be needed in what they were going to make and had been present in what von Eckardstein used, as supplied by Jenapharm.

301. So I accept that the skilled team would look to take von Eckardstein forward, and I accept that considered in isolation Teva's step i) would be undertaken. I make clear that I have not yet assessed the issue of whether the reverse-engineering type route was an obvious one to pursue.

302. Teva's next step, step ii) is to choose the co-solvent. Its contention is that benzyl benzoate was the leading candidate or at least an obvious choice. I agree that it was a well-known CGK one and probably would be on a skilled formulator's short list given a free hand. I touch on some of the relevant materials when dealing with step iii) (proportions of benzyl benzoate and castor oil) below, and they also justify the proposition that castor oil with benzyl benzoate was a combination which had been used before on a number of occasions.

303. Grünenthal contends that there were other choices too, such as isopropyl myristate and I find that there were. Teva did not say that this was a one-way street in any case.

304. This was one of a number of stages in Teva's argument where I think it was sliding from the notional instruction to recreate the von Eckardstein formulation into reliance on what was simply attractive or well known to the skilled team. The skilled team might think that benzyl benzoate was well known, but that does not mean that von Eckardstein had used it. Similarly, although this probably comes in at Teva's step iv), it might be desirable and hence relatively conventional to have only castor oil and benzyl benzoate in the formulation, but there would be no way for the skilled team to know that that was that Jenapharm had done. After all, to get 1000mg of TU into the formulation it had been necessary to use the unusually large volume of 4ml.

Proportions of castor oil and benzyl benzoate to obtain desired solubility

305. This is Teva's step iii). It would involve trying different proportions of castor oil and benzyl benzoate to find a range that solubilised 250mg/ml of TU. As Teva accepted, it is not known what the limits of this range would be, except that 100% castor oil would not work and with hindsight one knows that 40:60 castor oil to benzyl benzoate would work (since this is what Nebido uses).

306. I agree that this work would not be burdensome. But that is to view it in isolation, assuming as it does that benzyl benzoate was the right co-solvent and that there was nothing else in the formulation.

307. This step gives a range of proportions. The choice as to that range formed the next step in Teva's argument.

Selecting the formulation(s) to test

308. This was a major bone of contention. There are two aspects to it. The first one is what the CGK and/or results of research in the literature would have indicated was conventional as to the proportions of benzyl benzoate and castor oil. Grünenthal's case was that the proportion of benzyl benzoate required by the claims is very high, unusually or even uniquely so, judged by the standards at the Priority Date. Teva disagreed. The second aspect was how the skilled team would choose proportions for the candidate formulations to take forward into animal and/or human tests.

309. As to choosing proportions for candidate formulations, I have set out above what Prof Larsen said in her written evidence. In her oral evidence she changed this

again to say that a formulation with the maximum possible benzyl benzoate would be used to achieve greater solubility and thereby add to the depot effect. I have touched on this in my assessment of Prof Larsen as a witness. Prof Østergaard did not agree with the skilled formulator choosing a low viscosity for this reason.

310. I found Prof Larsen's evidence on this part of the analysis very unconvincing. The fact that her clarification came in reply evidence only presented a serious and elevated risk of hindsight and in my view a good deal of hindsight crept in. The analysis, even in her written evidence, presented a complex and artificial exercise which was not close to being shown to be a CGK approach. It was further undermined by Prof Larsen's invoking solubility in her oral evidence as just mentioned. It is difficult to be confident about whether the skilled formulator would think that more or less benzyl benzoate was likely to be a good thing, but what is clear is that it was a messy and uncertain thing to predict and, again, could not really help with what Jenapharm had actually done.

CGK/literature on castor oil with benzyl benzoate

311. It was not disputed that castor oil was CGK, or that benzyl benzoate was a CGK co-solvent. There were however disputes to a greater or lesser extent about what co-solvents were used with castor oil and, especially, the percentage of benzyl benzoate in the vehicle when it was used as a co-solvent. The latter was of particular importance to the obviousness case because Prof Larsen's evidence was that the skilled team would prepare and test a preparation with castor oil and with benzyl benzoate at the maximum percentage previously authorised.

312. Teva relied on the following CGK texts:

    i) Pharmaceutical Dosage Forms (1992) – states that "[b]enzyl benzoate may be used to enhance steroid solubility in oils if desired".

    ii) Handbook of Pharmaceutical Excipients (2000) – states that "[b]enzyl benzoate is used as a solubilizing agent and nonaqueous solvent in intramuscular injections at concentrations between 0.01-46.0% v/v". There is a footnote reference to Spiegel and Noseworthy (see below).

    iii) The Science of Dosage Form Design (Aulton) (2002) - identifies benzyl benzoate as a co-solvent with similar viscosity to ethyl oleate.

    iv) Use of Nonaqueous Solvents in Parenteral Products by Spiegel and Noseworthy (1963) – states that "[b]enzyl benzoate has found some use as a co-solvent in oleaginous injectables such as dimercaprol injection, and in commercial preparations of hydroxyprogesterone benzoate where it is present in concentrations of 30% for the 125-mg product in sesame oil, and 46% for the 250-mg product in castor oil."

    v) Murdan and Florence Non-Aqueous Solutions and suspensions as sustained-release injectable formulations, a book chapter (2000). This contained a number of castor oil formulations shown in table 5.1. The "oil used" column mentions only castor oil but in fact the drugs concerned all contained benzyl benzoate as well, as the cross-examination of Prof

Østergaard showed. The document also referred to isopropyl myristate, ethyl oleate and others as possible options, as well as benzyl benzoate.

313. Spiegel and Noseworthy was agreed to be CGK. I found this a bit surprising given its age, but in any event I am sure it would be found following up from the Handbook of Pharmaceutical Excipients in any event if the skilled team were embarking on the exercise contended for by Teva.

314. Teva also relied on other documents as evidence of what was known, although not saying that they were CGK themselves. These included Prof Larsen's own PhD thesis and a 1964 article by Riffkin ("Castor Oil as a vehicle for Parenteral Administration of Steroid Hormones") which Teva said would be found by a routine literature search once the skilled team had embarked on the exercise which Teva alleges was obvious. I agree that had the skilled team set off on that exercise they would have found Riffkin by routine searching because of its title. While Grünenthal attacked Prof Larsen's literature searches they did not undermine this conclusion.

315. Prof Larsen's thesis clearly was not something that would be found by a routine search and it was not said that it would. Its table 1 contained a number of drugs commercially available in Denmark or the US and meant for i.m. administration. A marked-up version of this table appeared in her report, emphasising four which contained both castor oil and benzyl benzoate. Counsel for Grünenthal chipped away at these on the basis that they were not available as injectables in the UK or were not sold in the UK under the company name given. Although what matters in law is the CGK in the UK, that does not mean that international reference works may not be considered and my overall conclusion is that it was CGK that combinations including both castor oil and benzyl benzoate were usable. But I reject Teva's contention that the combination stood out as being head and shoulders above any other, or that benzyl benzoate was far and away the co-solvent of choice. I do accept, relevant to the interpretation of the prior art, that it was reasonably common usage to refer to compositions in terms of their lead ingredient, as for example in Murdan and Florence.

Wider literature search; amounts

316. I have said already that Spiegel and Noseworthy, agreed to be CGK, refers to benzyl benzoate being present in amounts at 46% v/v, and that this is referenced in the Handbook of Pharmaceutical Excipients. I have also found that the skilled team would find their way to Riffkin by routine means.

317. This is the context for a very complex debate about whether the 46% figure referred to percentage of the vehicle or of the drug product as a whole. If the former it would be lower than what claim 4 of the Patent requires. On the other hand, for obvious reasons, 46% of the drug product as a whole would be a higher percentage of the vehicle.

318. In her second report Prof Larsen said that it was not clear from Spiegel and Noseworthy itself what the 46% benzyl benzoate meant although from the word "preparations" she thought it was probably the drug product as a whole. I agree

that it is unclear. I think Prof Larsen was attaching too much importance to the single word "preparations".

319. In any event, I consider that the skilled team would be assisted in trying to understand this by Riffkin, or at least would be open to getting help from it. Riffkin is a Squibb publication and contains two tables relevant to this point. Table V is as follows:

TABLE V.—EVALUATION OF 250 mg./ml. 17-HYDROXYPROGESTERONE CAPROATE SOLUTIONS IN VARIOUS OIL VEHICLES

Vehicle Composition	Animal Muscle Lesion Size, mm.[a]	Lot Number and Remarks on Clinical Testing
Sesame oil 50% Benzyl benzoate 50%	1049	Pr.142-53/15-7—238 injections, 20.6% reactions, rejected
Castor oil 58% Benzyl benzoate 40% Benzyl alcohol 2%	691	Pr.142-53/15-8—270 injections, 23.2% reactions, rejected
Sesame oil 60% Benzyl benzoate 35% Benzyl alcohol 5%	697	Pr.142-53/15-10—189 injections, 10.7% reactions, rejected
Castor oil 54% Benzyl benzoate 46%	258	Pr.142-53/15-11—503 injections, 4.2% reactions, accepted
Castor oil 52% Benzyl benzoate 46% Benzyl alcohol 2%	633	Pr.142-53/15-13—924 injections, 1.3% reactions, accepted

[a] Injection of 0.25 ml. into *vastus lateralis* muscle of rabbits and lesion size determined 2 days after injection.

320. And this is Table VI:

TABLE VI.—EVALUATION OF ESTRADIOL VALERATE IN VARIOUS OIL VEHICLES

Composition	Animal Muscle Lesion Size, mm.[a]	Lot Number and Remarks
20 mg./ml. in Castor oil 78%, Benzyl benzoate 20%, Benzyl alcohol 2%	197	Es.31-53/15-B—Commercially available
30 mg./ml. in Sesame oil 60%, Benzyl benzoate 40%	306	DEK-98-2—Not tested clinically; dosage increased to 40 mg./ml.
30 mg./ml. in Castor oil 80%, Benzyl benzoate 20%	194	Es.31-53-V—Not tested clinically; dosage increased to 40 mg./ml.
40 mg./ml. in Sesame oil 65%, Benzyl benzoate 30%, Benzyl alcohol 5%	803	SHX-94-4—Too irritating; not tested clinically
40 mg./ml. in Sesame oil 58%, Benzyl benzoate 40%, Benzyl alcohol 2%	496	Es.31-53-8—201 injections, 23.2% reactions, rejected
40 mg./ml. in Castor oil 58%, Benzyl benzoate 40%, Benzyl alcohol 2%	250	Es.31-53-A—826 injections, 2.67% reactions (all mild), accepted

[a] Injection of 0.25 ml. into *vastus lateralis* muscle of rabbits and lesion size determined 2 days after injection.

321. Table V has the number 46% twice, both in relation to hydroxyprogesterone caproate 250mg (with castor oil and in the second case with 2% benzyl alcohol).

322. However, table VI notes against its first entry that it is "Commercially available", and it is the only one in either table so marked.

323. Point 3 of the Summary and the footnotes are also relevant:

> 3. Examples of commercially available products are the estrogen, estradiol valerate[5] at 20 mg./ml. and 40 mg./ml., and the progestogen, 17-hydroxyprogesterone caproate[6] at 250 mg./ml.
>
> [4] Case reports: estradiol valerate, 20 mg./ml., in castor oil 78%, benzyl benzoate 20%, benzyl alcohol 2%—90 injections in 46 patients. Two mild local reactions. Estradiol valerate 40 mg./ml. in castor oil 58%, benzyl benzoate 40%, benzyl alcohol 2%—51 patients. Number of injections not completely tabulated. One report is in press.
>
> [5] Marketed as Delestrogen by E. R. Squibb & Sons, New York, N. Y.
>
> [6] Marketed as Delalutin by E. R. Squibb & Sons, New York, N. Y.

324. Footnote 6 reads very much in keeping with Spiegel and Noseworthy's reference to the "250mg product".

325. One's initial impression is that the 46% in Table V is likely to correspond to the 46% in Spiegel and Noseworthy, but Teva responds that the Table V products are not said to be commercially available, and are just preparations that Squibb was doing research on. Although this is possible, it does seem quite a coincidence that the percentage of benzyl benzoate remains exactly 46%.

326. Teva also pointed to a 1966 Physician's Desk Reference which referred to the 46% figure but I found it no less ambiguous in the overall context than Spiegel and Noseworthy. Its weight was also reduced by being introduced only in cross-examination.

327. In addition, Teva pointed to a post-priority article by Zhao and others (2014). That referred to Delalutin, referring to the 46% figure and to 2% benzyl alcohol. It said that Delalutin had been withdrawn and replaced by Makena, whose formulation was said to be identical. Makena was said to have 25% of the active, 28.6% castor oil, 46% benzyl benzoate and 2% benzyl alcohol. In that instance, the 46% was clearly of the total composition and not the vehicle, as Prof Østergaard accepted. Again, however, this document was only added into the case in cross-examination and it is post-priority; it cannot possibly be used to interpret Riffkin.

328. Grünenthal also relies on Riffkin for the point that the commercially available formulation in Table VI has benzyl benzoate at only 20%, and benzyl alcohol at 2%.

329. Prof Larsen also said that the skilled team's literature search would turn up a 1995 paper by Partsch et al (the last author is Nieschlag and the paper is referenced in von Eckardstein). This refers to TU in tea seed oil (not castor oil) with 15% benzyl benzoate.

330. Grünenthal also said that the skilled team would know from the literature as a matter of CGK that in the testosterone enanthate product Testoviron the vehicle

was 60% castor oil and 40% benzyl benzoate. I do not accept these numbers were CGK. The product's SmPC only gave ingredients and not percentages (a prevalent problem in trying to work out how much benzyl benzoate was the maximum used prior to the Priority Date), and Prof Østergaard said they were not CGK. Prof Larsen was in fact aware of the proportions from the literature (a review by Chien and others), but that does not mean they were CGK. I do accept however Prof Østergaard's evidence that the skilled team might well assume that benzyl benzoate was a more minor component of the vehicle.

331. It is worth reiterating that all of these materials were gone into in connection with Teva's case that the skilled team would set up human experiments with two compositions of TU with one having the highest percentage of benzyl benzoate in the vehicle previously used. The scrappiness and scarcity of the information available leads me to conclude that the skilled team would have little to no confidence in this exercise being meaningful. If they did it, they would be more likely to conclude that the 46% figure in Spiegel and Noseworthy was a percentage of the vehicle. Probably, however, they would think that considerably lower percentages of benzyl benzoate would lead to formulations that had a viscosity that was consistent with reasonable injectability. They would also observe a reasonably frequent use of benzyl alcohol when castor oil and benzyl benzoate were used together, as a preservative and local anaesthetic.

Assessing success

332. As I have said, Teva's case involves the idea of taking candidate formulations and using them in a single dose study, then comparing the serum T levels over time with the result in Behre, as reproduced in von Eckardstein.

333. I do not think that Teva had any sound basis for this being a CGK approach or any concrete conception of how similar results would have to be in order to say that success in the sense of replicating the von Eckardstein formulation might have been achieved. I say "might" because it was clear that different formulations could give very similar results. I asked Prof Anderson about this and his answer was fairly generic and vague. This is not a criticism of him and apart from anything else these are biological systems with appreciable variability, using small patient populations.

334. I reject any suggestion that testing successful reverse engineering in this way would be obvious to do or, if the skilled formulator did think of it, regarded as at all reliable. It would also involve very substantial effort, even leaving out of account the ethical concerns that might arise, and the skilled team would realise that if their first candidate formulations did not "match" they would have to go back and make more, with different co-solvents or proportions and try again. They would also, it seems to me, not know *why* they had failed the first time – whether they had the wrong co-solvent, or the wrong proportions, or whether there was a third ingredient would be no more knowable from their failure than before. Additionally, it was common ground that the skilled team would not think that only a close recreation of von Eckardstein would "match" the Behre result.

335. I also bear in mind the fact that Prof Larsen originally said that animal experiments on the candidate formulations would be appropriate but then changed

her mind. This was unconvincing and I think it reflects both hindsight and an unrealistic view of how much confidence the skilled team would have in the exercise as a whole. It is a minor part of the assessment, however.

Conclusion on obviousness

336. I reject the obviousness case. I do not think the sort of exercise proposed by Teva is of a kind that would be familiar to the skilled team or, if they thought of it, at all routine. Teva's formulation of the attack into four steps oversimplifies the analysis and conceals many problems. I have spelled out problems with the individual steps in a number of instances above. The attack is also strongly influenced by hindsight and I found Teva's expert evidence problematic and unconvincing for the reasons given above.

337. That is enough to mean the attack fails against the product claims. Even if those fell, Teva would also have had to show that the posology elements of the use claims were obvious. Teva's case on that depended critically on the skilled team having the perception that the work described in Nieschlag and then von Eckardstein could be seen as four loading doses followed by a number of maintenance doses, and then reducing the number of loading doses. I have rejected that above. It is more hindsight. I agree that once just the right view of the work described in the papers is taken then the figure in Nieschlag can be positioned to make it stand out that two "loading doses" could be better than four, but the positioning also comes from hindsight. In addition, there were various other posology options that could be tried. Just saying that loading doses as a concept were CGK does not mean that the skilled team would perceive the prior art in the particular way argued for by Teva, and seen in the overall light of these points, I do not think the answers of Prof Wu that loading doses would be no less obvious than other options, which Teva relied on heavily, means very much at all.

Insufficiency

Plausibility law

338. There have been a number of decisions in this area in the last decade. I summarised relevant principles in *Sandoz & Teva v. Bristol-Myers Squibb* [2022] EWHC 822, and *Gilead Sciences Inc & Anor v NuCana PLC* [2023] EWHC 611 (Pat). I drew particularly on the principles from Kitchin LJ's judgment in *Regeneron v Genentech* [2013] EWCA Civ 93, at [95]-[103], Lord Sumption in *Warner-Lambert Co LLC v Generics* (UK) Ltd [2018] UKSC 56, and Birss LJ in *FibroGen v Akebia* [2021] EWCA Civ 1279.

339. My decision in *Sandoz* was recently upheld by the Court of Appeal (([2023] EWCA Civ 472)). The judgment of Arnold LJ is significant because he was able to consider the decision of the Enlarged Board of Appeal in *G2/21* which had not been given at the time of my judgments in *Sandoz* and *Gilead*. He concluded that *G2/21* provided no reason for UK courts to depart from *Warner-Lambert*. The issue in *Sandoz* was about plausibility in respect of a single chemical compound rather than plausibility across the scope of a claim covering numerous possibilities; for the latter situation the key statement of the law is to be found in

Fibrogen at [53]-[57] (both sides before me cited this and neither said that it has been called into question by *G2/21*):

> 53. To apply the reasonable prediction principle one has to take three steps. First one must identify what it is which falls within the scope of the claimed class. Second one must determine what it means to say that the invention works. In other words what is it for? Once you know those two things, the third step can be taken: to answer the question whether it is possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim.
>
> 54. In a paradigm case of a Swiss style claim to the use of a class of compounds defined in a Markush formula to treat a disease, the first two steps are simple and the question will be whether it is possible to make a reasonable prediction that substantially all the molecules within the Markush class will work to treat the disease. In terms of functional and structural limitations in claims, in this simple case the structural limitation defines the class and is considered at the first step and the functional limitation defines the therapeutic effect and is addressed at the second step. The significance of the existence of inactive compounds within the Markush formula will be a matter of fact and degree but the fact they exist does not matter if it does not falsify the reasonableness of the prediction. Also and similarly the fact that active compounds within the formula turn out to be unsuitable as clinically approved agents for reasons unrelated to efficacy itself, such as side effects profiles, bioavailability and the like, is also unlikely to falsify the reasonableness of the prediction, depending again on this being a matter of degree. These issues will also play a role in analysis of any undue burden.
>
> 55. However in other cases the first step also involves a separate functional limitation too, in addition to the use to treat a disease. Claims with such double functional features are not so unusual. Twenty years ago the crucial claim in *Lilly ICOS v Pfizer* [2000] EWHC Pat 49) was to the use of a cGMP PDE enzyme inhibitor for the treatment of male erectile dysfunction. There was no structural limitation in that claim at all. The claim in *Regeneron v Genentech* is another example. Although there was a debate before us about how to characterise that claim, essentially it was a claim to the use of a product defined at least partially in functional terms for use in treating certain non- cancerous diseases characterised by excessive blood vessel growth. The functional definition of the products claimed was that they had to be antagonists to human vascular endothelial growth factor (VEGF). Amongst other things the court below in that case had held that it was possible to make a reasonable prediction that VEGF antagonism could be used to treat all the relevant diseases, and on appeal the Court of Appeal rejected the insufficiency attack holding at [134] that "The judge had ample evidence before him upon which to conclude that it was plausible that VEGF antagonism could be used to treat any non-neoplastic neovascular disease."
>
> 56. Thus *Regeneron* is an example of the three step test I have referred to applied to a claim with double functional features. To distinguish between

> these two kinds of functional feature I will refer to "step one functional features" (such as VEGF antagonism) and "step two functional features" (such as treating the relevant diseases). It will be a matter of construction to work out what sort of functional features one is dealing with.
>
> 57. In some cases the second step is the aspect which is a bit more involved. So in *Idenix v Gilead*, claim 1 was to a Markush class of molecules (see Kitchin LJ para [61]). The claim language did not include any reference to what they were for and so one could not answer the question at the second step by looking at the words of the claim. This is also not unusual. If the compounds are new, then a claim to those compounds will be novel without including a claim feature which refers to what they are actually for. However that does not prevent the reasonable prediction principle being applied. In fact the answer in *Idenix* was clear from the patent specification. That showed that the point of the invention was to treat infections caused by viruses in the *Flaviviridae* family. So one can assess the validity of the claim on the basis that it is a claim to compounds with anti- *Flaviviridae* activity, which is what Kitchin LJ said at paragraphs [113] and [124]. So, in the language coined above, anti-*Flaviviridae* activity was a step two functional feature. The issue in *Idenix* arose in the context of inventive step but the same approach applies to reasonable prediction/plausibility. Note that this does not mean that claims to compounds per se are actually limited to using the compounds for treating *Flaviviridae* infections, but for the purposes of assessing questions like inventive step and reasonable prediction/plausibility, one needs to know what the compounds are supposed to be useful for. In fact in *Idenix* the outcome of the third step was against the patentee. The court held that it was not plausible that substantially all the claimed molecules would be effective against *Flaviviridae* infections, and hence it was *Agrevo* obvious and also insufficient for lack of plausibility for the same reason (see paragraphs [129] and [140]).

340. So in the context explained in more detail in [54]-[57], the questions that must be asked are, as per [53]:

    i) First, what falls within the scope of the claimed class?

    ii) Second, what does it mean to say that the invention works?

    iii) Third, is it possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim?

341. Both parties before me referred to this three-part test as the correct legal analysis.

342. As to the standard for plausibility, I will again apply the Supreme Court's formulation in *Warner-Lambert* at [37]: "something that would cause the skilled person to think that there was a reasonable prospect that the assertion would prove to be true". It must be noted that the specification has positively to make it plausible, although only to this undemanding standard, that the invention will work across the scope of the claim.

343. I have also found it helpful to have in mind the following passage from the decision of Birss J sitting at first instance in *Illumina v Latvia* [2021] EWHC 57:

> 276. Now I come back to *Regeneron*. As mentioned already the descriptive term "mouse" in *Regeneron* was regard as encompassing a range. By the same token any descriptive or functional language will inevitably cover a variety of things and therefore will encompass what one could call a range. Thus it will be necessary to examine whether such a range is a relevant one in the *Regeneron* sense. If it is a relevant range then the consequences in *Regeneron* will follow if it is not enabled across the whole range (subject to *de minimis* exceptions) and the presence of a type or embodiment within that range which cannot be performed at the relevant date will be fatal even though, if it was able to be performed years later, it could be said to draw on the technical contribution made by the inventors. However if the range is not a relevant range then no difficulty of that kind arises. That is the point Lord Briggs is making at paragraph 42. Separately and in either case, the standard being applied is one of no undue burden.
>
> 277. To take an example mentioned in argument in this case, say an inventor invented a new teapot which was inventive and useful because its spout was shaped in a new way so as not to drip. The claim would be to a teapot with the spout shaped in that special way. The claim might well not say anything about the material from which to make the teapot, because it is irrelevant to the invention. Equally the claim might refer to "a tea pot made of any suitable material". There would be no difference between a claim which expressly said that or one which was silent. Either way the claim can be said to encompass a range of teapots made of different materials. Now the patent needs to enable the skilled person to make the product. In the example I will assume the skilled person could choose, identify and test suitable materials at the priority date without an undue burden. China would work and chocolate would not. However the claim would be infringed later on even if a teapot was made using a new inventive form of Pyrex glass which had not been invented at the teapot patent's priority date. Furthermore in my judgment this fact, that the claim covers types of teapot which it does not enable, does not reveal some insufficiency. The fact that the skilled person could not make such a teapot at the priority date of the teapot patent does not matter. What does matter is that the descriptive feature of the claim, which is at least implicit in the claim, that the teapot has to be made of a suitable material, is not a relevant range in the *Regeneron* sense. However note the potential for error here. The material from which a teapot is made is plainly crucial to its function as a teapot. There are materials which are not suitable to use for teapots. That is not the kind of relevance which Regeneron is referring to. Relevance in the *Regeneron* sense is a much more particular concept which depends on examining all the circumstances, and depends not simply on the invention (that is to say the claim as drafted) but also on what I can only think of calling the essence or core of that invention (closely related to the technical contribution and/or the inventive concept). Although the invention in this example is (by definition) a teapot since that is what is

claimed (s125 , 1977 Act), nevertheless the value, utility and purpose referred to by Lord Briggs in principle (vii) are concepts which in this example would be focussed on the shape of spout. In fact I doubt this teapot example has much of a relevant range (of spout shapes) at all. On the facts of *Regeneron* itself the range of numbers of segments was clearly relevant to the essence of the invention since it was the means for getting high antibody diversity, whereas different kinds of mice was not. In other words when applying this test one may need to examine the essence of the invention as well as the claim language itself.

278. Once the concept of a relevant range is properly understood, I think it will be an unusual case in which the kind of ordinary descriptive or functional language one sees in most patent claims will be regarded a relevant range in the Regeneron sense.

279. In summary, the principles I derive from these authorities are:

i) When examining any aspect of claim scope for the purposes of the enablement it is necessary to distinguish between ranges relevant in the *Regeneron* sense and other ranges.

ii) For ranges relevant in the *Regeneron* sense, to be sufficient, there must be enablement across the whole scope of the claim within that relevant range (subject to *de minimis* exceptions) at the relevant date. If a type or embodiment within such a range is not enabled at that date then the fact it could be made later, as a result of further developments not enabled by the patent, even though it never could have been made without the invention, will not save the claim from insufficiency.

iii) Not all claims will necessarily contain a range relevant in the *Regeneron* sense but if they do, then this principle applies to that range.

iv) An example of another range, not relevant in the *Regeneron* sense, will be a descriptive feature in a claim (whether structural or functional) which can cover a variety of things, but for which that variety does not significantly affect the value or utility of the claimed product or process in achieving its relevant purpose. The relevant purpose is judged in all the circumstances, starting from the terms of the claim itself but also, where appropriate, by reference to the essence or core of the invention.

v) For a claim feature which amounts to a range in this other sense, the skilled person must still be able to make a suitable selection, without undue burden, in order for the claim to be sufficiently disclosed. However provided that is so at the relevant date, such a claim feature will not be insufficient simply because it is capable of also covering within its scope things which had not been invented at that relevant date.

vi) When examining enablement of any kind, the test is always about what the skilled person is able to do without undue burden. The patentee is entitled to expect that the skilled person, in seeking to make the invention work, will exercise that skill. If need be that exercise will involve testing and experiments, as long as it is not unduly burdensome.

344. The reason this potentially matters in the present case is that a number of the parameters of any given formulation relied on by Teva as making the claims of the Patent insufficient for lack of plausibility are not mentioned in the claims. A particular example is volume. I wanted to be satisfied that the parameters relied on by Teva were legally relevant, although in the end Grünenthal's defence to the plausibility attack was not on this basis, and I return to this below.

345. It was common ground that as a matter of law a claim is not rendered insufficient simply because it literally covers absurd options that the skilled person would unhesitatingly reject. For example in the present case the stipulated percentages of castor oil and benzyl benzoate leave room for up to 20% of other ingredients. The claim is not insufficient on the basis that in a literal sense the inclusion of something toxic or hopelessly sticky is permitted. The chocolate teapot is an example of this sort of thing, and I discussed it in more detail in *Siemens v GE* [2022] EWHC 3034 (Pat) at [230ff] but since the point was not in dispute I need not go into it further.

346. Grünenthal referred to two other authorities worth mentioning at this stage:

i) In *GSK v Wyeth* [2016] EWHC 1045 (CH) [sic] an insufficiency attack on a vaccine composition claim failed; the attack was that the claim allowed for but did not specify an appropriate adjuvant. Teva says that the case is merely one where routine means, on the facts, were available to choose a suitable adjuvant; it says that in the present case its argument is different and is that having 20% of something else would affect whether there was a depot effect at all in an unpredictable way. As will appear below, I agree with this distinction but in any case the argument over GSK on both sides before me revolved around comparing facts rather than identifying principles and I therefore do not think it assists.

ii) In *MSD v Ono* [2015] EWHC 2973 (Pat) Birss J rejected an insufficiency attack against a broad claim to a class of antibodies for treating cancer despite there being some types of cancer that probably could not be treated with them. In doing so, he referred to the fact that the claim was a "reasonable generalisation" – see at [166]. I agree that the notion of allowing patentees to make reasonable generalisations rather than being unfairly limited to preferred embodiments informs a proper analysis and has been part of the basis of the development of this area of the law, but a freestanding assessment of reasonable generalisation is not on its own or in itself the legal test. I also note that Birss J regarded the situation as one where the prediction had only turned out to be wrong in two instances and was generally correct, in the context of an invention which was a major advance.

347. Finally in relation to the law, I note that Teva sought to rely on aspects of the general teaching of the Patents which were not reflected in the claims, for example [0034] referring to a vehicle with 98% castor oil. This is not legitimate and Teva cited no authority in support of it. A patentee has to render plausible the *claims* across their scope, not wider teachings which were not claimed.

348. I turn to the three *Fibrogen* questions.

349. There is no dispute as to the first.

350. As to the second, this is a situation where it is necessary to look to the specification; the claims, and especially the product claims do not give the answer on their own. Claims 1 and 4 do say that the claim has to be [suitable] "for intramuscular injection" and that has some functional implication, but it is not the whole answer because the Patent is not about the mere physical possibility of getting the claimed compositions into patients' muscles, it is about the pharmacokinetics thereafter.

351. In my view the answer to the second question is that for a composition of claims 1 and 4 to "work" they must be capable of providing physiological levels of testosterone for a prolonged period of time, and significantly longer than the 2-3 weeks recognised by the Patent as being achieved by the prior art. See in particular [0001], [0006] and [0015]. Based on the CGK the skilled team would understand that this depended on achieving a depot effect, and the Patent spells this out at [0023ff].

352. The use claims (7, 15, 16) are to similar overall effect but more specific about what "prolonged" means: long enough for the 6 weeks between loading doses and 9+, or 10, 12 or 14 weeks between maintenance doses to be used consistently with achieving and maintaining physiological levels.

353. Given the way the arguments developed, I do not think this difference between the product claims and the method claims mattered, though.

354. The real bone of contention was therefore Fibrogen question 3.

355. Teva's argument, in its essence, was that:

    i) There are many factors that affect the achievement and duration of a depot effect. This was not materially in dispute.

    ii) Prediction of a depot effect is not possible or at least very difficult, especially in relation to lipophilic compounds.

    iii) The claims allow unbounded or at least very substantial variation of the following parameters:

        a) Amount of TU (the use claims do specify this precisely at 1000mg);

        b) Volume;

        c) Concentration;

d) Percentage of castor oil in the vehicle;

e) Percentage of benzyl benzoate in the vehicle;

f) Percentage of other excipients in the vehicle.

iv) The claims also allow the TU to be in solution or in suspension.

v) In consequence of iii) and iv) the claims cover formulations with widely varying viscosities and diffusion rates.

vi) There is only a single example of a working formulation in the Patent - this is not in dispute - making it hard to generalise.

vii) The poor presentation of the Examples of the Patent would further undermine the skilled reader's confidence.

356. I am satisfied that the matters listed in iii) relate to "relevant ranges" in the sense developed in the authorities that I have referred to above. They are either explicitly referred to in the claims or are called out in the specification (in particular at [0023]) as relevant to achieving the necessary depot effect. I am slightly more doubtful if the solution/suspension point qualifies as a separate "range" – suspension is mentioned more peripherally and only briefly at [0038] and Prof Østergaard's evidence was really the skilled person would not have suspensions in mind in this context – although clearly if it did it would increase the unpredictability. My conclusion as to the very high degree of unpredictability that I reach below does not depend on taking the possibility of using a suspension into account.

357. I return to points ii), iii) and iv) below as part of my overall assessment.

358. In relation to excipients, Teva accepted, as I have said already, that obviously foolish choices were not relevant, but argued that otherwise sensible choices that the skilled team might want to make could lead to unpredictable results on the depot effect. I agree with this.

359. Grünenthal relied on:

i) The reasonable generalisation point to which I have already referred.

ii) The fact that the claim is not especially broad, and much narrower than the very wide Markush-type claims seen in other patents. I agree that those other kinds of claims can often be somewhat grasping and may well be insufficient by reason of their breadth but it does not help me decide this case merely that other patents are worse than the present one.

iii) That it would be unreasonable and impractical for a patentee in this sort of situation to do multiple clinical trials just to support generalising in patent claims. I agree that there could be a lot of effort in going so far as clinical trials and that requiring their performance in all cases would be undesirable. I also recognise that the burden in time and money of doing clinical trials has fed into the policy analysis underlying the law on sufficiency under the

EPC – it is part of the reason for the relatively benign treatment given to second medical use claims. I also note that evidence supporting sufficiency does not have to consist of clinical trials, though: theory, models and laboratory or animal experiments are also open to the patentee. In the end this sort of consideration has already been factored into the legal test for plausibility, in my view. I have to make my decision based on the work that is in the Patent (and the CGK) and I should not apply any more lenient standard in the light of this factor.

iv) That the claim had only two "main variables" – the percentages of castor oil and benzyl benzoate, two specifically identified ingredients. I agree that this is so, although for reasons given above I think other parameters not explicitly stated in the claims are "relevant ranges".

v) That the claimed products can be made, and there is no classical insufficiency attack. I think this is irrelevant. Plausibility is a distinct basis for insufficiency although of course if the products could not even be made one would not have to consider it.

vi) That although the amount of TU is not specified for the product claims, there would be a practical limit to how much could be dissolved in an amount of fluid capable of being injected into a human. I agree that my analysis should be guided by reality in this respect. I should not, for example, take into account what would happen with a ridiculous volume of, say, 100ml. But Teva's argument does not depend on that; it is founded on the range of reasonably possible volumes (up to low single digit mls) being quite broad in terms of the ratio of the minimum to the maximum.

vii) That Teva had not led evidence of any particular inoperative embodiment. Such is not Teva's case. Indeed it would be quite hard for Teva, on its case, to say what an inoperative embodiment was, since its main argument is that there is an impossible degree of uncertainty.

viii) For any particular formulation within the claims, routine tests would enable assessment of whether it "worked". This argument is essentially the encouragement-plus-ability-to-test one that I held was bad in law in *Sandoz* (see [223]).

360. At a more general level, I think it worth articulating the overall nature of Grünenthal's case. Counsel for Grünenthal accepted in discussion during oral closing submissions that its case is a negative one, in the sense that it does not put forward any positive basis on which it is possible to predict that formulations across the scope of the claims will "work", but instead says that Teva has not discharged the ultimate legal burden of proving that such a prediction cannot be made. That sets the present case apart from the more common situation in recent reported trials, where the patentee has been able to point to e.g. an animal model or cell assay making a second medical use plausible, or a structural argument that because e.g. fluorine "works" so will other halogens, or e.g. the similarity of a number of worked examples. I agree that the burden lies on Teva, but Grünenthal's inability to put forward some positive basis for prediction is telling.

361. Grünenthal also pointed to the limited extent of Teva's written evidence. The high point of that was, as Grünenthal said, paragraphs 39-46 of Prof Larsen's second report. Quite a lot of that is concerned with the question of whether the absolute amount of TU would prevent prediction, a point which does not apply to the use claims, but it also covered the effect of volume, of room for other ingredients and the implications of changing viscosity on the depot effect. I do agree with Grünenthal overall that the evidence was brief, but that does not necessarily mean it was inadequate and anyway I have to assess all the evidence that came out at trial as well.

362. As to that:

    i) Prof Wu said that the effect of dose was unpredictable and at points he also accepted that changes in solvent and co-solvent percentages would also give rise to unpredictability, but his main position was that these were matters for the formulator and not the clinician.

    ii) Prof Østergaard was asked about predictability in a passage of cross-examination at T5/663-674. At two points he referred to extreme cases being unpredictable and Grünenthal relied on that as limiting the relevance of what he said, but his evidence in the main did not concern extreme cases. I think he accepted the general lack of predictability urged by Teva, for example. He also accepted that lipophilicity made the situation all the more unpredictable (a point also accepted by him at T4/541), and it was pointed out to him effectively that he had invoked the unpredictable effect of formulation changes when arguing against obviousness.

    iii) Grünenthal's cross-examination of Prof Larsen on the relevant paragraphs of her second report was extremely brief and limited to trying to establish with her that it would be possible to choose some alternative co-solvents for use along with benzyl benzoate and giving equivalent viscosity to benzyl benzoate and castor oil alone. This was a very narrow point indeed and not a challenge to her other evidence on unpredictability. In its written closing submissions Grünenthal then sought to pick apart her paragraphs 45 and 46, but I found that unconvincing given the lack of cross-examination.

363. My overall conclusion is that this is context in which the degree of predictability is simply extremely low, verging on nil for significant changes to relevant parameters. The evidence supporting this conclusion is brief, and I have borne that very much in mind, but it is not a conclusion that necessarily needs long articulation or a lot of detail.

364. As I have said, I agree with Grünenthal that the claims could in theory have been much wider, but they are not in fact all that narrow. What I mean is that claim 1, for example, allows any ratio of castor oil to co-solvent, with claim 4 allowing ratios from 25:65 up to 45:55 (about 2:5 up to almost 1:1). Additional ingredients including further co-solvents can be present in amounts from 0% up to 20%. The volume can range significantly even assuming as I do that there are realistic limits on the total amount injectable. These variable parameters have knock-on effects on solubility, viscosity, partition coefficient and hence ultimately on the depot effect.

365. All of this is without considering the total amount of TU, which is unspecified for the product claims. I note that Grünenthal has had to propose to limit the use claim from the range of 500-2000mg down to specifically 1000mg. It is plain from the development of Grünenthal's evidence that this was driven by the fact that its witnesses would not support plausibility for the range, and I think the implicit acceptance of lack of plausibility on that basis is a relevant consideration supporting my assessment of similarly wide ranges on the other parameters, although I would have reached the same conclusion without it.

366. I have touched above on Grünenthal's argument that patentees ought to be allowed to generalise from preferred embodiments. I am not making a finding that they ought not, or cannot. Grünenthal has a narrower claim (claim 5) which avoids many of the problems by having a specified amount, volume and ratio of castor oil to benzyl benzoate. That claim is not alleged to be infringed, but there was nothing in principle to prevent Grünenthal during prosecution seeking a claim wider than claim 5 but narrower than the claims now in issue. See for example the options for volume in [0045]. I am not saying that claim 5 would necessarily be valid, or trying to come up with a specific claim that would have been all right, but only to make the point that generalisation remains possible in principle, albeit constrained by unpredictability of this science.

367. Grünenthal might also have been better placed to generalise with more data or more explanatory teaching in the specification. As I have said above, I recognise that additional clinical trials would have been a burden, but the specification does describe the use of two different dosing intervals (Example 4) so I do not see any absolute reason why more than one dose might have been tried. I also do not see why Grünenthal might not have improved its position by testing in animals or even by tests to show that different compositions maintained the same viscosity and/or solubility. Again, I am not trying to describe in detail what Grünenthal should have done, but just testing, and rejecting, the argument that it would have been impossible to make an appropriate, narrower generalisation which could have met the legal test.

368. I do not attach any importance in my analysis of this issue to the deficiencies in the description of the Examples in the Patent. The skilled reader would see that they were there, but would start from the overall view that the single composition described "worked", both in the more general sense of the product claims and according to the posologies in the use claims (subject to the point about 9 weeks and the unbounded upper limit of claim 7, which I address below).

369. These findings lead to the conclusion that the product claims are insufficient for lack of plausibility.

370. If the product claims are insufficient in this way then so are the use claims, since I have interpreted the Patent and its claims such that for the product claims to "work" requires a prolonged depot effect in general and the use claims require a specific and quite ambitious duration. The detailed and demanding posology of the use claims makes them harder for Grünenthal to defend.

371. I think that I should make some additional findings about the use claims in case I am wrong about the product claims.

Claim 7 – 9 week lower limit, no upper limit

372. Claim 7 has a lower limit for the maintenance dose interval of 9 weeks and no upper limit. Teva said that each of these gave rise to an additional insufficiency.

373. Since I have found all the claims insufficient for lack of plausibility in the light of Teva's main attack on unpredictability, this does not arise, as I have said above. Additionally, the attack is not run against claim 16, which specifies the maintenance dose interval, so that would survive anyway. I will therefore be brief in what I say about this.

374. As to the law on this, I was referred to the decision of Roger Wyand KC sitting as a Deputy High Court Judge in *Anan Kasei Co. Ltd & Anor v Molycorp Chemicals & Oxides (Europe) Ltd* [2018] EWHC 843 (Pat). That was a case about ceric oxide products, with claim 1 being to:

> A ceric oxide which is an oxide consisting essentially of ceric oxide, and wherein said ceric oxide has a specific surface area of not smaller than 30.0 m2/g when subjected to calcination at 900°C for 5 hours.

375. The judge said at [106]-[108]:

> 106. Neo's objection is that the numerical limit in claim 1 is unbounded in that there is no stated upper limit to the surface area of the product but the Patent does not teach infinitely high surface area after the calcination.
>
> 107. Professor Burch stated that it would be obvious to a skilled person reading the Patent that there is a practical upper limit and that not all values above 30 m2/g would be achievable. Dr Brophy agreed.
>
> 108. Rhodia's answer is that the skilled person would be able to identify the upper limit enabled by the teaching of the Patent by routine trial and error. I agree. I do not think that this is a case, as alleged by Neo, that the claims of the Patent exceed its technical contribution. This insufficiency attack also fails.

376. He did not identify the authorities that had been cited to him on the point about the skilled person being able to identify the upper limit by routine trial and error, but at my request the parties looked into the EPO case law (which I had understood was cited to him), and that does indeed acknowledge such a standard: see e.g. T1022/09. The parties also confirmed that it was their understanding that that line of cases was cited in *Anan*.

377. Teva's case on this was put only as a squeeze. It said that if Dr Peeters' evidence that single-patient data was needed to be able to make any prediction was right (as formed part of Grünenthal's case on obviousness) then applying the same standard to insufficiency would imply that the upper end of the range could not be identified by routine means. However, I have not placed any reliance on the single-patient data point and disagreed with Grünenthal's related case about the PK member of the skilled team. More generally, I do not think Teva had any evidence that, if the product claims were valid because adequate predictions could

be made (contrary to my main findings) then the further step of establishing the upper end of the range would not be routine.

378. As to the lower limit of 9 weeks, I agree with Teva that there is no specific evidence or rationale for it in the Patent. It is not entirely arbitrary, however, in the sense that it is close to the specific 10 week period that was tested.

379. There was very little evidence on the point. Prof Batchelor said that the data in Figure 1 implied that there was a risk of supraphysiological levels of testosterone if the maintenance period was truncated from 10 weeks to 9. Teva did not really explore the point with Prof Wu; in closing written submissions it said he had accepted the point, but to my mind he was talking about the uncertainties arising from the formulation issues, which he had made clear were not properly within his expertise. I hold that Prof Batchelor's evidence that there was a risk did not rise to the level of a prediction of efficacy, in the sense of maintaining normal testosterone levels, not being plausible to the low standard required. But any difficulty of prediction in changing 10 weeks to 9 is trivially small compared to the grave difficulty of making predictions across the scope of the product claims as explained above, so as well as being a minor point it is somewhat artificial to judge it in isolation.

Scope and development of Teva's insufficiency case

380. There was a dispute about the scope of Teva's insufficiency case at the start of the trial. I propose to explain that a little more, because it provides some background to what I have said above and to the evidence. It is not of any great importance to my conclusions or reasoning, as matters have turned out, not least because Teva has succeeded on the points that I ruled that it was permitted to run and has not needed the ones that I said were outside its pleading.

381. Teva's pleading of insufficiency as it stood at the start of the trial was in paragraph 3 of the Re-Re-Re-Amended Grounds of Invalidity and was as follows:

> *Insufficiency*
>
> 3. Insofar as the Patent is not invalid as aforesaid, the specification of the Patent does not disclose the alleged invention in the relevant claims, clearly and completely enough for it to be performed by a person skilled in the art.
>
> PARTICULARS
>
> *No technical contribution over the prior art*
>
> a) If and insofar as any of the relevant claims in the Patent are not obvious as aforesaid, the Claimant will say that the disclosure of the Patent is no more enabling than that of the common general knowledge and prior art

and is, accordingly, insufficient. In particular, if or to the extent that it would not be obvious to:

> i. make any change(s) to the composition of the prior art so as to obtain a composition within claim 4 as proposed to be unconditionally amended, and/or
>
> ii. use such a composition in accordance with claims 7, 15 and/or 16 as proposed to be conditionally amended
>
> because of:
>
> i. an alleged uncertainty/unpredictability as to the release properties and/or stability of such compositions, and/or
>
> ii. an alleged lack of motivation or an alleged undue burden to carry out in vivo studies using such compositions, and/or
>
> iii. an alleged lack of clinical data and/or PK data in the prior art on which credible further analysis and modelling could be performed to devise and select potential dosing regimens, and/or
>
> iv. an alleged uncertainty/unpredictability as to the effectiveness of such compositions

the Claimant will say that the Patent is no more enabling in those regards. In particular, the limited data in the Examples have been generated using a single composition yet the relevant claims encompass a range of materially different compositions (and the use of such compositions as medicaments). There are no data in the Patent relating to such different compositions and no teaching in the Patent that enables the skilled person to make a reasonable prediction as to the release properties and/or stability and/or effectiveness of such compositions as medicaments.

No plausibility across *the breadth of claims*

b) The specification does not enable the skilled person to make a reasonable predication (nor does it otherwise make it plausible) that (1) substantially all treatment regimens falling within claim 7 as proposed to be amended (wherein injections in the maintenance phase of treatment are separated by "at least" 9 weeks) and/or (2) the use of substantially all medicaments falling within claim 7 as proposed to be amended in accordance with the treatment regimens of claims 7, 15 and/or 16 as proposed to be amended will:

> i. Result in a clinically desirable mean serum level of testosterone in patients with primary or secondary hypogonadism or patients with deficient levels of testosterone who are in therapy with a progestin or a gonadotropin suppressive agent.
>
> ii. Cause a discernible beneficial or discernible desired clinical result in relation to patients with primary or secondary hypogonadism or

patients with deficient levels of testosterone who are in therapy with a progestin or a gonadotropin suppressive agent.

382. Thus, all of Teva's insufficiency case is pleaded as a squeeze. Its starting point is that all or any of the Patent's claims are held to comprise an inventive step.

383. I do not think that the pleading is very clear or well-structured. Leaving aside for a moment the sub-headings "No technical contribution over the prior art" and "No plausibility across the breadth of the claims", it fall into three parts:

    i) First, a "shepherding" squeeze that the Patent is no more enabling than the prior art. This is set out in Particular a) down to the words "… in those regards". This kind of pleading is intended to keep the patentee honest, preventing it from saying that the prior art is not enabling if the Patent is no better, and, more generally, to enforce a consistent standard when considering the prior art and the Patent.

    ii) Second, a "reasonable prediction" plea from "In particular …" down to "medicaments". While also part of sub-paragraph a) and expressed to be a specific, particular instance of the enablement squeeze this is really a different, plausibility point (as can be seen by the words "reasonable prediction").

    iii) Third, under sub-paragraph b), another plausibility point, again denoted by the expression "reasonable prediction".

384. As to the shepherding squeeze, Grünenthal did not seek to meet the obviousness case by relying on lack of enablement in the strict sense, but it did to some extent argue that the way forward from the prior art was beset by uncertainties. I agree with Teva that a consistent standard has to be applied as to the ability of the skilled team to make predictions (while of course bearing in mind that the Patent contains information not present in the prior art) and to that extent the squeeze did its job.

385. The two plausibility points have similarities and differences but essentially the first is directed to the composition claims and the second to the use claims.

386. Paragraph 3 was heavily amended between the two rounds of expert evidence with the result that key evidence about plausibility was only included in reply evidence on both sides. I return to this below.

387. The procedural argument at the start of trial arose from Teva's opening skeleton argument. That put front and centre the arguments under paragraph 3, particularly under the banner of lack of technical contribution and of the claims exceeding any technical contribution if there was one. It de-emphasised the obviousness case significantly, and certainly compared with Teva's written evidence, which was heavily direct to a traditional, classical obviousness case over the prior art.

388. The procedural argument took the best part of the first morning of trial, which was unfortunate as it squeezed out any opening on the substantive issues.

389. Grünenthal's objection was that Teva's skeleton ran *Agrevo* obviousness and various other points relating to the technical contribution of the Patent that were not pleaded.

390. During the argument, Counsel for Teva took me through the pleading, Teva's skeleton, and the written evidence. I was satisfied that the pleading and evidence contained a proper, if rather terse, basis for the two plausibility points that I have described above (and which have succeeded), and in due course Counsel for Grünenthal did not dispute this.

391. But there were various other arguments that I concluded were not founded in the pleading, for example an allegation that the Patent did not disclose or contain proof that two loading doses was better than four. Counsel for Teva said that that was covered by the sub-heading in the pleading "No technical contribution over the prior art". I disagree; that is just a heading to denote the general nature of what follows (in which respect it is not in fact accurate – see above) to orient the reader. It does not contain any comprehensible allegation of fact to allow the patentee to understand the attack. I found Teva's other points diffuse and hard to understand and I sympathise with Grünenthal's position that it did not understand them and was not in a position to deal with them.

392. I therefore ruled on the first day of trial that it was open to Teva to run the three points described above but not more. Of course, the traditional obviousness case might also lead to the conclusion that there is no inventive step at all; that is a different matter. I also make clear that my decision was not based on whether the arguments were organised under the ultimate legal heading of insufficiency or obviousness, it being clear on the authorities that both can apply when addressing plausibility and it does not matter which (this may be subject to some modification following *G2/21* and *Sandoz & Teva v. BMS* but not in a way relevant to my decision, and anyway both post-date Teva's pleading).

393. Teva's written closing still contained a lot of submissions about technical contribution. To some extent this seemed like an attempt to go behind what I had decided on the first day of trial and I reject that. However, I think it was perfectly legitimate for Teva to cover "what it meant for the invention to work" since that is step 2 in the *Fibrogen* analysis of plausibility and an exercise in construing the specification of the Patent. I also agree with Teva's overarching submission that a basic reason for the objection of insufficiency is to ensure that the monopoly obtained corresponds to the technical contribution, but that does not mean that a party can run anything at trial that touches on technical contribution in some way. Insufficiency pleadings still have to put the patentee properly on notice of what will be argued.

394. Finally on this point, I should say that I attach no importance to Grünenthal's contention that Teva pivoted away from the thrust of its written evidence, which, in particular in the first round, was on classical obviousness and towards plausibility/lack of technical contribution. It is true that Teva did that, and it signalled the shift to some extent in its skeleton for the PTR, but a party is entitled to change emphasis so long as it stays within the proper scope of its pleaded case, and in particular parties attacking patents may legitimately do so in reaction to a patentee's developing position. Still less do I think there is anything in

Grünenthal's contention that Teva's change of emphasis was down to its losing confidence in the obviousness case. I must decide the case on the evidence as it relates to the substantive legal issues and in Lord Hoffmann's words in another context "life is too short" for spending time on why a party has taken a particular litigation strategy.

The German decision

395. As I have mentioned above, on 1 February 2023 the German Federal Patent Court (Bundespatentgericht) announced the revocation of the German designation of the Patent in proceedings between ratiopharm GmbH (a Teva company) and Bayer. At the time of the trial before me reasons had not been given. They were given on 1 June 2023 and I directed further written submissions on them.

396. I note that the claims in issue in Germany, including various auxiliary requests, were similar to but not identical to those before me.

397. Unsurprisingly, Teva said that I should give weight to the decision and Grünenthal said that I should not.

398. It is well-recognised that decisions of national courts on issues such as obviousness can differ simply because the procedure and/or evidence is different, and that this does not mean there is any inconsistency of approach.

399. In the present case, having read the German decision closely and with the assistance of the parties' written submissions on it, I reach the clear conclusion that the obviousness attack was quite different from that advanced before me. In Germany, the case was a traditional obviousness case that the skilled team would work from von Eckardstein towards a useful TU formulation for prolonged action by simultaneously optimising viscosity and solubility, that one possible and well-known co-solvent was benzyl benzoate, and that something within the claims would be produced without invention.

400. That is not at all the same as Teva's case before me, which was one of reverse-engineering the von Eckardstein formulation by means I describe above.

401. In addition, the evidence was materially different in multiple ways. For example, in Germany ratiopharm relied on experiments ("Nik5") to show what would happen during the optimisation process. These were not part of the case before me, though Prof Larsen was aware of them and counselled herself to put them out of her mind. And a significant part of ratiopharm's evidence, relied on by the Court in its decision, concerned documents relating to a commercial formulation called Proluton Depot which were not before me (Nik6, Nik9). Teva's written submissions after trial argued that there was similar or equivalent evidence in the trial before me, but I found that unconvincing.

402. Teva does not contend that I am bound by the German decision. But since the German Court decided that the Patent was obvious and I have reached the opposite conclusion, I have considered the matter carefully and reflected on whether the German judgment should make me reconsider. I do not think it should; it is simply that a different case on different evidence succeeded there.

403. Lack of plausibility was not in issue in the German proceedings.

CONCLUSIONS

404. My conclusions are:

i) The obviousness attack from von Eckardstein and the documents to which it cross-refers fails.

ii) All the claims of the Patent as proposed to be amended either conditionally or unconditionally are insufficient for lack of plausibility across their scope and therefore invalid.

405. I will hear Counsel as to the form of Order if it cannot be agreed. I direct that time for seeking permission to appeal shall not run until after the hearing on the form of Order (or the making of such Order if it is agreed). I draw attention to paragraph 19.1 of the Patents Court Guide, which says that a hearing on the form of Order should take place within 28 days of hand down. In the present case that will not be possible because of the long vacation but the hearing can take place in September 2023.