THE HIGH COURT

2014 No. 2 PAP

Between:

IN THE MATTER OF IRISH PATENT NUMBER EP (IE) FILED ON THE 27th DAY OF MAY 2002 AND REGISTERED IN THE NAME OF BOEHRINGER INGELHEIM PHARMA GmbH & CO. KG IN RESPECT OF AN ALLEGED INVENTION FOR 'INHALATION CAPSULES'

AND

IN THE MATTER OF THE PATENTS ACT 1992 AND THE PATENTS (AMENDMENT) ACT 2006

JUDGMENT of Mr Justice Max Barrett delivered on 26th July, 2017.

I. Background

1. Norton (Waterford) Limited t/a Teva Pharmaceuticals Ireland ('Teva') has come to court seeking an order for the revocation of the Irish designation of European Patent No. (IE) 1379220 entitled 'Inhalation Capsules' (the '220 Patent'), which patent is owned by Boehringer Ingelheim Pharma GmbH & Co. KG ('Boehringer'). Application has also been made by Boehringer to amend the patent claims. However, the court has been asked in the first instance to address the revocation application on the basis of the proposed amended claims, with the application for amendment to be prosecuted, if at all, at some future stage. Teva reserves its position in relation to any such future application. As part of the pleadings, two notices of experiments have been served; the response to each from Teva has been that for the purposes of the within proceedings, but without any wider concession or admission, it does not contest the results arising (if the steps prescribed in the protocols to those notices are taken) and does not require repeat performance of the experiments.

2. The invention that is challenged in the within proceedings comprises capsule-based powdered formulations of tiotropium for inhalation where the capsules are made from a cellulose derivative (hydroxypropylmethylcellulose or 'HPMC') of reduced moisture content. Tiotropium comes within a class of medicaments known as 'anti-cholinergics' and is a medication for chronic obstructive pulmonary disease ('COPD') and asthma. More particularly, the 220 Patent protects Boehringer's SPIRIVA® product. SPIRIVA® is an important product on the market for the relief of symptoms of persons with COPD. Back in 2012, for example, SPIRIVA® was the most prescribed COPD treatment worldwide and generated annual global sales of a remarkable €3.552bn.

II. The Patent

3. The first part of the 220 Patent sets out a general description of the invention, being in essence powdered preparations of tiotropium in capsules for inhalation where the moisture content of the capsules is reduced. This part of the 220 Patent outlines the benefits of the invention, *viz*. the stability of the active ingredient, the high metering accuracy of the dose released during inhalation, the efficient emptying of the capsule, and the good perforation qualities, good stability, and low brittleness of the capsule.

4. The detailed description of the 220 Patent notes that it has been found that desired capsule properties can be attained by using capsule material with reduced moisture content. Having outlined the methodology used to measure moisture content, the description proceeds to discuss the materials from which the capsule can be made. These include: gelatin in admixture with polyethyleneglycol; and HPMC. The moisture content for those materials is prescribed and methods of manufacturing and filling the capsules outlined.

5. The patent then gives instructions for (i) the proportions of tiotropium or recommended salts of tiotropium in the powdered preparation, (ii) the type and particle size of carrier, (iii) the type of inhaler that can be used, (iv) the amounts of inhalable powder to be loaded into the capsules, (v) the process of preparing homogenous mixtures of the inhalable powder, (vi) the drying of the capsules to the required moisture content (pre- or post-filling). The patent also gives instructions for the preparation of the materials used in the examples of the invention given in the patent.

6. The priority date of the 220 Patent, and hence the date by reference to which its patentability falls to be assessed, is 1st June, 2001.

III. Revocation of a Patent

7. Section 57(1) of the Patents Act 1992 provides, *inter alia*, that "[A]*ny person may apply to the Court or the Controller for revocation of a patent*". Section 58 provides that an application for revocation of a patent may be made on the grounds that, *inter alia*, "*(a) the subject-matter of the patent is not patentable under this Act" and "(b) the specification of the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*". The essence of what is patentable is stated in s.9(1) of the Act of 1992, as amended by s.3 of the Patents (Amendment) Act 2006; this provides that "*An invention, in all fields of technology, shall be patentable under this Part if it is susceptible of industrial application, is new and involves an inventive step.*" Section 13 of the Act of 1992 provides, *inter alia*, as follows: "*An invention shall be considered as involving an inventive step if, having regard to the state of the art*, it is not obvious to a person skilled in the art". Of relevance also are ss. 19(1) and 20 of the Act of 1992 which respectively provide as follows: "*19.–(1) A patent application shall disclose the invention to which it relates in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art"; "20.– The claim or claims shall define the matter for which protection is sought, be clear and concise and be supported by the description.*"

IV. Grounds of Challenge

8. Broadly, Teva has levelled a three-fold attack on the validity of the claims in issue, being (1) an obviousness attack, (2) an insufficiency attack, and (3) an AgrEvo attack, all of which grounds of attack have been resisted by Boehringer.

9. The last of these grounds of attack, the *AgrEvo* attack, is a ground of challenge that has been developed at the European Patent Office. It takes its name from the decision of a Board of Appeal of the European Patent Office in *AgrEvo/Triazoles* (Case No. T0939/92, 12th September, 1995) and has been accepted as a ground of challenge in the courts of the neighbouring jurisdiction. (See, *e.g.*, *Generics (UK) Ltd (t/a Mylan) v. Yeda Research & Development Co. Ltd* [2013] EWCA Civ. 925 and *Idenix Pharmaceuticals Inc. v. Gilead Sciences Inc.* [2016] EWCA Civ. 1089). It applies where a development may not be obvious but where the elements of the development which distinguish it from what went before make no technical contribution to the subject-matter. These features are adjudged 'arbitrary' and incapable of contributing to inventiveness. Plugged into the European Patent Office's problem-solution approach ('PSA') to identifying inventive step, such features solve no technical problem and thus fail on that ground.

10. So far as obviousness is concerned, Teva claims that the protected invention is obvious in light of three prior publications, referred to in the within proceedings by reference to the relevant author-names, being the Barnes, Maesen, and Ogura publications (Barnes, P., "Tiotropium bromide" (2001) 10(4) *Exp. Opin. Invest. Drugs* 733; Maesen, F.P.V., "Tiotropium bromide, a new long-acting anti-muscarinic bronchodilator: pharmacodynamic study in patients with chronic obstructive pulmonary disease (COPD) (1995) 8 *Eur. Respir. J*. 1506; and Ogura T., "HPMC Capsules – An Alternative to Gelatin" (1998) 10(11) *Pharmaceutical Technology Europe* 32). As will be seen later below, there was also mention at the hearings and otherwise in the evidence of an additional article (Casaburi, R. and entitled "The Spirometric Efficacy of Once-Daily Dosing with Tiotropium in Stable COPD" (2000) 118(5) *CHEST* 1294) that was not cited as part of the prior art in this jurisdiction but which, the court understands, has been cited by Teva in other jurisdictions as the closest prior art.

11. So far as insufficiency is concerned, Teva claims that the specification of the 220 Patent does not disclose the invention clearly and completely enough for it to be performed by a person skilled in the art.

12. So far as the *AgrEvo* attack is concerned, Teva claims that insofar as the invention covered by the relevant claims is not obvious in light of the publications aforesaid, it is obvious for lack of technical contribution to the art.

V. Onus of Proof
13. In the course of the hearing of the within application, some comment was made as to where the onus of proof lies in revocation proceedings. It may therefore be useful for the court to observe that the burden of proof in revocation proceedings lies on the applicant for revocation; however, the evidential burden may shift according to the state of the evidence. Thus if something is inherently improbable, more weighty evidence is required to establish that it probably occurred than if it were inherently probable.

VI. Comity

(i) Proceedings in Other Jurisdictions.
14. The within proceedings do not represent the first time that the wider Teva and Boehringer families have tilted with each other in the courts of European states as regards the 220 Patent. It is of interest to pause briefly and consider such other proceedings as have been brought.

a. Germany.
15. The relevant proceedings in the Federal Republic of Germany are *Cinfa v. Boehringer Ingelheim* (Federal Court of Justice, Germany, 12th January, 2016, Case No. XZR 38/14). The German patent was challenged by the Spanish pharmaceutical company Laboratorios Cinfa. At first instance, the Federal Patent Court held on 12th November, 2013, that the German part of the patent was partially invalid. However, on 12th January, 2016, even this narrower patent was revoked by the German Supreme Court due to lack of inventive step. There is no further right of appeal within Germany.

b. Norway.
16. The relevant proceedings in the Kingdom of Norway are *Teva Norway A.S. v. Boehringer Ingelheim PharmaGmbH & Co. KG* (Case No. 15-082184 TVI–OTIR/04). There, Teva filed a revocation action against the Norwegian national equivalent of the 220 Patent. On 17th June, 2016, the District Court of Oslo, assisted by a panel of experts in pharmaceutical technology, found the amended claims, which correspond to the amended claims in the within application, to lack inventive step. An appeal in Norway is due to be heard this year.

c. Spain.
17. The relevant proceedings in the Kingdom of Spain are *Laboratorios Liconsa SA v. Boehringer Ingelheim Pharma GmbH* (Ordinary proceedings No. 24/2012-F). Since the commencement of the within application, the Spanish court has handed down judgment in corresponding proceedings taken by a third party which may or may not (it is not clear from the submissions) be a member of the Teva group. The Spanish court dismissed the amended claims on grounds of amended matter (noting also that they were invalid, *inter alia*, on grounds of obviousness). The prior art cited in the Spanish proceedings was different to that referred to before this court.

d. The Netherlands.
18. The relevant proceedings in the Kingdom of the Netherlands are *Teva Pharmaceuticals Europe B.V. v. Boehringer Ingelheim Pharma GmbH & Co. KG* (Case No. C/09/489185/HA ZA 15-625). There a revocation action was filed by Teva. Boehringer subsequently amended the Dutch patent in a similar way to that now sought to be done in respect of the 220 Patent. On 7th September, 2016, the Dutch court held that claim 6 was invalid for lack of inventive step and that the lower moisture contents of claims 7 and 8 were arbitrary parameters which do not confer an inventive step. The case in the Netherlands was, it seems, argued on the agreed basis that a clinician and a formulator would form part of the relevant skilled team; by contrast, in the within application the issue as to who is the notional skilled person was left to the court to decide. An appeal has been lodged by Boehringer against the first instance judgment.

e. United Kingdom.
19. The relevant proceedings in the United Kingdom are *Teva UK Ltd v. Boehringer Ingelheim Pharma GmbH* [2015] EWHC 2963 (Pat). The proceedings there were argued on the agreed basis that a clinician and a formulator would form part of the relevant skilled team; in the within application, by contrast, the issue as to who is the notional skilled person was left to the court to decide. Permission to appeal the decision at first instance in *Teva* was refused in *Teva UK Ltd v. Boehringer Ingelheim Pharma GmbH* [2016] EWCA Civ. 1296.

20. The judgment of Morgan J. in *Teva UK* was the subject of particular focus at the hearing of the within application, with Boehringer offering two principal reasons as to why the court should feel free to depart from the findings of the trial judge in that case, being that the learned judge, it was alleged: (i) misunderstood the evidence of Professor Buckton, a distinguished expert witness who also gave evidence before this Court and whose contributions are considered later below; and (ii) erred in his approach to the case before him, proceeding on the basis of an incorrect characterisation of the invention and an incorrect understanding of the common general knowledge of the skilled person. It seems to the court, with respect, that these contentions involve something of a misunderstanding as to the role of persuasive authority. As will be seen from the consideration below of the decision of Clarke J. in *Ranbaxy*, the international decisions to which reference in this case (in particular, the decisions of the courts of the United Kingdom which, at this time, derive from an almost identical statutory regime and have yielded an analogous jurisprudence) have, to borrow from the wording of Clarke J. in his judgment in *Ranbaxy*, 607, "*the status, **as to their principles**, of persuasive authority*." (Emphasis added). The Irish courts do not presume to sit in judgment on the decisions of the courts of foreign courts and judges. Nor would they presume to point to, let alone correct, an alleged error made by a foreign court or judge in an understanding or application of the evidence before that court or judge. The Irish courts (i) look, in cases where there may be doubt as to the position at Irish law, for guidance by foreign judges who have previously travailed a path identical or akin to that along which an Irish court is being invited to tread, and

(ii) benefit from the elucidations of principle provided, and the identification of pitfalls recognised, by those foreign judges when they so proceeded. The court has every interest in the judgment of Morgan J., a distinguished patent law judge, insofar as he can offer insight into applicable legal principle, but that is the respectful extent of the court's interest; and were the attentions of an English court drawn to a decision of an Irish court in a case before it, no doubt similar constraints would apply. Judicial interpretation of applicable principle by reference to the decisions of foreign courts is essentially a co-operative venture that is neither competitive nor combative in nature; it is concerned with overall advancement towards a better understanding of legal principle, recognising that proper interpretation and elaboration of principle is a task un-bounded by national frontiers. The court has no view and makes no comment on Morgan J.'s interpretation or treatment of the evidence before him in Teva UK.

(ii) The Law as to the Comity of Courts.

21. The leading Irish decision on comity and the decisions of the courts of other jurisdictions is that of the High Court in *Ranbaxy Laboratories Ltd v. Warner-Lambert Co.* [2009] 4 I.R. 584. Giving judgment in that case, Clarke J. observed as follows, at 606–7:

> "[53]…[I]t is important that I deal with the question of the status of other litigation. It is important not to confuse two different concepts. Appropriate decisions from other common law countries are, of course, afforded persuasive status by the courts in this jurisdiction and, indeed, by the courts in many common law countries. That status is wholly independent of any connection between the litigation in which the decision was handed down on the one hand and the litigation under consideration on the other hand. What is afforded the status of persuasive authority are the legal principles to be derived from the decision rather than the decision itself.
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> [54] An entirely separate consideration has to be given to the result of foreign litigation which touches upon the same actual matters (rather than the same legal principles). The principle of the comity of courts requires that the courts in one jurisdiction should not lightly depart from a decision on the same issue made by a court of competent jurisdiction in another country which had to deal with that issue as part of litigation properly under its consideration….
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> [55] This latter principle, it seems to me, ought also apply, though obviously to a more limited extent, where the issue, while not identical, is very similar. For those reasons it seems to be appropriate, subject to the caveats relating to differences in [1] statutory law, [2] jurisprudence, [3] the patents themselves, and [4] the evidence which I have already identified, to pay appropriate regard to the international decisions in the related cases.
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> [56] However, it is important also not to lose sight of the fact that the international decisions in this case (and in particular the decisions taken by the courts of the United Kingdom which derive from an almost identical statutory regime and analogous jurisprudence) have also the status, as to their principles, of persuasive authority…."

22. Three points might perhaps be made arising from or in relation to the foregoing.

23. First, Ireland is a signatory to the Agreement on a Unified Patent Court (O.J. 20.6.2013, C175/1), the Unified Patent Court is in the process of being established, and the Government's Legislative Programme of 8th June, 2016, expressed an intention to publish an Amendment of the Constitution (Unified Patent Court) Bill. So it seems that Ireland, subject to the approval of the people in a referendum (if forthcoming), is moving in common with many other current European Union member states towards a situation in which issues of comity, in the patent law context, may soon be of less significance than hitherto, with decisions in this area to be taken by a European court of first instance and appealed to a European court of appeal, thus avoiding the protracted litigation that presently occurs in the various states of Europe and the concomitant potential for discrepancy between those decisions, notwithstanding the notion of comity.

24. Second, it is perhaps open to question just how long the situation described by Clarke J. in the above-mentioned text will continue to pertain. Following 'Brexit', and in a world where (i) much of Ireland's domestic law will continue to derive, as it does now, from European Union legislation, but (ii) a divergence seems likely to arise in the longer-term future between the laws emanating, respectively, from the European legislature and the Westminster Parliament, that primacy of persuasiveness which Clarke J. ascribes to certain United Kingdom legislation, in para. [56] of his judgment in *Ranbaxy*, may yet shift, post-'Brexit', to the decisions of the courts of then fellow European Union member states. For it is those latter courts and not the courts of the United Kingdom that one seems increasingly likely then to find are the courts whose decisions are concerned with an almost identical legal regime emanating ultimately from a single legislator.

25. Third, notwithstanding all of the foregoing, it suffices at this time for the court to note, having regard to para. [55] of the above-quoted text from Clarke J.'s judgment in *Ranbaxy*, that so far as the within proceedings are concerned, there is no material difference between the respective statutory regimes of Ireland and the United Kingdom, no material difference between the jurisprudence of the two jurisdictions, and many parallels, it seems, between the evidence tendered in both jurisdictions – though obviously this Court's attentions are confined to the evidence before it. Thus, for the reasons stated by Clarke J. in the above-quoted extract from *Ranbaxy*, the judgment of Morgan J. in *Teva UK Ltd v. Boehringer Ingelheim Pharma GmbH* [2015] EWHC 2963 (Pat), so far as the legal principles to be derived from the decision are concerned, falls to be viewed as particularly persuasive. As for the views of the other European courts referred to above, they likewise have the status, with regard to the legal principles to be derived therefrom, of persuasive authority, albeit, for the reasons stated by Clarke J., comparatively less persuasive authority at this time.

VII. Inventive Step/Obviousness: Some General Observations

(i) Overview.

26. The proper scope of the protections afforded by a patent regime has come to be demarcated in many patent systems by a requirement as to inventive step. In Ireland, s.13 of the Act of 1992, as mentioned above, provides, *inter alia*, that "*An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art*". Inventive step and obviousness are often equated but that there is a distinction cannot be doubted: a patentee might suggest a step which is not obvious, but if the taking of that step yields no accretion to the sum of human knowledge then it cannot be described as an inventive step.

27. In the course of deciding, pursuant to s.13, whether an alleged invention is obvious, it is customary to derive assistance from methodologies that seek to provide a rationalised framework or structure for just such analysis. Either or both of two recognised approaches falls or fall to be deployed in this regard, being: (i) *the Windsurfing/Pozzoli* methodology (as formulated by Oliver L.J. in *Windsurfing International v. Tabur Marine* [1985] R.P.C. 59, re-ordered by Jacob L.J. in *Pozzoli SPA v. BDMO SA* [2007] F.S.R. 37, and previously employed in this jurisdiction by Charleton J. in *In re Glaxo Group* [2009] IEHC 277); and (ii) the PSA favoured by the European Patents Office.

28. It is a feature of the within proceedings that despite Teva's initially appearing not to have an especial preference for which of the two aforementioned approaches came to be employed by the court in its reasoning – on the basis that either should lead the court to the same conclusion, being (per Teva) that Teva should succeed in the within application – Teva did not, in its submissions, address, in a substantive manner and by reference to the evidence at hand, how the PSA would work in the context of the within proceedings. Thus it did not seek to identify the closest prior art as such, it did not seek to establish the technical problem to be solved, and thus it could not indicate, starting from the closest prior art and the technical problem, whether or not the ostensible invention that is the subject of the 220 Patent would have been obvious to the skilled person. This had the result that on the last day of legal submissions, Boehringer rested without addressing the PSA as there had been no substantive case made in this regard by the petitioner. Teva then ended up urging the court to adopt only the *Windsurfing/Pozzoli* methodology.

29. In light of the manner in which the proceedings were conducted, the court, as indicated at hearing, considers that it can only properly proceed in this judgment by reference to the *Windsurfing/Pozzoli* methodology. But it may perhaps be that, notwithstanding Charleton J.'s stated personal preference in *In re Glaxo*, at para. 28, to the effect that he "*would prefer in future to use the European [PSA] test*", the application of the *Windsurfing/Pozzoli* methodology in the within proceedings is in any event a not entirely undesirable outcome, given the observations of Jacob L.J. in *Actavis UK Ltd v. Novartis AG* [2010] EWCA Civ. 82, para. 26, that although he considered the PSA to be useful in that case, more generally he considered the PSA to be an approach which may make more sense for "*an examining office which needs a common structured approach*" but is an approach that might be used less often by "*a national court making a full multifactorial assessment of all relevant factors*", *i.e.* the very task that this Court is now undertaking.

30. In *Pozzoli*, Jacob L.J., at para. [23], re-ordered the *Windsurfing* questions so:

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

31. Perhaps four preliminary observations might be made regarding the *Windsufing/Pozzoli* methodology:

> (1) it is a recognised rational skeleton upon which a trial judge can build the meat of a comprehensive, reasoned deciding judgment.
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> (2) the initial three steps identified are effectively procedural; it is the fourth step that sees the court engage in what is in effect the measuring required by statute. Or, to borrow from the wording of Jacob L.J. in the post-Pozzoli case of Actavis, at para. 21, "The first three steps merely orientate the tribunal properly. Step 4 is the key, statutory step". Likewise, in Medimmune Ltd v. Novartis Pharmaceuticals UK Ltd [2013] R.P.C. 27, Kitchin L.J. observed, at para. 89, that "It is step (4) which is key and requires the court to consider whether the claimed invention was obvious to the skilled but unimaginative addressee at the priority date."

A complaint made by Boehringer at the outset of the within proceedings was that Teva had not rigorously run through Steps (1) to (3) in its submissions but had concentrated instead on Step (4) of the re-ordered *Windsurfing/Pozzoli* test. It is true, as Teva responded, that the *Windsurfing/Pozzoli* test is not a mandatory statutory test. However, it is one of two tests that are generally used in the context of a challenge based on obviousness/inventive attack, it is the sole test that Teva ended up urging the court to apply, and it is a four-step test. As it happens, perhaps because of the dogged insistence of Boehringer in this regard, perhaps not, the court was in any event taken by both sides through the various aspects of the four steps and their application and implications in the within proceedings.

> (3) The *Windsurfing/Pozzoli* methodology involves an objective assessment between the prior state of the art and what the patentee claims was invented.
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> (4) Although technical advance over prior art is not required, its absence may be a factor in determining whether the necessary inventive step presents.

(ii) Obvious to Try.

32. In the quest for novel pharmaceuticals, a breakthrough with a particular class of drugs may make further investigation a relatively straightforward choice from one of a number of laborious paths. Indeed, this seems to be a feature of chemical and biotechnological inventions more generally. It is within this context that the notion of 'obvious to try' has evolved. Among the most prominent of the early cases in this regard, in the neighbouring jurisdiction, is the decision of the Court of Appeal in *Johns-Manville Corporation's Patent* [1967] F.S.R. 327. There, the Court of Appeal was concerned with the use of a known flocculating agent in a slurry of materials to which it had not previously been applied. Diplock L.J., as he then was, approached matters by considering whether a person versed in the relevant art, having regard to the prior art, would have realised that there was a flocculating agent which was well worth trying out in a filtration process used in his own industry in order to see whether it would have beneficial results. The courts of the neighbouring jurisdiction have been cautious in applying the 'obvious to try' concept and, as will be seen in the court's consideration below of a trio of relevant cases therefrom, they require in effect an assessment as to the strength and rationale, as of the priority date, of and for engaging in an 'obvious to try' investigation.

33. In *Mills & Rockley (Electronics) Ltd v. Technograph Printed Circuits Ltd* [1971] F.S.R. 188, Lord Reid made the following observations as to that issue, at 193–4:

> "Whether or not it was obvious to take a particular step is a question of fact; it was formerly left to a jury. But the question is not whether it is now obvious to the court (or to the jury) but whether at the relevant date it would have been obvious to the unimaginative skilled technician. A thing which now seems obvious to anyone may at that date have been far from obvious to him. In this case he would have been faced with a large variety of different methods, none of which had proved commercially useful. He would have had no assurance that any successful solution was possible, still less would he have known in what direction to look for it. He would be expected to try out all obvious modifications or combinations of these methods which seemed to him worth trying."

34. In *Brugger v. Medic-Aid (No. 2)* [1996] R.P.C. 635, Laddie J., at 661, observed that obviousness to try is not to be equated with certainty of success or an absence of other options, stating, also at 661:

> "First a route may still be an obvious one to try even if it is not possible to be sure that taking it will produce success, or sufficient success to make it commercially worthwhile. The latter point is inherent in Johns-Manville Corporation's Patent [1967] R.P.C. 479 , a decision of the Court of Appeal under the Patents Act, 1949 which is just as relevant to obviousness under the 1977 Act. Secondly, if a particular route is an obvious one to take or try, it is not rendered any less obvious from a technical point of view merely because there are a number, and perhaps a large number, of other obvious routes as well. If a number of obvious routes exist it is more or less inevitable that a skilled worker will try some before others. The order in which he chooses to try them may depend on factors such as the ease and speed with which they can be tried, the availability of testing equipment, the costs involved and the commercial interests of his employer. There is no rule of law or logic which says that only the option which is likely to be tried first or second is to be treated as obvious for the purpose of patent legislation."

35. More recently, the issue of obviousness to try has been the subject of some consideration by the Court of Appeal of England and Wales in *Medimmune Ltd v. Novartis Pharmaceuticals*, Kitchin L.J. observing as follows, at 683–4:

> "90 One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of technology such as pharmaceuticals and biotechnology which are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them worthwhile. But denial of patent protection in all such cases would act as a significant deterrent to research.
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> 91 For these reasons, the judgments of the courts in England and Wales and of the Boards of Appeal of the EPO often reveal an enquiry by the tribunal into whether it was obvious to pursue a particular approach with a reasonable or fair expectation of success as opposed to a hope to succeed. Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way. Lord Hoffmann summarised the position in this way in Conor [*Medsystems Inc. v. Angiotech Pharmaceuticals Inc.* [2008] UKHL 49] at [42]:
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> > 'In the Court of Appeal, Jacob L.J. dealt comprehensively with the question of when an invention could be considered obvious on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock L.J. in Johns-Manville Corporation's Patent [1967] R.P.C. 479, by saying that the notion of something being obvious to try was useful only in a case where there was a fair expectation of success. How much of an expectation would be needed depended on the particular facts of the case.'
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> 92 Moreover, whether a route is obvious to try is only one of many considerations which it may be appropriate for the court to take into account. In H*. Lundbeck A/S v Generics (UK) Ltd* [2008] EWCA Civ 311, [2008] R.P.C. 19 at [24] and in Conor [2008] UKHL 49, [2008] R.P.C. 28 at [42], Lord Hoffmann approved this statement of principle which I made at first instance in [*Generics (UK) Ltd v. H.*] Lundbeck [A/S [2007] R.P.C. 32, para. 72]:
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> > '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.'
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> 93 Ultimately the court has to evaluate all the relevant circumstances in order to answer a single and relatively simple question of fact: was it obvious to the skilled but unimaginative addressee to make a product or carry out a process falling within the claim. As Aldous L.J. said in *Norton Healthcare Ltd v Beecham Group Plc* (unreported, 19 June 1997, CA):
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> > 'Each case depends upon the invention and the surrounding facts. No formula can be substituted for the words of the statute. In every case the Court has to weigh up the evidence and decide whether the invention was obvious. This is the statutory task.'"

36. Two overriding observations might usefully be made at this juncture:

– first, it seems to the court that 'obvious to try' can only be a metric for obviousness if there is an expectation of success prompting the trial. Care must be taken by a court not to conclude that (i) a matter would have been obvious to try, solely on the basis that (ii) the notional skilled person would have assessed the likelihood of success as sufficient to warrant trial. Why so? Because that is a circular argument which, in next to every case, would render developments, at least in the pharmaceutical sector (given the resources invested in them) obvious.

– second, the 'obvious to try' test takes its place in the multi-factorial test identified by Kitchin L.J. in *Generics* and quoted by him in the above-quoted text from *Medimmune*, *viz*:

"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."

37. The just-quoted test is in effect the test applied by the court later below.

VIII. The Notional Person Skilled in the Art

(i) General Attributes.

38. Who is the notional person skilled in the art to whom Jacob L.J. makes reference in *Pozzoli*, being the person whose mental processes fall to be considered by a court engaged in an assessment of obviousness? The following attributes can be identified:

– first, she is, per Lord Reid in Mills & Rockley (Electronics) Ltd v. Technograph Printed Circuits Ltd [1971] F.S.R. 188, 193 "a skilled technician who is well acquainted with workshop technique."

– second, Lord Reid, at 193, considered her to be someone "who has carefully read the relevant literature", a point that was helpfully amplified upon by Jacob L.J. in Technip France SA's Patent [2004] R.P.C. 6., para. 8, when he stated that the notional skilled person "reads all the prior art, but unless it forms part of his background technical knowledge, having read (or learnt about) one piece of prior art, he forgets it before reading the next unless it can form an uninventive mosaic or there is a sufficient cross-reference that it is justified to read the documents as one."

– third, her field of interest is the field/s of interest of the person/s who are the addressees of the patent, i.e. "those likely to have", per Lord Diplock in Catnic Components Ltd v. Hill & Smith Ltd [1983] R.P.C. 183, 242, as approved by Clarke J. in Ranbaxy, para. 3.9, "a practical interest in the subject-matter of the invention".

– fourth, she is possessed of the common general knowledge in her relevant field/s. This aspect of matters is considered in more detail later below.

– fifth, where research is normally conducted by a team, the notional person may be a notional group and, as is clear from the judgment of Charleton J. in In re Glaxo, consistent with English law and the case-law of the European Patent Office, this may be a notional group of notional skilled persons from different disciplines. As Jacob L.J. memorably observed in in Technip France SA's Patent [2004] R.P.C. 6, para. 10, "He [the notional skilled person] could, in appropriate cases, be a team—an assembly of nerds of different basic skills, all unimaginative. But he would not be a complete android, for he would share the common prejudices or conservatism which prevailed in the art concerned."

– sixth, the notional skilled person does not come to court: the court must make its own assessment of obviousness after hearing evidence from real-life witnesses who tend in practice to be rather more skilled than the notional person skilled in the art. There was some misplaced discussion at the hearing of the within application as to whether Professor Geddes, a distinguished clinician proffered by Teva as an expert witnesses, ought properly to be viewed as a 'super-skilled' witness who ought not therefore to be perceived as the witness most proximate in skills to the notional skilled person. Professor Geddes was certainly a very well-qualified witness; however, there is nothing in the point as to whether he should be viewed as skilled, highly skilled or even 'hyper-skilled'. No expert witness, however skilled, is proffered as the notional person made flesh. As the learned authors of Terrell on the Law of Patents (18th ed., 2016) observe, at para. 12-96:

> "[E]xperts are not called as living embodiments of the unimaginative and uninventive skilled person….[I]t is not a contest to see whose expert most closely represents the skilled person. As well as being over-qualified…experts may come to the case with personal prejudices or preferences that must be discounted."

(ii) The Notional Skilled Person and the 220 Patent.

39. A formulation patent is a patent that seeks to cover the pharmaceutical formulation of an active pharmaceutical ingredient, *i.e.* the unique combination of the active pharmaceutical ingredient with excipients that make up the dosage form that is administered to a patient. In the very first paragraph of its outline legal submissions, Teva states that "*This action concerns the validity of a formulation patent owned by* [Boehringer]", being the 220 Patent. At no point in the within proceedings has Teva managed to get around this stark fact as stated by itself. The person to whom the 220 Patent is addressed is a pharmaceutical formulation scientist with experience in formulating pharmaceuticals for delivery by dry powder inhaler. Expert evidence before the court is supportive of the foregoing conclusions:

– Professor James Birchall, currently the Professor of Pharmaecutical Sciences at Cardiff University and an expert witness called by Boehringer in the within proceedings, states at paras. 14-15 of his first witness statement that "*The* [220] *Patent…is concerned with capsules for inhalation containing the active pharmaceutical tiotropium….The person who is addressed by the* [220] *Patent and who has an interest in giving effect to the technical teaching of the Patent is a pharmaceutical formulation scientist with experience in formulating pharmaceuticals for delivery by dry powder inhaler*".

– Professor Graham Buckton, an emeritus professor of the University College of London School of Pharmacy and an expert witness called by Teva in the within proceedings, substantially agrees with this conclusion at para. 1.11 of his first witness statement. However, he considers the patent to be addressed to a skilled team tasked with formulating an inhaled product for the treatment of COPD and/or asthma, which team he maintains would include a formulator with experience and interest in respiratory formulation and, per para. 1.13 of his first witness statement, a clinician with experience in the treatment of respiratory conditions.[1]

[1] Both Professors Birchall and Buckton are distinguished professional gentlemen. However, the court's impression as to the degree and relevance of the respective expertise of each of the two professors when it comes to the issues at play in the within proceedings was significantly coloured by the fact that, under cross-examination, it emerged that Professor Buckton had himself done no dry powder inhaler ('DPI') -related work before 2005 and thus no work involving, let alone focusing on, capsules for inhalation medicines by or before the priority date. Additionally, he was never involved in any project or task at any time in which he formulated a capsule-based DPI using a gelatin capsule. He therefore had no personal experience of using gelatin or other capsules for inhalation products either at the priority date or in the period prior thereto, or of using gelatin capsules for such formulations. By contrast, from 1994 onwards Professor Birchall was

working in a laboratory on the delivery of medicines to the lung using different types of inhaler devices and was working specifically on DPIs and propellant-driven metered dose inhalers from 2000. Thus he brought additional 'working at the coalface' experience to his expert evidence that Professor Buckton, with respect, did not.

– The court prefers the evidence of Professor Birchall, as buttressed by certain other evidence recited hereafter, that the person addressed by the 220 Patent is a pharmaceutical formulation scientist. The subject-matter of the 220 Patent is clearly not directed to clinicians in that it instructs a reader on the making of capsules for inhalation containing preparations of tiotropium. Thus Professor Richard Costello, a consultant respiratory physician and Associate Professor of Medicine at the Royal College of Surgeons in Ireland, and an expert witness called by Boehringer, states at para. 11 of his expert report, *inter alia*, that "[T[*he details of the formulation described in the Patent….would not be within the expertise of any respiratory clinician. I do not think that a respiratory clinician would be reading the* [220] *Patent with a view to putting its teaching into effect*….[I]*n my view a respiratory clinician would not be regarded as the person addressed by the* [220] *Patent*". Professor Duncan Geddes, a consultant respiratory physician at Royal Brompton Hospital and an expert witness called by Teva, states at paras. 7.1-7.2 of his expert report, *inter alia*, that "*The* [220] *Patent concerns the formulation of a capsule for inhalation containing tiotropium bromide….The skilled respiratory clinician would have known that, as set out in the* [220] *Patent, reproducibility of dose, high metering accuracy and complete emptying of the capsule were important aspects of a drug formulation for use as an inhalable powder, and…would have wanted a drug that permitted uniform dosing. However, the details of the formulation which produced this behaviour would not have been something the skilled respiratory clinician would have known, and is something which is not within my expertise*." Perhaps worth quoting at some length are the observations of Professor Birchall in this regard; he states as follows at paras. 17-19 of his expert report:

> "17. I note that Professor Buckton indicates…that in addition to the skilled formulator, a team developing an inhalation product for the treatment of asthma and/or COPD would include a clinician with experience in the treatment of respiratory conditions and that the skilled team would further have access to regulatory and commercial advice.
>
> 18. That may be true of the persons involved generally in an overall project of developing 'an inhalation product' for the treatment of asthma and/or COPD. However, as I have indicated, the [220] Patent appears to me to be specifically concerned with making capsules for inhalation containing the active ingredient tiotropium; it is addressed to the formulator asked to formulate capsules containing that active ingredient for inhalation and there is nothing in the substantive teaching of the Patent in so far as I can see, that addresses a clinician.
>
> 19. On that basis, I do not agree that the skilled team, as that concept has been explained to me for the purposes of assessing the Patent, would include a clinician. Accordingly, when discussing the skilled person in this report, for the purposes of discussing that person's common general knowledge in 2001 or otherwise, I am referring to a formulation scientist with experience in formulating pharmaceuticals for delivery by dry powder inhaler".

IX. Common General Knowledge of Notional Skilled Person

(i) General.

40. What is the relevant common general knowledge of the notional person skilled in the art? As mentioned above, the notional person skilled in the art is possessed of the common general knowledge in her relevant field/s. In the courts of the neighbouring jurisdiction, the most renowned statement of this common general knowledge was given by Sachs L.J. in *General Tire & Rubber Co. v. Firestone Tyre & Rubber Co.* [1972] R.P.C. 457, which statement has previously been adopted in this jurisdiction in *Ranbaxy* and *In re Glaxo*. In *General Tire*, Sachs L.J., commencing at 438, is careful to distinguish common general knowledge from prior art, of which cited prior art is obviously a sub-set. Following, *inter alia*, a consideration of the judgment of Luxmoore J. in *British Acoustic Films Ltd v. Nettlefold Productions Ltd* (1935) 53 R.P.C. 221, Sachs L.J. then proceeds, by way of elaboration upon that earlier judgment, to define common general knowledge as knowledge that is generally known and generally regarded as a good basis for further action by the bulk of those who are engaged in the particular field. It is useful to quote the relevant segment of Sachs L.J.'s judgment not just because it is of interest in itself but also because it contains a renowned extract from the judgment of Luxmoore J. in British Acoustic Films which, as will be seen later below, is of some significance in the context of the within application. Per Sachs L.J., at 440:

> "As regards scientific papers generally, it was said by Luxmoore, J. in *British Acoustic Films* (53 R.P.C. 221 at 250):
>
> > 'In my judgment it is not sufficient to prove common general knowledge that a particular disclosure is made in an article, or series of articles, in a scientific journal, no matter how wide the circulation of that journal may be, in the absence of any evidence that the disclosure is accepted generally by those who are engaged in the art to which the disclosure relates. A piece of particular knowledge as disclosed in a scientific paper does not become common general knowledge merely because it is widely read, and still less because it is widely circulated. Such a piece of knowledge only becomes general knowledge when it is generally known and accepted without question by the bulk of those who are engaged in the particular art; in other words when it becomes part of their common stock of knowledge relating to the art'.
>
> And a little later, distinguishing between what has been written and what has been used, he said:
>
> > 'It is certainly difficult to appreciate how the use of something which has in fact never been used in a particular art can ever be held to be common general knowledge in the art'.
>
> Those passages have often been quoted, and there has not been cited to us any case in which they have been criticised. We accept them as correctly stating in general the law on this point, though reserving for further consideration whether the words 'accepted without question' may not be putting the position rather high: for the purposes of this case we are disposed, without wishing to put forward any full definition, to substitute the words "generally regarded as a good basis for further action'."

(ii) Distinguishing Common General Knowledge and Cited Prior Art.

41. The distinction between common general knowledge and cited prior art is of significance in obviousness challenges in patent law cases. This is because the common general knowledge represents what might be styled the 'general mental furniture' that the skilled person brings to everything she looks at in her field and which informs her actions. Prior art that is not also common general knowledge represents an item of information that is sitting in the public domain (i) in the light of which the court must consider the inventiveness or obviousness of the impugned invention, (ii) which the notional skilled person is taken to consider in the light of her common general knowledge, but (iii) which the notional skilled person must, as a matter of law, approach without any preconception that it may hold the solution to any problem or issue that may exist in the field in question. As Laddie J. observes in *Inhale Therapeutic Systems Inc. v. Quadrant Healthcare Plc* [2002] R.P.C. 21, para. 47, in a passage later approved by the Court of Appeal in *Amersham Pharmacia Biotech AB v. Amicon Limited* [2001] EWCA Civ. 1042, para.45:

> "A fiction in patent law is that the notional uninventive skilled man in the art is deemed to have read and assimilated any piece of prior art pleaded by the party attacking the patent claim. If the invention is obvious to that person in the light of a particular piece of prior art, the claim is invalid. It is no answer to say that in real life the prior art would never have come to the attention of a worker in the field, for example because it was tucked away on the top shelf of a public library or because it was in a language which nobody in the art knew. The notional skilled person is assumed to have read and understood the contents of the prior art. However that does not mean that all prior art will be considered equally interesting. The notional skilled person is assumed to be interested in the field of technology covered by the patent in suit, but he is not assumed to know or suspect in advance of reading it that any particular piece of prior art has the answer to a problem he faces or is relevant to it. He comes to the prior art without any preconceptions and, in particular, without any expectation that it offers him a solution to any problem he has in mind. Some pieces of prior art will be much more interesting than others. A document directed at solving the particular problem at issue will be seized upon by the skilled addressee. Its very contents may suggest that it is a worthwhile starting point for further development. But the same may not be the case where a document comes, say, from a distant and unrelated field. For example, in theory a notional skilled person engaged in trying to improve the operation of an internal combustion engine is assumed to know, have read and assimilated the contents of all published material including those, say, in the baking field. It may be that a document in the latter field discloses something which, if applied to the internal combustion art, would produce a marked improvement in performance. However, the person skilled in the art is not deemed to read the baking document in the knowledge, or even with a suspicion, that it is of significance to the problems he has to deal with. It may be that it is written in such a way that, although he understands it, the skilled person will dismiss it as irrelevant to his work. The more distant a prior art document is from the field of technology covered by the patent, the greater the chance that an intelligent but uninventive person skilled in the art will fail to make the jump to the solution found by the patentee."

(iii) Common General Knowledge and the 220 Patent.

a. Identifying the Common General Knowledge.

42. The court proceeds below to consider the evidence of Professors Birchall and Buckton concerning the issue of common general knowledge. However, it notes firstly certain aspects of the case, and the evidence rendered in this regard, that rather coloured its impression generally in favour of Professor Birchall in terms of the evidence as to common general knowledge. It turned out that when it came to Professor Buckton's commencing upon the process of familiarising himself with the relevant field so that he could give his opinion on the common general knowledge of the skilled person at the priority date, he was given up-front by Teva's solicitors all of the prior art cited in the within proceedings. Professor Buckton then consulted a textbook, the name of which he unfortunately could not remember, and as to the content of which he gave no evidence, to confirm that what he was saying at a particular time was known at that time. In this regard, the following exchange occurred, at Day 4: 111, 17–113, 21), between counsel for Boehringer and Professor Buckton:

> *"Q. …Casaburi, Barnes and the other papers…it was the solicitors gave you those papers, isn't that right?*
>
> *A. Casaburi and Barnes?*
>
> *Q. And Maesen?*
>
> *A. Yes, the [London solicitors]…before the London case gave me those papers. That's true.*
>
> *Q. And they also gave you Ogura, isn't that right?*
>
> *A. That's true.*
>
> *Q. And as I understand your evidence, and correct me if I'm wrong about this, the position you adopted was: 'I'll try and think of what the skilled person was doing at the time. I then get these materials from the solicitors, and you then checked the textbook, is that right?*
>
> *A. That is correct.*
>
> *Q. To see whether your opinions were right or wrong?*
>
> *A. I did check the textbook to make sure that I was correct in relation to what had happened by what time and that was true.*
>
> *Q. Yes . And just so I understand that, what was that textbook? Who was the lead author of it?*
>
> *A. I genuinely can't remember now but I think it was called something like 'Drug Delivery to the Lung', or something like. It was an edited textbook so there were different authors for different chapters, if my memory serves me correctly….*
>
> *Q. And you can't remember now, Professor, and you were asked this in London as well, you can't remember the author of the textbook, is that right?*
>
> *A. Well, no, I can't. It's a long time since I looked at it. We should be clear that the process with the lawyers was a real drip-feeding exercise over a year or so of checking different little bits of information, so I knew very little and it was sometime during that process that I looked at it. It was a long time now.*

Q. You didn't exhibit it to your witness statement, isn't that right, that textbook?

A. I didn't exhibit it, no, because I simply used it as, just to make sure that the stuff I was saying about what was known at a particular time – its advantage, that textbook, was its publication date was pretty much, more or less, the priority date of the patent and I don't want to guess what it was just now, but it was very similar in time. So I just was checking that I was doing the right thing by having the correct knowledge of the priority date….

Q. So when you were reading the patent what you had in your mind was Maesen, Barnes, Casaburi and Ogura, isn't that right?

A. In as much as I had seen those prior to seeing the patent that is, I think, true. I think it is. If I'm wrong I will no doubt be corrected but I think it's true."

43. When it comes to sketching a landscape of the common general knowledge of the notional skilled person, the testimony of expert witnesses in patent law cases is generally carefully heeded. But even the greatest maestro, if handed a cluster of brown temperas by the commissioning client, will likely produce a landscape that features the colour brown, and the fault in that does not lie with the artist but with the client. The court would have been more persuaded by Professor Buckton's evidence as to the issue of common general knowledge had his familiarisation process been conducted otherwise than it was and, of course, had the name of the forgotten textbook been remembered so that its contents might be interrogated. In any event, Professor Buckton confirmed that he had not seen Barnes or Maesen before the priority date, perhaps unsurprisingly given that he appears not to have been among the target readership. But, curiously, despite the weight he attached to the Ogura article as the only pre-priority date mention of HPMC for inhalation, Professor Buckton could not recall whether or not he had seen it before the priority date, perhaps surprisingly given that his oral testimony was that the formulator community was "*a small community*" (Day 3: 121, 23) and that the type of development referred to in the Ogura article would have been talked about. Having regard to all of the foregoing and to the observations made previously above as to Professor Buckton's want of 'coalface' experience in the DPI capsule context, when compared with Professor Birchall, the court respectfully does not accept the contention of Teva, in its written submissions that, when it comes to the within proceedings and the issues here at play, Professor Buckton, though a distinguished professional, was, in the circumstances of this case, a witness "*well placed to address all of the formulation issues in the case*"; certainly, he was not as well placed as Professor Birchall.

b. Some Broad Agreement between Professors Birchall and Buckton.

44. Notwithstanding the foregoing, there was in fact broad agreement between Professors Birchall and Buckton as to much of the common general knowledge to be attributed to the notional skilled person. They largely agreed that the aim of the formulation scientist was in producing a formulation that was robust, reproducible, maintained the drug in a stable form and delivered the drug to the patient at the appropriate concentration for therapeutic effect. They largely agreed on the use of the metrics of delivered dose ('DD'), fine particle dose ('FPD') and fine particle formulation ('FPF') as parameters for the aerosolisation performance of a formulation. They largely agreed on the kinds of inhalation devices that were available in 2001; these included propellant-driven metered dose inhalers ('pMDIs') and DPIs, which in turn encompassed varying approaches to containing the drug, including single-dose devices, multi-dose devices using coils or magazines of sealed foil blisters, and multi-dose reservoir devices (from which a device would single-use doses for inhalation).

c. Some Initial Dissent between Professors Birchall and Buckton.

45. Some initial dissent emerged between Professors Birchall and Buckton as to when gelatin capsules had been superseded by HPMC capsules. Professor Birchall's consistent and preferred evidence was that gelatin capsules were the only capsules used in capsule-based DPI products that existed at and before the priority date, and he maintained, used very satisfactorily. So, for example, in his expert report he opines, *inter alia*, as follows at paras. 66–69:

> "66. Gelatin was, and still is the established capsule material for containing medicines and was known to be very safe and effective. Hundreds of millions of patients have received oral medicines contained in gelatin capsules and their use was absolutely accepted, with no significant issues being reported, and in no way controversial. With regard to DPI medicines, as of 2001 the capsules used in DPI products were exclusively made of gelatin.
>
> 67. Having regard to those facts, I disagree with what I believe to be the implications of the statements at paragraph 2.41 of Professor Buckton's report relating to gelatin capsules being the 'only real option available' for DPIs 'in the periods well prior to 2001' and that it was logical for the formulators of the 1960s and 1970s to use gelatin capsules. The implications of those statements appear to me to be that gelatin was not thought of as a perfectly good material for a container for a drug/powder blend in a DPI but was rather considered the only 'real option available' and had to be 'put up' with by formulators for a period of time but that that era was consigned to the past 'well prior to 2001'.
>
> 68. As I mentioned gelatin capsules were the only capsules in use in any DPI product on the market in 2001 and well beyond it….
>
> 69. In 2001 gelatin was taken for granted as the type of capsule used in any DPI involving a capsule container….Furthermore…gelatin capsules are still used in the majority of DPI products on the market".

d. Some Lingering Dissent Between Professors Birchall and Buckton.

46. There was lingering dissent between Professors Birchall and Buckton as to the carrier/excipient to be employed. Both gentlemen accepted that lactose would be a principal option for excipient by the skilled person. However, Professor Buckton went further, opining that it would be the inevitable choice and was less than willing to accept that glucose would also have constituted a frontrunner as a possible choice of excipient.

47. There was complete disagreement between Professors Birchall and Buckton as to how a skilled person would approach the formulation of an inhaled medicine, the steps she would take and the capsule material she would use. In particular, they disagreed on the question of whether or not the skilled person at the priority date would ever dry a capsule so as to obtain good performance in a DPI, and also on the question of whether or not the use of HPMC capsules had been assimilated to the common general knowledge by the priority date.

e. Drying Capsules.

I. General.

48. To succeed in its obviousness case, *i.e.* that the impugned development was obvious over the disclosure in any of Barnes, Maesen or Ogura, Teva had to show that it was part of known and accepted practice on the part of formulators of medicines formulated in DPIs at the priority date, to dry capsule containers in order to obtain satisfactory performance of the medicine contained therein. Significant differences arose between Professors Birchall and Buckton in respect of the common general knowledge relating to gelatin capsules used in DPIs. They agreed that the skilled person in 2001, and now, would not want to have excessive water in the formulation or to have a situation where water was transferring through or from a capsule into the drug/powder blend contained in it or *vice versa*. This is because such a situation could cause problems for the stability of the formulation and could affect negatively the flow characteristics/aerosolisation performance of the drug/powder blend. But there is disagreement when one delves into the precise nature of the concern arising, what was thought to amount to excess water in formulations at the priority date and what the implications of those matters were for how the notional skilled person would have thought about gelatin capsules for inhalation use by the priority date. It is necessary to focus on these aspects of matters in a little further detail.

II. Professor Buckton's Written Evidence.

49. In his first witness statement, Professor Buckton appears to state that there was a methodology in formulation that was directed to limiting water generally, and an *ex ante* prescription of specific limits to moisture content at the outset of the formulation process, with constant testing of moisture content limits throughout the formulation process, stating in this regard. More particularly, he states that water was regarded as a general enemy in formulation, that the focus would always have been on drying formulations and that to ensure a good performance for a DPI, the skilled formulator would use the driest conditions necessary to achieve physical and chemical stability, and routinely test for the effect of water on the stability and functional performance of a product. Thus, per Professor Buckton, at paras. 2.32–2.35 of his first statement, under the heading "*Water*":

> "2.32 Water can be present in a DPI product due to it being absorbed within, or adsorbed onto, the API [active pharmaceutical ingredient] excipients, or, the capsule (for capsule based devices), and present in the ambient air. The presence of water is a major consideration when seeking to formulate a DPI and changes in water content can lead to a number of problems arising:
>
> 2.32.1 Water can be adsorbed at contact points between the API and the carrier….such effects were commonly observed and were known to be damaging to product performance
>
> 2.32.2 Additionally where the API was chemically unstable in the presence of water, then plainly the formulation needed to be kept suitably dry….
>
> 2.32.3 As mentioned above water can greatly increase the rate at which amorphous regions on the surface of the API (or any excipient) recrystallize….
>
> 2.33 Consequently a skilled formulator at the priority date would usually seek to keep the formulation dry enough to ensure physical and chemical stability.*
>
> [*At this point in Professor Buckton's statement, the following author footnote appears:
>
> "In my first report in the UK and Norwegian proceedings I wrote 'as dry as reasonably possible in this sentence, that was taken to mean that I regarded the best approach to formulating DPIs to be 'the drier the better'. Despite the wording that was used that was not what I intended to say. While it is always true that water will be an enemy in DPI formulation and as such it will always be necessary to set strict limits for water content, it is also true that using very low water contents is at the very least uncomfortable for operators and expensive to achieve. I clarified this point in cross examination in London, but have adjusted the text here in order to make it clear from the outset. It is more accurate to say that the skilled formulator will use the driest conditions that are necessary to achieve physical and chemical stability, which means the water content must be assessed and suitable control limits established."

Professor Buckton could not be clearer in this re-wording of his written evidence, of which the court understands itself to be the unique beneficiary to this time. It represents, it seems, a significant re-wording of the written evidence that was before the Norwegian and United Kingdom courts.]

> [2.33 (cont'd)]…This is reflected in the FDA draft guidance 1998 [US Food and Drug Administration, Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, Chemistry, Manufacturing and Documentation, Draft Guidance (October 1998)] (which remains the current advice to this day) which states: 'Water in the drug product [DPI] should be strictly limited since it may have a significant effect on characteristics such as aerosolization of the particles, particle size distribution, crystallinity, dose content uniformity, microbial content and stability' (p.23). The document defines stability as 'a means for checking acceptable performance of the inhalation unit as well as the physical and chemical stability of the drug product, including the compatability of the formulation with the components of the device.' (p.37.)
>
> 2.34 Were an issue with poor emitted dose, or fine particle dose, to be identified during initial formulation work, in my view to address this the skilled formulator would, at least initially, try changes to the specification of a lactose carrier or reduce the water content of the formulation. Likewise, if chemical stability (which is often a water medicated reaction) were found to be an issue then reducing the water content would be a logical initial thing to do. As water is generally regarded as an enemy in DPI formulation minimising it, to a level that gave adequate improvement in performance, without being over burdensome in terms of the complexity of handling and controlling ware content, would be expected to be advantageous to physical and chemical stability. Lactose is advantageously a low hygroscopicity material (it does not adsorb much water from the atmosphere) meaning that a switch to an alternative carrier would not be a first strategy unless there was an overriding reason to do so, such as a chemical incompatibility between API and lactose that could not be controlled with suitable processing in a reasonably dry environment.
>
> 2.35 In 2001 the skilled formulator would routinely test for the effect of water on the stability and functional performance of the product, as set out below. It was often the case that DPIs were packaged with extra protection against water, such as storage with a desiccant to minimise water content or packaging in materials such as aluminium foil to protect from water ingress during storage. As discussed further below, the success of these strategies in keeping product performance over a shelf life would need to be investigated."
>
> 50. Moving on, at paras. 2.40-46 of his first witness statement, Professor Buckton depicts gelatin capsules as problematic products on the basis that they contain a significant amount of water that is free to leave the gelatin, with a consequent

need arising for a skilled formulator to reduce the available water by drying. Professor Buckton also mentions the undesirable quality of brittleness that dried gelatin possesses, indicating that this becomes a problem at <10% moisture content. Per Professor Buckton at paras. 2.40-2.46, under the heading "*Capsules*":

"2.40 As at 2001, capsules would contain API and, depending on the device and formulation, would usually contain in the region of 10mg of lactose carrier (with a reasonable range above or below this for different devices).

2.41 Originally, and in the periods well prior to 2001, two-piece hard gelatin capsules were the only real option available and had been used for solid oral dosage forms and for inhalation devices for many years. They were (and still are) made and sold as empty shells and machines were available to hold the capsule, remove the cap, fill a powder into the body and replace the cap. When making the first DPI formulations in the 1960s and 70s, it was logical for the formulators to use these well-established capsules as holders for the unit dose of an inhalation formulation….

2.42 Gelatin capsules were, however, not without their drawbacks, especially for inhalation products. Obviously, as they have been used for inhalation, these problems were not necessarily such that the product could not be formed, but they certainly could cause serious formulation issues.

2.43 The major issue with gelatin capsules is, and was, that they contained a considerable amount of water that is free to leave the gelatin (typically up to about 13–15%). As mentioned above, if water is taken into the DPI powder formulation (such as from a gelatin capsule) this can cause problematic changes in product performance and stability. To seek to minimise the problem when using gelatin capsules, the skilled formulator could reduce the available water by drying. The skilled formulator would know, however, that as the gelatin capsules were dried the shell would become brittle and liable to fracture (typically this becomes a problem at below about 10% water content).

2.44 Brittleness can be problematic during the filling of capsules, as the brittle dry gelatin capsules can break in the filling machines which will make production difficult. The brittleness of the dry gelatin capsules would also be expected to alter how they break when punctured by the pins in the inhaler. The change from a pin hole puncture in a capsule to a fracture (of a dried brittle shell) will give a different air flow when the device is used and will tend to alter the detachment of the API from the formulation and potentially the amount of the formulation that can be removed from the device on inhalation. Whether these changes increase or decrease the proportion of API delivered is less significant than the fact that they can be expected to give a different dose and different is bad when reproducibility is desired.

2.45 Additionally gelatin suffered from other drawbacks due to its animal origin – there were concerns over the risks related to TSE [transmissible spongiform encephalopathy] (which led to additional pressure and requirements from regulators including the use of gelatin from certified TSE-free herds), and whilst that concern was generally low for a DPI (in which the capsule is not intended to enter the patient), it may become a concern if the brittle dry capsule fractured to give fragments that were inhaled and either deposited in the throat or the lung. Additionally, some patients had ethical (vegan) or religious concerns about the use of these animal products.

2.46 Gelatin was also known to react with certain excipients and drugs, leading to chemical stability issues."

51. Overall the impression created by Professor Buckton was that water transfers from gelatin as a matter of course, that consequent efforts were made by formulators to dry the capsules, and that this yielded the undesirable end-result of brittle capsules. Professor Buckton has made clear that he is not championing the notion of 'the drier the better', but rather the more nuanced position that is referred to in the footnoted clarifying text referred to in the above-quoted extracts.

III. Some Aspects of Professor Buckton's Oral Evidence.

52. Perhaps three additional points arise from Professor Buckton's oral testimony that have not previously been touched upon above. These are considered below.

53. First, Professor Buckton's opinion that the drying of capsule containers in DPI formulations was part of the common general knowledge of formulators of inhaled medicines at the priority date was based on two sources, *viz.* one paragraph at p.243 of M.E. Aulton, ed., *Pharmaceutics: The Science of Dosage Form Design* (2nd ed.) and the FDA Draft Guidance referred to previously above. Again, the court would but note in passing that this reliance on Aulton and the FDA Draft Guidance appears to result ultimately from the fact that Professor Buckton was unable to pray in aid any personal experience of formulating DPIs at the relevant time.

54. The relevant segment of Aulton states as follows:

> "Ambient RH [relative humidity] can vary widely and continually depending on the weather and air temperature and these cyclic changes lead to constant variations in the moisture content of unprotected bulk drug and excipients. For this reason pharmaceutical air conditioning is usually set below 50% RH and very hygroscopic products, which are particularly moisture sensitive, are stored below 40% RH."

55. The court notes that this extract from Aulton is but dealing with the conditions under which unprotected substances that may absorb water should be stored so as to maintain their integrity prior to use in manufacture. In his oral testimony, Professor Buckton sought to divine from this text the proposition that formulations and capsules containing them should be dried via low-humidity manufacturing conditions. Professor Birchall, by contrast, confirmed what one would perhaps instinctively expect, *i.e.* that the text refers to the storage of potentially hygroscopic unprotected bulk drug and excipients before use. It is perhaps worth quoting the exchange that transpired between counsel for Boehringer and Professor Birchall in this regard. It commences with counsel reading out the above-quoted segment from Aulton; the following series of questions and answers then ensues, at Day 9: 99, 23-100, 29:

> *"Q….[Y]ou may recall that Prof. Buckton was saying that you can extrapolate from that and the skilled person would have done so, that manufacturing conditions should be subject to the same requirements, do you have anything to say about that?*
>
> *A. Well, only as I read it, it talks about 'variations to moisture with the unprotected bulk drug and excipients', so what you are trying to avoid is moisture getting into your ingredients of your formulation and that is why it is saying they should be set at a certain level. I consider that to do with the ingredients going to be used in the formulation. We should also point out of course that this chapter is about all sorts of formulation. This is a comprehensive chapter on pre-formulation that…covers everything.*

Q. When you say everything, are you drawing a distinction between the focus that has come into this case on inhalation dry powder formulations or are you talking about formulations in general or all delivery methods of medicines?

Q. Yes, all delivery of medicines. This is about pre-formulation as a science, about all sorts of dosage forms. And so, what is probably more important is to understand what is going to happen in our dry powder inhaler product. So we are going to be using gelatin capsules, we're going to be using the standard manufacturing conditions of 40–60% for those capsules, okay. So that is what I read into this. It is a broad comment, it's about the unprotected bulk drug and excipients. Then it talks about particularly moisture sensitive materials below 40%.

Q. And do you read in that, as Prof. Buckton suggested to the court that he could, that this is a reference to manufacturing conditions?

A. No."

56. Second, as to the FDA Draft Guidance, the court found Professor Buckton's reliance on same to be un-founded. He pointed to the FDA Draft Guidance as authority for the proposition that formulators ought to set specific water content limits and/or dry their DPI formulations. It seemed to the court to be wrong to read into the FDA Draft Guidance either an assumption of responsibility on the part of regulators to teach or even to seek to teach to formulators how they should formulate medicines. All the FDA seems to the court to have sought to achieve through the FDA Draft Guidance is to indicate what has to be demonstrated to it by way of (i) the stability of a formulated product, and (ii) the effectiveness of manufacturing and packaging steps in maintaining the integrity of a particular formulation. Indeed, Professor Buckton seemed to accept precisely this point in the course of his evidence in the proceedings before the High Court of England and Wales, evidence which was read out at the hearing of the within application by counsel for Boehringer (Day 7: 33, 22–35, 1):

"Q….[W]hen you were asked about these guidelines in the United Kingdom, professor….if you look then at a [particular segment of the transcripts from the High Court of England and Wales]….the question is

'[Q.] What this document is about is about ensuring that the product to be approved and marketed consistently meets the quality and performance characteristics both at the outset and after storage.

A. That is correct. Yes. I think that is right.

Q. It is not providing guidance as to how to go about producing a formulation in the first place.'

And your answer is:

'A. I do not believe that it does. I think regulators seldom do that. I think they give you guidance for – well, kind of inadvertently they do by virtue of what their guidance at the end will be, but you are left free to make your decisions about how you do things.'

Isn't that right?

A. Yes, I should just make that clear. The regulators don't say you must do this, you must do this, you must do this, but what they do is give you these detailed guidelines which will direct you and then – so, for example, they don't say you must dry, what they do say is you must set a limit for water content."

57. It is correct that the FDA Draft Guidance contains no requirement to dry. Nor, however, is there any mention of reducing moisture content. What it does and seeks to do was well explained by Professor Birchall in course of direct examination, as follows, at Day 9: 161, 22-162, 20:

"Q….[C]ould you just give the court a general outline of your view of the FDA Guidelines?

A. Yes. So these are guidelines that were in place in 1998, so, in context, this should be considered in [the] context of the time these were in place, and this is guidelines for metered-dose inhaler and dry powder inhaler drug products. So, as we know, the capsule-based products are gelatine capsules and the guidance is within that context, if you like. So the guidance is telling – not telling, but advising people thinking of developing products, of the sorts of things they must consider or should consider when trying to demonstrate to the regulators this is a quality product. Now, this is a good document and one that should be read all the way through, really, because it really gives you the context, but just to break it down into three sections. It's talking about what the risks, if you like – and regulators are all about risk, I suppose – so it's what is the risk of damaging the performance of the product during making the product? What is the risk of the product getting damaged during use of the product? And it's within that context that the guidelines give you information of the sorts of tests that you should do to try and de-risk that, to demonstrate to the regulator it's going to be fine under all of those three conditions",

and, in a later answer, at Day 9:171, 12-22:

"A…[T]he whole guidance is not about how you design your formulation. This is about what happens to your formulation during processing, during storage and during use. There is no mention of reducing moisture content. The only mention of moisture content is either contamination or control. Control in that aspect, of course, is making sure that you are not exceeding the amount of moisture that you should have in your product, and I think that's – actually, if you read the guidance, it's quite clear the context it's being used."

58. It is clear from the foregoing and indeed from Professor Birchall's evidence more generally that he did not agree with Professor Buckton that the FDA Draft Guidance is teaching a formulator about the water-content to stipulate in a formulation.

59. Third, Professor Buckton's initial opinion that a formulator disappointed with gelatin capsules would move to dried HPMC capsules rested, to a significant part, on his opinion that a formulator who started out with a capsule-based formulation would stick with a capsule-based formulation. As Professor Buckton stated, at Day 7:107, 23-27: "[T]he question is what have you been asked to do? And if you've been asked to make one out of a capsule then you will look to make one out of a capsule. If you've been asked to make

one out of a blister, you will look to make one out of a blister." However, later that day, having reviewed certain charts of authorised inhalation products that were placed in evidence by Boehringer and which showed 72 marketing authorisations granted since 1995 for inhaled medicines, with DPI products being a minority, the following exchange occurred between counsel for Boehringer and Professor Buckton, at Day 7: 153, 17–24, and effectively reversed Professor Buckton's previous evidence in this regard:

> *"Q… [C]an I suggest to you that the skilled formulator, in 1995 and up to the priority date being 1st June 2001, would not be confining him or herself to only capsule-based DPI products?*
>
> *A. I think that's reasonable. I think the skilled formulator would look at other formulations as well as capsules. I think that's reasonable."*

IV. Professor Birchall's Evidence.

60. There is a problem with Professor Buckton's notion that formulations in 2001 began with the *ex ante* prescription and limitation of water referred to above and the subsequent drying of capsules that rendered them brittle. Such a notion, it seems to the court, cannot be sustained in light of Professor Birchall's evidence, generally preferred for the reasons stated previously above, as to the standard practice of formulators in 2001 and the logic and science underpinning same. At paras. 87–88 of his first statement, Professor Birchall states as follows:

> "87. In 2001, the skilled person would simply use the conditions necessary to achieve physical and chemical stability, not the driest conditions necessary to achieve physical and chemical stability – which were normally, and not exceptionally, achieved for DPI products in the presence of the water content of the drug/powder blend and gelatin capsules at ambient conditions. By the same token the skilled person in 2001 would have been focused on obtaining a good performance for the formulation and on testing the functional performance in general terms and not on testing for the effect of water per se.
>
> 88. Of course excess water would have been and still would be regarded as something to avoid, but if the ingredient was not reactive in ambient conditions and could be filled into the DPI capsule at the equilibrium water content of each and then packaged to prevent any subsequent impact from atmospheric conditions, it appears to me that the notion that formulators would have sought in 2001, as a matter of principle or general practice, to minimise the water content of the formulation in 2001, as apparently suggested by Professor Buckton, is an incorrect one. Seeking to dry out the formulation in those circumstances would have been regarded as unnecessary, as a cause for needless expense in manufacture and packing, and an independent source of potential problems."

61. Some further relevant aspects of Professor Birchall's written evidence might also usefully be noted at this juncture:

> – first, Professor Birchall notes that, at the priority date, the capsule used in DPIs was regarded as a container for the formulation, not part of the formulation itself, observing as follows, at para. 64 of his first witness statement:
>
> > *"[In 2001, the] view of those working in the area of formulation of pharmaceuticals for DPIs at the time was that the capsule…was very much a 'container' for the active ingredient in the chosen formulation. Accordingly, I am not aware of published scientific research having been done by formulators on the capsules themselves at the time. The person of ordinary skill in the field in 2001 focused on the formulation of the active ingredient and carrier excipients, and on the DD [delivered dose], FPD [fine particle dose] and FPF [the fine particle fraction, being the ratio of FPD to DD] of the formulated drug/powder blend."*
>
> – second, at para. 73 of his first witness statement, Professor Birchall explains that the capacity of gelatin to absorb water could in some instances be beneficial, acting "*as a 'buffer' by absorbing moisture from the environment* [and] *thus preventing that moisture from reaching the drug/carrier powder and hence improving stability*".
>
> – third, at, *inter alia*, paras. 75-77 of his first witness statement, Professor Birchall describes a simple process that appears commonly to have been used at the priority date to deal successfully with the issue of potential moisture transfer, stating as follows
>
> > "75….[F]ormulation scientists were used [at the priority date] to dealing with the issue of potential moisture transfer and normally it was not a significant problem. They would understand the risk that gelatin might release a certain amount of water to the encapsulated powder, or vice versa, and would seek to address this issue by using the gelatin capsule and active drug/powder blend at their equilibrium moisture contents.
> >
> > 76. In that regard, the amount of water a powder or capsule will take up depending on the surrounding conditions is termed its equilibrium water content and this can be regarded as the 'natural' water content of a powder (or a capsule) in those conditions. The term 'equilibrium' applies because the powder or capsule has a moisture content in equilibrium with the moisture that is naturally present in the air.
> >
> > 77. Gelatin equilibrates at around 15% moisture under ambient conditions (temperatures of around 22 C and humidities around 50%RH (relative humidity) are commonly regarded as ambient conditions). The equilibrated moisture content of the drug/powder blend will vary depending on the active ingredient and carrier being used. The idea is that by allowing the gelatin capsule and the drug/powder blend to reach their equilibrium, or natural, moisture content before filling, and then filling them under ambient conditions, the formulation scientist would be working with materials where the risk of any transfer of water – either by absorption from one material to another or evaporation to the air – had been minimised by neutralising the conditions for such processes."
>
> – fourth, Professor Birchall moves on to explain in the next succeeding paragraph, para. 78, of his first witness statement that if a drug/powder mixture was itself unstable at its equilibrium moisture content level, a skilled formulator might have adjusted the grade or type of carrier, or the proportion of carrier to active ingredient so as to lower the equilibrium moisture content of the drug/powder mix, and if the foregoing or some combination of them did not work, the skilled formulator would sought to put the formulation in a foil blister, or formulated it as a multi-dose formulation or MDI (a pressurised metered dose inhaler, often sometimes referred to as pMDIs). (By way of shorthand, nothing more, the court

refers hereafter to the afore-described process as 'equilibration' or the 'equilibration process'). Professor Birchall concludes para. 78 with the observation that "*None of these options would usually be necessary as gelatin capsules were routinely and successfully used in many different DPI products containing many different actives of very different chemical properties*."

– fifth, equilibration appears to have been such a commonly known solution to any concerns as to water that, at para. 85 of his first witness statement, Professor Birchall goes so far as to state that as tiotropium had been formulated as both a lactose-based dry powder inhaler and a water-based nebulised formulation in 2001, "*the skilled person in 2001, if given this information, would be likely to assume that water was unlikely to be an issue in terms of stability when the powder was filled into a capsule at an equilibrated water content and in ambient conditions*."

62. One additional point might usefully be noted at this juncture by reference to Professor Birchall's oral testimony. Thus:

– sixth, in his first written statement, at para. 95, Professor Birchall, bringing to bear his practical experience as a professional working 'at the coalface' of enterprise at the relevant time, states as follows:

> "I disagree with Professor Buckton when he indicates…[in] his report that the reaction of the skilled person in 2001 to issues with DD or FPD would be to reduce the water content of the formulation (having first tried to change the carrier) if he is referring to anything other than the step of trying to lower the equilibrium water content of the drug/powder blend by adjusting or changing the carrier as I have already mentioned. I am not aware of any other water-reduction approach having been taken with respect to any DPI product on the market at the time and certainly not one directed towards the capsule container",

with this last point being touched upon by him more than once in his oral testimony; so, for example, at Day 9: 75, 3–6, one finds the following exchange between counsel for Boehringer and Professor Birchall:

> *"Q….[C]an you tell the court, as of the 1st June, 2001, was the skilled person drying the capsule?*
>
> *A. No. Not at all. No.",*
>
> *and, later in the same series of questions, following an explanation of the equilibration process, the following exchange occurs at Day 9: 98, 3 –27:*
>
> *"Q….I think you have already told the court that as of the priority date, the 1st June, 2001, nobody was drying capsules or the powder formulations, is that right?*
>
> *A. True, yeah.*
>
> *Q. If you dried, for example, cognisant of the problems you'd have if you dried the gelatin capsule, if you dried powder and put it into the gelatin capsule what would happen?*
>
> *A. What most people would expect to happen is that the powder would want to reassume its natural moisture content and it would draw water out of the capsule.*
>
> *Q. Could that potentially lead to the difficulties you have been discussing about the properties of gelatin?*
>
> *A. It leads to a few difficulties. One is, you are starting from a proposition of dry powder and that's going to change with time. So that powder is going to change when the moisture comes into it, so you won't know how it's going to perform with that change. The second issue is, yes, it might draw enough moisture out of gelatin to bring it into the brittleness range.*
>
> *Q. And I think you've confirmed to the court that nobody was doing either of those –*
>
> *A. No.*
>
> *Q. – things as of the priority date?*
>
> *A. That's right."*

V. The Teaching of Zeng.

63. Professor Birchall in his evidence made reference to the learned text written by Zeng, X., and ors, *Particulate Interactions in Dry Powder Formulations for Inhalation* (London, 2001) and the, therein discussed, potential for water-content to disrupt the adhesive balance between active ingredient and carrier that is necessary for the effective operation of a DPI. (It seems capillary forces make particles adhere more strongly to one another at high water contents, but electrostatic forces make particles adhere more strongly and in unpredictable ways at lower water-contents). In his oral testimony, Professor Birchall spoke at some length about Zeng's work under direct examination. To begin with, Professor Birchall was brought by counsel to paras. 89-90 of his first written statement, which reads as follows:

> "89. First of all and in general terms, water will always be present in a DPI product – some of it will be tightly bound to the powder mixture and some of it will be free. The presence of certain amounts of water plays an important part in the functioning of such products in that it plays a part in the adhesion of the API to the carrier already discussed.
>
> 90. In this regard, the inter-particulate forces between two solid materials are a result of van der Waal's forces (i.e. weakly attractive, non-covalent molecular forces), electrostatic forces (i.e., forces based on electrical charges), capillary forces (i.e., force between particles mediated by water bridges) and mechanical interlocking (i.e. physical interlocking between rough particle surfaces). Water significantly affects two of these forces – the electrostatic and capillary forces between the API and the carrier and is therefore crucial to the subtle adhesive balance of the API and the carrier that permits powder processing while also promoting efficient dosing from the capsule and into the lung upon inhalation."

64. The following exchange then ensued between counsel for Boehringer and Professor Birchall, at Day 9: 110, 28–112, 24:

> *"A…..So what I was trying to get at here is, going back to where I started about this subtle balance you must achieve between getting the drug to stick to the carrier and get the drug to be released from the carrier, and water plays an important function in that. Because water can be involved in capillary forces, so water just acting at the adhesion point in holding it together, and also absence of water plays a role in electrostatic forces, where the electrical charges between particles are affected by water as well.*
>
> *Q. And I think in that context, professor, could I ask you then to go forward to Zeng…and can I ask you in particular to go to page 23 of it….Can you just walk the Court through your understanding of what this is teaching?*
>
> *A. Okay. It talks about relative humidity, so this is the amount of moisture in the air. And if we probably start at the second paragraph it's talking about low relative humidities, capillary forces usually do not contribute towards adhesive interaction. So low relative humidity, water is not interacting at that interface between the drug and the carrier system when we talk about dry powder inhalers. Then if you raise the humidity you get more of an effect of capillary forces. So water is starting to predominate now and really affect the way that things are going to stick together. But if you go to low humidities you can go the other way, and you don't have capillary inter-reactions now, you have electrostatic interactions. So this is where you have gone to a low humidity and you are increasing, at low humidity you are increasing the charging of the substance. You are increasing the electrical charges between the drug and powder and the carrier in the case of dry powder inhalers. And so, what this is teaching is, it's saying that charging and capillary forces are both important. It is saying you can go too high with moisture and you can go too low. It's saying there is a sweet spot in between where the charges won't be predominating and you won't get either of them sort of dominating the interaction.*
>
> *Q. And this is what you have referred to a number of times, you have been describing the position to the Court, professor, as the subtle interaction between the particles themselves, is that right?*
>
> *A. This whole book, it's a big book, is focused on the interactions between particles and dry powder inhalers, that is what the book is about."*

65. It seems to the court that Professor Buckton hit very real difficulty as regards his opinion, volunteered by reference to the FDA Draft Guidance, that formulators set strict *ex ante* water-content limits for DPI formulations and the capsule containers used in them. He suggested that when it comes to inter-particulate forces arising at low humidities (<40%), essentially from a form of static electricity, this was just another aspect to be taken into account, in addition to chemical stability and capillary forces, when setting the specification for the formulation. However, it quickly proved that such a task is practically impossible. And Professor Buckton eventually appeared to accept this when the relevant extract from Zeng was read to him and his response was invited. The relevant text appears at p.26 of Zeng and reads as follows:

> "In conclusion, the predominant inter-particulate forces between the particles of a powder are the van der Waals forces of attraction. Electrostatic forces are only important at low environmental humidities whereas capillary forces become manifest at high humidity. All these forces will only be noticeable for particles with dimensions in the order of a few micrometers in diameter or smaller. Although the inter-particulate forces can be qualitatively estimated using a mathematical model, it is practically impossible to predict the actual force of particulate interaction on a quantitative basis since many factors are involved in this process. Thus, great caution must be exercised when attempting to extrapolate findings derived from hypothetical models to real systems encountered in pharmaceutical and other processes."

66. Professor Buckton was asked to comment on this text and the following exchange then occurred between counsel for Boehringer and Professor Buckton, at Day 5: 53, 15–54, 18:

> *"A. I would say that this is saying it's practically impossible to predict, is the key bit. What they're telling you is absolutely right. I agree with everything that they've said that you will have different forces dominate at different water contents and that is just fine. You will study at those and you will make a practical assessment based on your study.*
>
> *Q. If you're being told it's impossible? If you're being told here that it says it's 'practically impossible to predict the actual force of particulate interaction on a quantitative basis since many factors are involved in this process.'*
>
> *A. Yes.*
>
> *Q. Then you will depart at your peril –*
>
> *A. No, no, no, no.*
>
> *Q. – from – sorry, Professor, you might let me finish my question.*
>
> *A. I will.*
>
> *Q. You will depart, at your peril, from the teaching of general principles that Zeng is communicating?*
>
> *A. No. What he's saying, quite rightly, and with time I have agreed with everything that is in this chapter. It looks pretty good. I don't necessarily agree with everything he writes but this all, I'm in line with, what it's saying is that you really can't take these general views of which forces dominate at which place as being some kind of written rule. What he's saying is it's practically impossible to predict actually what's going to happen. So these are nice general statements to make but he's acknowledging that in real life you don't work on those general statements. In essence what he's saying is, you go and do the work and go and look and see how they perform."*

67. The court must admit that when it got to this point in the hearings, it was rather struggling to see what the difference was between the type of empirical exercise described by Professor Birchall by reference to his experience and Professor Buckton's "*you go and do the work and go and look and see how they perform*"; they seemed to the court to be essentially the same approach. So it was with some interest that the court found that in Boehringer's final submissions, it makes precisely this point (which is accepted by the court), while drawing attention also to the fact that counsel for Teva, when engaging with Professor Buckton on a later day and

on a different point, expressly solicited and elicited the professor's imprimatur to the empirical approach to formulation, notwithstanding that the broad thrust of his evidence had been and was in support of a prescriptive approach to evidence. The relevant exchange, at Day 11: 55, 28–56, 14, is worth quoting:

> *"Q. Would this be fair: in formulation the touchstone is testing?*
>
> *A. Testing is what we do in formulation, yes.*
>
> *Q. Yes. So you make a change to the product in some way and you test it –*
>
> *A. You do.*
>
> *Q. – to see whether it has had an effect?*
>
> *A. Yes, you do.*
>
> *Q. It is an empirical science, correct?*
>
> *A. Yes.*
>
> *Q. Because in order to try [to] predict from first principles, just eyeballing the molecule how it will behave is so impossibly complicated that the only thing that you would really do is test it to see if it works?*
>
> *A. You can learn from what's been done with other molecules, but you're right, you would test it."*

VI. Some Conclusions.

68. What conclusions does the court draw from the foregoing as to the common general knowledge by the priority date, additional to those already stated? It seems to the court that, by the priority date, the gelatin capsule was perceived to be a very useful container for formulations for inhalation in DPIs, it was not regarded as problematic, it was not dried to get around notional problems, and there was not, whether by reference to moisture content or some other factor, some hankering for an alternative container. Additionally, though the point falls to be considered later below, it is perhaps worth noting that the court also concludes by reference to the evidence before it that there was nothing in the history of tiotropium giving rise to any water-related concern (and, of course, even if there was, it would have been resolved via the equilibration process described by Professor Birchall and considered above).

f. Use of HPMC capsules assimilated to common general knowledge?

I. Two Preliminary Legal Issues.

A. The Nature of Common General Knowledge.

69. Continuing with a consideration of the issue of common general knowledge, the court turns now to the question of whether or not the use of HPMC capsules had been assimilated to the common general knowledge by the priority date. Before doing so, however, it is worth recalling again the insightful observations of Luxmoore J. in *British Acoustic Films*, as largely affirmed by Sachs L.J., in *General Tire*, which latter statement of applicable law has previously been adopted in this jurisdiction in *Ranbaxy* and *In re Glaxo*. Per Sachs L.J., at 440:

> "As regards scientific papers generally, it was said by Luxmoore, J. in British Acoustic Films (53 R.P.C. 221 at 250):
>
> > 'In my judgment it is not sufficient to prove common general knowledge that a particular disclosure is made in an article, or series of articles, in a scientific journal, no matter how wide the circulation of that journal may be, in the absence of any evidence that the disclosure is accepted generally by those who are engaged in the art to which the disclosure relates. A piece of particular knowledge as disclosed in a scientific paper does not become common general knowledge merely because it is widely read, and still less because it is widely circulated. Such a piece of knowledge only becomes general knowledge when it is generally known and accepted without question by the bulk of those who are engaged in the particular art; in other words when it becomes part of their common stock of knowledge relating to the art'.
>
> And a little later, distinguishing between what has been written and what has been used, he said:
>
> > 'It is certainly difficult to appreciate how the use of something which has in fact never been used in a particular art can ever be held to be common general knowledge in the art'.
>
> Those passages have often been quoted, and there has not been cited to us any case in which they have been criticised. We accept them as correctly stating in general the law on this point, though reserving for further consideration whether the words 'accepted without question' may not be putting the position rather high: for the purposes of this case we are disposed, without wishing to put forward any full definition, to substitute the words "generally regarded as a good basis for further action'."

B. The Status of Pleaded Prior Art.

70. It is helpful to deal as a preliminary matter with a submission made as to the status of pleaded prior art. When it comes to the issue of whether HPMC capsules had been assimilated to the common general knowledge by the priority date, Teva submitted that the answer to this question does not matter because the Ogura article (which discusses HPMC capsules) is before the court and is assumed to be before the skilled person when assessing the question of obviousness. That is not a complete and correct reflection of the position at law. As touched upon by the court in its consideration previously above of the judgment of Laddie J. in *Inhale Therapeutic Systems Inc.*, para. 47, which passage was approved by the Court of Appeal in *Amersham Pharmacia Biotech AB v. Amicon Limited* [2001] EWCA Civ. 1042, para.45, material that is before a court (having donned the mantle of notional skilled person) as an item of cited prior art is something that is taken to be read by the skilled person with interest but without any pre-conceived idea that it may offer a solution to any particular problem or issue. It may even be substantially discounted depending on the common

general knowledge and the mind-set that the skilled person would bring to it on the priority date. Information that is part of the common general knowledge is part of the general stock of knowledge of the skilled person, it is information that the skilled person treats as a good basis for further action, and hence information that informs the manner in which the skilled person views new information.

II. Overview.

71. There was a clear divergence of view between Professors Buckton and Birchall as to whether the use of HPMC capsules for inhalation devices was common general knowledge among formulation scientists working in the field of inhaled medicines in June, 2001. Looming large in Professor Buckton's reasoning in this regard were the publication of the Ogura article (cited as prior art), certain text in the second edition of Aulton (published post-priority date in 2002), and the mention of HPMC in certain patent applications (not published at the priority date). It appears to be common case between the two professors that tiotropium would not have been part of a formulator's common general knowledge at the priority date.

72. By way of orientation, it is useful to quote certain passages from the first written statements of the two professors. Thus Professor Buckton, at paras. 2.47-2.51 of his first written statement observes as follows:

> "2.47 In the 1990s the capsule manufacturers started to introduce capsules made of HPMC, as a non-animal based alternative to gelatin capsules. For example, Shionogi, a well-known capsule manufacturing company, launched HPMC capsules under the name Quali-V capsules. Shionogi became a well-known company in the field during the early 1990s during which time they acquired the long-established and world-renowned hard gelatin capsule manufacturing business from Eli Lilly. I understand from the timeline on the Shionogi website that the HPMC capsules were developed in 1990, and subsequently were launched for pharmaceutical use, becoming well-known towards the late 1990s. It is standard practive for excipient manufacturers to actively promote innovations such as the launch of HPMC capsules, by advertisement, conference exhibits and providing technical information to likely customers. Although Aulton 2nd ed. focuses on gelatin capsules, it too contains reference to the availability of these HPMC alternatives.

[The court notes in passing that those of Professor Buckton's comments which derive from his consultation of the Shionogi website are hearsay evidence and do not come from the experience or knowledge of Professor Buckton himself.]

> 2.48 Concurrent with the [220] Patent, which I discuss further below as relating to capsule materials with low moisture content, especially hydrxypropylmethyl cellulose (HPMC) capsules, many other companies were also using HPMC capsules for inhalation purposes. I was provided with copies of and asked to comment upon, the following patent applications for inhalation delivery by Wikborg Rein (during preparation of my report for this case in Norway) and such comments are also relevant to the issues in these proceedings. These applications describe the use of HPMC capsules and were all filed prior to the publication of the patent in suit (27 November 2003) and prior to the publication of the German priority patent application De 101 26 924.2 (5 December 2002)….

[Professor Buckton details the various patent applications, then continues as below.]

> 2.50 These patent applications, whilst not prior art per se, demonstrate that the existence of HPMC capsules was well known and that they were generally accepted as a logical choice for use in DPI formulations by a skilled formulator at a time period in keeping with the priority date of the patent in suit. The applications show that in the same time period, and without knowledge of the [220] Patent in suit, or of each other, a number of companies in different countries around the world had all accepted HPMC as a suitable capsule material for inhalated drug delivery and as such the existence of these HPMC capsules for inhaled delivery had become common general knowledge of the skilled formulator.
>
> 2.51 As some of the patent applications above indicate, HPMC capsules were also understood to have benefits over gelatin (besides their non-animal source and lower chemical reactivity), in particular a lower free water content and lack of brittleness and in the patent application WO0126630 a lower tendency to electrostatic charging. Because of this a skilled formulator in 2001 would have been likely to start a DPI formulation with HPMC, rather than (or at least in comparison with) gelatin capsules, there were clear advantages of HPMC capsules over gelatin, but no obvious technical disadvantages, as described in the Ogura paper."

73. By contrast, Professor Birchall maintains that:

> (i) the Ogura article, which discusses HPMC capsules for oral use, (a) only makes a slight reference to HPMC capsules for inhalation (giving no information relevant to data use), (b) was not a peer-reviewed article, (c) was more in the nature of a manufacturer advertisement for oral use capsules, and (d) it was not until 2003 that Quali-V-I capsules for inhalation became commercially available;
>
> (ii) (a) the Aulton text was not published until after the priority date, (b) the chapter relied on by Professor Buckton (I) was written by the capsule specialist who was working for Shionogi/Qualicaps on developing the HPMC capsules, and (II) makes only a passing reference to HPMC capsules and not in connection with their use for inhalation, and the chapter, and (c) the Aulton chapter on pulmonary drug delivery (written by a DPI formulator) makes no mention of capsules for inhaled use; and
>
> (iii) the content of unpublished patents was not in the public domain, let alone part of the common general knowledge of the notional formulator. Professor Birchall writes as follows, at paras. 97 to 118 of his first written statement:
>
> > "97. At paragraphs 2.47 to 2.51 of his report Professor Buckton goes on to discuss capsules made out of hydroxypropylmethylcellulose ('HPMC') as follows:
> >
> > > (a) at paragraph 2.47, Professor Buckton indicates that HPMC capsules were introduced in the 1990s as a non-animal-based alternative to gelatin capsules;
> > >
> > > (b) that HPMC capsules became well known for pharmaceutical use towards the end of the 1990s; in this regard Professor Buckton references Chapter 29 in Aulton (2nd edition, published in 2002) saying that while it focuses on gelatin capsules, it contains reference to the availability of HPMC alternatives;
> > >
> > > (c) that 'many other companies were also using HPMC capsules for inhalation purposes' and relies upon

copies of patent applications provided to him for the purposes of his evidence in the parallel Norwegian proceedings as the demonstration of such use (paragraph 2.48);

(d) Professor Buckton then lists the various patent applications featuring HPMC capsules provided to him by the legal team for the purposes of the Norwegian proceedings.

98. Professor Buckton then indicates (at paragraph 2.50) that the patent applications listed, while not published before June 2001, were applied for before that date and 'demonstrate that the existence of HPMC capsules was well known and that they were generally accepted as a logical choice for use in DPI formulations by a skilled formulator at a time period in keeping with the priority date of the patent in suit' and that 'a number of companies in different countries around the world had all accepted HPMC as a suitable capsule material for inhaled drug delivery and as such the existence of these HPMC capsules for inhaled delivery had become common general knowledge.'

99. Professor Buckton then goes on to say (at paragraph 2.51) that 'HPMC capsules were also understood to have benefits over gelatin (besides their non-animal source and lower chemical reactivity) in particular a lower free water content and lack of brittleness and…a lower tendency to electrostatic charging' and that 'because of this a skilled formulator in 2001 would have been likely to start a DPI formulation with HPMC, rather than (or at least in comparison with) gelatin capsules; there were clear advantages of HPMC capsules over gelatin, but no obvious technical advantages, as described in the Ogura paper'.

100. Professor Buckton then goes on to give a summary of his reading of the Ogura paper.

101. I have quoted extensively from Professor Buckton's report on the topic of the thinking on HPMC among formulators in the field of inhaled medicines in 2001 to allow me to address his conclusion that the use of HPMC capsules in DPI formulations should be regarded as common general knowledge in 2001, and the reasons expressed for it – in respect of both of which I am in sharp disagreement.

102. HPMC capsules were initially develeoed by Shionogi & Co. Limited and Shionogi Qualicaps ('Shionogi/Qualicaps') for oral use. These capsules were described by Dr Shunji Nagata on an article in 2002 [Nagata, S., "Advantages to HPMC Capsules: A New Generation's Hard Capsule", (2002) 2(2) Drug Delivery Technology 34] and were known as Quali-V capsules. It was not until 2003 that Quali-V-I capsules for inhalation use were introduced (being described in an article published by Brian Jones published in 2003 [Jones, B., "Quali-V®-I: A New Key for Dry Powder Inhalers" (2003) 3(6) Drug Delivery Technology 52]).

103. Apart from the Ogura article of 1998, which could not be regarded as having itself been common general knowledge – which I come back to below – I am not aware of any other articles before June 2001 which concern HPMC capsules for inhalation use. I am not aware therefore of any way in which their use for inhalation could have come to a formulation scientist's attention, let alone form part of the common general knowledge to be ascribed to the skilled person in 2001, such that the notional skilled person would have been likely to treat HPMC capsules for inhalation as an established basis for action in 2001.

104. Further, I do not believe that HPMC inhalation capsules for inhalation use could even be argued to have been common general knowledge among formulators until after Shionogi/Qualicaps started to promote Quali-V-I capsules in 2003. These capsules were HPMC capsules specially optimised for use in DPIs and were described in an article by Brian Jones published in 2003 2003 [Jones, B., "Quali-V®-I: A New Key for Dry Powder Inhalers" (2003) 3(6) Drug Delivery Technology 52], which I believe to be the first article to consider HPMC capsules for inhalation use (apart, as I say, from the brief mention in the Ogura article which I come back to below).

105. I have tried as best as I can to recall when I first became aware of HPMC capsules. In the early 2000s I worked in a laboratory next to Brian Jones at the Welsh School of Pharmacy. I believe that some of the work described at the end of his 2003 article was done in this laboratory in 2001 and it is possible that he mentioned that work to me at the time, but I cannot now recall that. If I did know about HPMC capsules in 2001 it would only have been through the unique situation that Brian was working as a consultant for Shionogi/Qualicaps at the time and I happened to have him as a neighbour and colleague at work.

106. HPMC capsules for inhalation could not be accepted as having become common general knowledge on the strength of what seems to today appear on the Shionogi website or the Ogura article – which Professor Buckton appears to accept were in the nature of an advertisement.

107. I set out in paragraphs 218-247 the reasons why I believe that, even if the skilled person's attention was drawn to Ogura in 2002, that the development of a tiotropium lactose powder mix in prescribed or reduced-water content HPMC capsules would not have been obvious to him or her. In summary the main reasons are that: Ogura provides no information on the likely performance of HPMC capsules in inhalation applications – specifically their ability to be punctured in a dry powder inhaler reliably and without fragmentation and their performance as regards to aerosolisation performance of the drug/powder blend to be contained within them. It is unsurprising that these data are not given since HPMC capsules for inhalation had not been developed at the time of the Ogura article. Ogura is mainly directed towards the promotion of HPMC capsules for oral pharamaceutical use. In so far as Ogura introduces capsules by way of a comparison with gelatin capsules, the lower water content of HPMC is presented as a feature in itself and little indication is given in relation to its behaviour and/or that its water content should be controlled at specific limits or reduced for actives where ready hydrolysis was not an issue. In so far as Ogura does characterise the behaviour of the water present in HPMC capsules, the message would be worrying for an inhalation medicines formulator as it says that 'the HPMC film does contain some adsorbed water that is readily released' but does not expand upon the impact of this 'adsorbed'. i.e. surface, water that could be 'readily released' into a dry powder inhaler formulation.

108. However, leaving aside the reasons why I do not believe a reading of Ogura would have led the uninventive skilled person to the invention in 2001, I understand Professor Buckton to say that the contents of Ogura were anyway common general knowledge. I disagree with that proposition.

109. First, Ogura was published in Pharmaceutical Technology Europe, which is essentially a trade magazine for the pharmaceutical industry. If any peer review of articles was conducted for the publication at the time (and I do not believe that it was), I do not believe that it would have been robust.

110. I also do not agree that the majority of formulators would have access to Pharmaceutical Technology Europe and even if they did, that they would necessarily have taken a scientific interest.

111. Pharmaceutical Technology Europe is supported by advertising. As a scientific publication however which are peer reviewed, it is still only ranked 193 out of the 205 pharmaceutical science journals listed in SCImag Journal and Country Rank. This ranking results from relatively low citation indices of articles published in this journal. Citation data show how many other authors of subsequent scientific articles have referred to papers published within the journal, which is itself a compound measure of the readership of the journal/article, the scientific perception of the journal/article and the insight and impact of the article in the scientific field. Citation indices for Pharmaceutical Technology Europe are amongst the lowest for any pharmaceutical science journal, hence its 4th quartile ranking. It should also be explained that whilst my own (i.e. Cardiff University) authored publications on capsule puncturing performance have cited Ogura, this was due to the fact that these publications were co-authored by Qualicaps employees and/or consultants and based upon work supported by Qualicaps. My co-authors on these publications were of course keen to reference the track-record of Qualicaps in the area of HPMC capsules.

112. I disagree with Professor Buckton that the mention of HPMC as a new capsule material in chapter 29 of the 2002 edition of Aulton, shows that HPMC capsules generally, and certainly HPMC capsules for inhalation were part of the common general knowledge. The chapter in question was written by Brian Jones who is a vastly experienced and eminent capsule expert having helped develop the capsule business at Eli Lilly, that ultimately through de-mergers and acquisitions became Qualicaps. Mr Jones was working very closely with Shionogi/Qualicaps at the time HPMC capsules were being developed and therefore had, what I would regard as unique access to knowledge of HPMC capsules at that time. Even then, while the chapter makes mention of HPMC, it is entitled 'Hard gelatin capsules'. Whilst referencing HPMC as a capsule material, via the Ogura paper, the narrative actually shows that gelatin was the only real option at the time by stating 'The raw materials used in the manufacture of both types of capsule (meaning hard and soft capsule) are similar. Both contain gelatin…'. It later states 'Gelatin is the major component of the capsule and has been the material from which they have traditionally been made.'

113. It is also worth noting that the chapters on hard capsules in Aulton 3rd edition (2007) and 4th Edition (2013) still focus nearly exclusively on gelatin capsules with only fleeting reference to HPMC, which is not even mentioned in the contents notes on the Chapters.

114. Furthermore, it seems more appropriate, when trying to assess what should be regarded as being common general knowledge with respect to containers for inhaled medicines in 2001 to have regard to the chapter in Aulton (2002 ed.) concerning Pulmonary Drug Delivery. This chapter was written by Professor Kevin Taylor who is not, and at that time was not, a capsule specialist, but rather a DPI formulator (i.e. the discipline of the skilled person). In his chapter, Professor Taylor only refers to gelatin capsules for DPI use. If the use of HPMC capsules as containers in DPIs were common general knowledge in 2001, then Prof Taylor whom I would regard as achieving a level of knowledge and ability considerably higher than that of a formulator of ordinary skill (and no imagination) would be referring to them in his chapter in the 2002 edition of Aulton.

115. As regards Professor Buckton's views that various patent applications featuring HPMC in one way or another, demonstrate that HPMC capsules were generally accepted as a logical choice for use in DPI formulations by the person of ordinary skill in the art of 2001, I am not sure how (in circumstances where my understanding is that the common general knowledge is information that is generally known and treated as a good basis for further action) it could be said that the formulator of ordinary skill in the field would accept as the logical choice HPMC capsules for inhalation, which were not then commercially available or approved, and in respect of which the only publication was a promotional piece done by the manufacturer of HPMC capsules majoring on oral use and in which the potential use for inhalation was briefly referred to and accompanied by no performance information.

116. In so far as I am aware, patents published after the priority date could not themselves contribute to common general knowledge in 2001 and neither, I believe, could the inclusion in a patent application, by itself, be evidence of common general knowledge or even of the use of HPMC capsules by any of the applicants for the patent application concerned.

117. At paragraph 2.51, Professor Buckton says that the patent applications he mentions show that HPMC capsules were known to have advantages over gelatin with respect to lower free water content and lack of brittleness. Leaving aside the point that the availability of unbound water is dependent on the conditions to which the capsule material is subject and that no comparative studies in relation to gelatin and HPMC capsules have been done in 2001 and for many years after that, I do not see any mention of these properties in the patents listed in Professor Buckton's report. There is one reference to hygroscopicity, but no reference to water content or brittleness. In fact, the use of an aluminium foil bag and a dessicant for packaging the HPMC capsules 'for additional moisture protection' (US20030125236) might tend to discourage, rather than encourage, the skilled person to try HPMC capsules. This echoes certain content of Ogura which refers to a tendency of HPMC for adsorbed water to be readily released and I shall come back to this point when I discuss the Ogura paper as cited prior art below.

118. Contrary to what I believe Professor Buckton implies in his report, gelatin capsules were not seen as problematic for the vast majority of DPI formulations as explained above. I believe that Professor Buckton's statement that the skilled person would have essentially been looking around for a capsule material with a low water content because of a generalised dissatisfaction with gelatin is not accurate. In my view the skilled person would be much more likely to stick with tried and tested methods of using gelatin capsules."

III. Ogura.

74. Ogura T., "HPMC Capsules – An Alternative to Gelatin" (1998) 10(11) *Pharmaceutical Technology Europe* 32 is a five-page article that contains many diagrams and is spread over ten pages of the journal in which it appears, which in size is about the dimensions of a glossy periodical that one might buy from a newsagent. Each of the various pages is separated by one or more full-page advertisements pertaining to the wider pharmaceuticals industry; the last page contains a one-third page advertisement for compliance seminars. The title gives a good sense of the thrust of the article, which is touting the virtues of HPMC capsules to a world in which gelatin capsules have hitherto been the dominant form of capsule. Though the Ogura article is undoubtedly an article, it is very much a promotional article. The introductory blurb reads as follows:

> "Hydroxypropyl methylcellulose (HPMC) capsules are made of plant-derived materials and do not contain components of animal origin, eliminating problems with religious or vegetarian dietary restrictions, Unlike gelatin, HPMC does not have chemically reactive groups, dramatically decreasing the potential for reactions between the drug and the capsule shell. HPMC capsules have a naturally low moisture content, maintain mechanical integrity under extremely low-moisture conditions and are, therefore, ideally suited for use with formulations containing water-unstable drugs."

75. This is followed by a first paragraph which reads like something of a paean to hard capsules stating as follows:

> "Hard capsules were developed as an edible container to mask the taste and odour of medicines. As a result of the introduction of mass-production techniques and high-speed capsule-filling machines, capsules have become one of the most popular dosage forms for pharmaceuticals. Capsules have traditionally been used for powder or granule formulations, but in recent years have been adapted to contain oily liquids, tablets, and even powders for inhalation. Capsules enjoy widespread popularity because of their relative ease of manufacture (compared with other dosage forms such as tablets) and flexibility of size to accommodate a range of fill weights. They are readily able to achieve bioequivalence between different strengths of the same formulation."

76. There then follows a paragraph which identifies certain deficiencies of gelatin capsules, gelatin being the main material used, at least at the time of the article, for the manufacture of capsules:

> "Capsules do have some drawbacks. Capsule shells made from gelatin, the main material used for this purpose, generally contain 13-15% water and therefore may not be suitable for use with readily hydrolysable drugs. Some drugs may react with the amino groups of gelatin, causing dis-colouration or formation of crosslinks between gelatin molecules, which retard capsule dissolution. Gelatin products are sometimes shunned as a result of religious or vegetarian dietary restrictions."

77. In the third paragraph, the potential of HPMC gets its first mention:

"For these reasons, work is under way to develop capsules made of starch, cellulose or polyvinyl alcohol/vinyl acetate mixtures. Yamamoto et al. recently succeeded in making capsules from hydroxypropyl methylcellulose 2910 (HPMC), a material also used as a water-soluble film coating. We have confirmed the applicability of the HPMC capsule to products. As USP, EP and JP (the United States, European and Japanese pharmacopoeia) monographs all describe capsules made of cellulose or methylcellulose, in addition to gelatin, the HPMC capsule conforms to pharmacopoeial standards".

78. Following this paragraph, the article is structured as follows: a section entitled "*Manufacturing HPMC capsules*" (p.32), a section entitled "*Physical characteristics of HPMC capsules*" (starts on p.32, broken by a one-page advertisement, ends on p.34), a section entitled "*Biopharmaceutical characteristics*" (starts on p.34, broken by a one-page advertisement, ends on p.36), section entitled "*Application to formulations*" (p.36), a section entitled "*Addressing potential discolouration problems*" (starts on p.36, broken by three pages of advertisements, ends on p.40), a section entitled "*Addressing potential problems with readily hydrolysable drugs*" (starts on p.40, broken by a one-page advertisement, ends on p.42), a section entitled "*Other applications*" (p.42), and then the "*Conclusion*" (p.42). It is only when one gets to "*Other applications*" on p.42, assuming one has waded through the various pages of advertisements, that one gets to the potential usefulness of HPMC capsules in the context of inhalation devices. The relevant text reads as follows:

"Capsules have also been used as unit-dose containers to administer finely divided powders with specially designed inhalation devices. In the past, such delivery systems have encountered problems, including adherence of the powder to the gelatin capsule because of static electricity and capsule breakage because of the brittleness that results from storage under very low humidity. The HPMC capsule avoids these problems and would be appropriate for use in these situations."

79. In its closing written submissions, Teva contends that it is clear from the last-quoted paragraph of Ogura that HPMC capsules were not just proposed for inhalation use "but had already been used for this purpose". The court respectfully does not accept that this is so. Breaking the last-quoted paragraph into segments, is the reference to "Capsules" in the first sentence to non-HPMC capsules or to all capsules? In fact, when one reads the paragraph as a whole it is entirely clear that it is to non-HPMC capsules. The first sentence states that "Capsules have also been used…". The second sentence describes problems identified with gelatin capsules as a result of such usage. The last sentence shifts tense and says that "The HPMC capsule…would be appropriate for use in these situations", i.e. not '…is appropriate for use in these situations', not '…has been used and found appropriate for use in these situations', but "…would be appropriate for use in these situations". How do the learned authors know that the HPMC capsule "would be appropriate for use in these situations"? However they know, there is no assertion in the text that such knowledge derives from previous use; if it did derive from previous use, the deployment of the conditional tense would be wrong, and there is nothing in the article, or in the evidence before the court, to suggest that the Ogura article is grammatically flawed.

80. Professor Birchall, in his written and oral testimony, offered convincing reasons as to why the proposition concerning the potential for use of HPMC capsules in inhalation devices would not have impacted significantly on a skilled formulator. These can be summarised as follows. First, the suggestion of inhalation use was made towards the end of the article and in the context of a focus on oral use of HPMC capsules. Second, the absence of data in relation to inhalation-relevant properties was a notable omission in itself but would also have implications as regards the skilled person's understanding of what had really been considered by the authors and what was being promoted. Third, Professor Birchall, at Day 9: 136, 1-15, referred to the practical reality that formulators only have so much time for reading and that the nature and ranking of Pharmaceutical Technology Europe would have implications as regards the likelihood that time would have been spent reading Ogura:

> "[I]t's not meant to be a very impactful scientific journal, it's not meant to be academically very strong and read by a lot of academics, if you like. It is [focused on]…interesting things that might happen in a very sort of basic way, that sort of thing. And so…it has a very, very low ranking and that does determine which journals we read….[W]e have only got enough time in the day to read a certain amount of material and formulation scientists can be focusing their time on reading the things that give them more benefit….articles that have more information in them and are more respected in the field, so they would be focusing on other journals."

81. In passing, there was suggestion in Teva's closing submissions that Professor Birchall agreed in his oral testimony that HPMC capsules were not just proposed for inhalation use but had already been used for such purpose. In fact, when the court looks to the relevant section of the transcripts (Day 11, Q.862), it is clear that Professor Birchall is simply agreeing that the article says what it says, *i.e.* that it expressly refers to use of HPMC capsules in inhalation products, not that it says, or that Professor Birchall reads it to say, that there has been such use.

g. Some Additional Points Arising from the Oral Evidence.

82. In the course of the oral evidence some further points of note concerning the issue of common general knowledge arose from the testimony of Professors Birchall and Buckton. These are considered below:

– first, although Professor Buckton asserted that the reference in Ogura to the use of HPMC capsules for inhalation purposes would have been noticed by formulators because the formulation community is relatively small, he could not say that he had himself seen the article before the priority date, yielding the following exchange between Professor Buckton and counsel for Boehringer, at Day 7: 166, 26-168, 23:

Q….You can't remember whether you had even seen the Ogura article before the UK solicitors sent it to you, isn't that right?

A. I can't remember whether I'd seen it or not, no.

Q. No. And can I suggest to you, Professor, that if was a paper of any import, and certainly of the import you have been suggesting to the Court, you would refer it?

A. I think that the notion of HPMC capsules was the area of import. I don't know that the paper, as such, was the area of import.

Q. No, but you've been telling the Court in your evidence, Professor, as I understood it, that this was important, it was a new development in inhalation, isn't that right?

A. Well, the arrival of HPMC capsules would be important and the Ogura article would provide detail for those of you who are in the field looking to act on it at that time.

Q. Can I suggest to you, Professor, that the reason you don't even remember whether you had seen it before the solicitors gave it to you, is because you regarded it as of no importance?

A. I think the reason you don't remember seeing whether you saw things or not is you see an awful lot of things over an awful lot of years and it would be wrong for me to say I remember any particular one of them with any great detail….

Q. Your evidence about Ogura was, that this was significant because in the landscape of inhalation devices, this was a new departure, isn't that right?

A. I'm saying that HPMC capsules were significant and Ogura gives you the detail in relation to that and what I'm saying is that for a person at the priority date looking to make a dry powder inhaler formulation, it would be very significant but I'm talking about me sitting here today, can I remember what papers I read at that time? No, I can't.

Q. Well, did you write any papers after 1998 referring to the Ogura paper and commenting on the significance of it?

A. No, because that's not the field of research I was publishing in in terms of the essence of the capsule shell. My field of research was different to that.

Q…. Professor, you had precisely the reaction to Ogura that the skilled person would have: Nothing for me here?

A. I don't think that's reasonable. I think sitting here today, what can I remember having read many years ago is very different to sitting there at that time, looking to say what would I make of this paper?

Q. But that's precisely my point, Professor. That's the danger of hindsight…".

– second, and by contrast, Professor Birchall was a model of clarity in his evidence in this regard. He confirmed in direct examination, at Day 9: 134, 17–135, 13, that he had not seen the Ogura article before the priority date and that no-one had mentioned it to him or otherwise mentioned the potential of using HPMC capsules for inhalation formulations:

"Q. Can I ask you, did you see the Ogura article before the priority date?

A. No.

Q. Had anybody mentioned the Ogura article to you or the potential of using HPMC capsules prior to the priority date?

A. No.

Q. Were you engaged with dealing with other people or consulting with other people or talking to other people who were involved in formulating with capsules as of June 2001?

A. Formulating with capsules?

Q. With capsules

A. So I was doing capsule work myself –

Q. Yes.

A. – that is what you mean?

Q. Yes.

A. Was I working with –

Q. Were you liaising with others who were engaged in similar activities?

A. Well, within the community –

Q. Yes.

A. – I was talking to people about our research, yes.

Q. Did anybody bring to your attention the potential that HPMC capsules might be available?

A. No."

Professor Birchall acknowledged the possibility that HPMC capsules might conceivably have been mentioned to him before the priority date by Brian Jones, the individual behind Shionogi's work in developing HPMC capsules, who happened to be a neighbour and colleague at the Welsh School of Pharmacy at the time; however, he had no recollection of any such conversation having taken place.

– third, although Professor Buckton maintained that the text in Ogura to the effect that HPMC capsules would be appropriate for use in inhalation devices was a message which would likely have been communicated to formulators in the field by way of conferences, neither he nor Teva were able to point to a single pamphlet or paper from a conference on inhaled medicines that contained any reference to using HPMC capsules for inhalation purposes. In his oral testimony, on Day 9: 127, 9-21, Professor Birchall did not accept that the notion that HPMC capsules would be appropriate for use in inhalation devices was a message which would have been communicated by way of pre-priority date conferences to formulators:

"Q. Will you tell the Court what, to your knowledge, was the availability of HPMC capsules as of June 2001?

A. Yeah. So to my knowledge, so we were working on a dry powder inhaler formulation and we had within our laboratory gelatin capsules, just got them from various suppliers and used gelatin capsules. I had no awareness of HPMC capsules. I don't think the skilled formulator would have awareness of HPMC capsules. They would - the reference point for that awareness would be publications, it would be textbooks, it would be conferences, etc., and I don't see how they would become aware of it through those avenues. So that's my view on where HPMC was in 2001."

– fourth, in the course of Professor Buckton's oral evidence before the High Court of England and Wales (put to him in a question at Day 4: 92, 1–8), he was asked "*Are you aware of any DPI marketed or not by 2001 that had anything other than gelatin in its capsule*?" and responded that he did not know about unmarketed capsules "*but the ones that I would know of were the marketed [ones] and up to that time they were gelatin*". Before this Court, Professor Buckton (at Day 5: 108, 18–24) accepted, when it was put to him by counsel, that the commercial launch of HPMC capsules for oral use was in 2002 and the commercial launch of HPMC for inhalation use was in 2003.

– fifth, it will be recalled, from the overview previously above of Professor Buckton's first written statement, that in the Norwegian leg of the ongoing pan-European battle between the wider Teva and Boehringer groups concerning what in Ireland is the 220 Patent, Professor Buckton was given a list of patent applications by Teva's Norwegian lawyers, all of which were published post-priority date, and on the back of which he has constructed a theory that because HPMC capsules were mentioned in these applications, this shows that HPMC capsules were, by the time of those applications, being commonly used and thus comprised common general knowledge for the purposes of the within application. For the reasons that follow, the court is unpersuaded by this approach to identifying the relevant common general knowledge as of the priority date:

(1) all of the said patent applications were published post-priority and thus not available to the skilled person at the priority date.

(2) Professor Buckton, for what it is worth, also could not have known of the patent applications as of the priority date (because they were not published) and indicated, at Day 4:108, 16–109, 8, that he did not know of know of them the whole way through the proceedings in London and only became aware of them once they were handed to him by the Norwegian lawyers.

(3) it is perhaps notable as to the general lack of awareness of the patents aforesaid, that this lack of awareness on the part of Professor Buckton subsisted despite his being a founder and onetime CEO of Pharmaterials Ltd., a successful company and onetime Queen's Award-winner for enterprise in international trade, with which company Professor Buckton was involved from 2000-2012 and which, on his own account, turned to DPI formulation in 2005.

(4) there was no acknowledgement on the part of Professor Buckton that HPMC was referred to among an array of materials in the said patents, not least for the purpose of outlining an adequate breadth of alternative materials for the invention so that the inventive concept could best be expressed.

(5) in a segment of his first written statement not quoted previously above, Professor Buckton, having considered one of the patents given him by the Norwegian lawyers notes as follows, at para. 2.49.3: "*This shows that the desire was to use HPMC capsules having low hygroscopicity. The inventors have not made the selection of the HPMC capsule as part of the claimed invention indicating that they considered the selection of HPMC as capsule material as an obvious choice*." Two points might be made in this regard. First, it seems to the court that this is a form of reasoning that blurs the distinction between common general knowledge and obviousness. Second, HPMC capsules did feature among the claims in three of the applications in question which suggests that there is, at the least, a difficulty with Professor Buckton's logic in this regard. As will be seen in the court's consideration of the Aulton texts below, the fact that those texts in 2002 and afterwards focused on gelatin capsules would also appear significantly to undermine the nature of the reliance sought to be placed by Professor Buckton on the patents given to him by the Norwegian lawyers.

I. Aulton.
83. It will be recalled that in his first witness statement, Professor Buckton, at para. 2.47, having recounted his understanding of the evolution of HPMC capsules, in large part by reference to hearsay evidence, as opposed to his own experience or knowledge, concludes by stating that "*Although Aulton 2nd ed. focuses on gelatin capsules, it too contains reference to the availability of these HPMC alternatives*." This was a reference to a leading textbook, Aulton, M.E., ed., *Pharmaceutics, The Science of Dosage Form Design* (2nd ed., 2002). At p.449 of that text, which is clearly a post-priority date publication, the introductory text to ch.29, authored by Mr Brian Jones and entitled "*Hard gelatin capsules*", it is noted that "[I]*n recent years hard capsules have been manufactured also from hydroxypropyl methylcellulose in order to produce a shell with a low moisture content*" and then references the Ogura article from 1998.

84. Professor Buckton's observations concerning Aulton met with a number of criticisms from Professor Birchall in his first written statement. First, Professor Birchall noted that Brian Jones was closely associated with Shionogi/Qualicaps at the time that HPMC capsules were being developed and thus had unique access to knowledge as to the properties of HPMC capsules. Second, Professor Birchall observed that the focus of the chapter, as its title suggests, was on hard gelatin capsules; thus, while it referenced HPMC capsules its text in fact shows that, even as of 2002, gelatin remained the only real material for manufacture at the time, containing the statement, at 449, that "*The raw materials used in the manufacture of both types of capsule [hard and soft] are similar. Both contain gelatin*", and later on that page that "*Gelatin is the major component of the capsule and has been the material from which they have traditionally been made*." Third, Professor Birchall notes that in the next two succeeding editions of Aulston, *i.e.* the 3rd and 4th editions which were published respectively in 2007 and 2013, the near-exclusive focus remained on gelatin capsules with only fleeting reference to HPMC capsules. Fourth, Professor Birchall contends that when trying to assess the common general knowledge with respect to containers for inhaled medicines it is more appropriate (it is certainly equally appropriate; the court is not persuaded that it is 'more' appropriate) to have regard to ch.31 of the text ("*Pulmonary drug delivery*") as opposed to ch.29 ("*Hard gelatin capsules*"). Chapter 29 was written by Professor Kevin Taylor of the University of London, a DPI formulator, and so belonging to the discipline of the notional skilled person. Professor Birchall notes that, tellingly, ch.31 contains no reference to the use of HPMC capsules as containers in DPIs, notwithstanding that Professor Taylor is a person to whom Professor Birchall, it seems to the court rightly, ascribes a level of knowledge and ability considerably higher than that of the notional skilled person.

85. Aulton was also the focus of some attention when Professors Buckton and Birchall took successively to the witness-box. Perhaps two further points of interest arose from that evidence. First, Professor Buckton acknowledged, at Day 5: 112, 13-14, when it came to the gelatin capsule/hard gelatin capsule chapters in each of the 2002, 2007 and 2013 chapters of Aulton, that "*The chapters do focus on gelatin, all three of, them yes*." Second, the court was struck by the exchange that transpired between counsel for Boehringer and Professor Buckton on Day 5 when counsel led the professor through successive relevant learned pre-priority date texts in which there was no mention either of HPMC capsules or the drying of any such capsules, thus putting into perspective the post-priority date reference in ch.29 of Aulton (2002), which reference is in any event vulnerable to all the criticisms made by Professor Birchall. The relevant exchange lasted for about an hour and thus is too long to quote in the within judgment. However, it established that each of the following learned pre-priority date texts make no mention of HPMC capsules or the drying of capsules: Ashurst, I. and ors., "Latest advances in the development of dry powder inhalers" (2000) 3(7) PSTT 246, Banker S. and Rhodes, C., *Modern Pharmaceutics* (3rd ed., 1995), Lachman, L. and ors, *The Theory and Practice of Industrial Pharmacy* (3rd ed., 1986), Tee, S.K. and ors., "The use of different sugars as fine and coarse carriers for aerosolised salbutamol sulphate*" International Journal of Pharmaceutics* 208 (2000) 111, and Voigt, R.., *Pharmaceutical Technology* (9th ed., 2000).

86. A couple of supplementary observations might be made. First, as touched upon previously above, it seems to the court that the focus on gelatin capsules in Aulton in 2002 and afterwards is a significant fact, given the nature of the reliance sought to be placed by Professor Buckton on the patents given to him by the Norwegian lawyers. Second, the focus on gelatin capsules in Aulton in 2002 and afterwards also seems to the court to undermine further the reliance sought to be placed by Teva on the Capsugel documentation (considered below) which reliance in any event suffers from the various deficiencies identified by the court hereafter.

II. The Capsugel Capsules.
87. In the course of Teva's closing written submissions the following submission appears:

> "6.22 During the course of Professor Birchall's cross-examination the court was shown a number of brochures by Capsugel Vcaps. The first, a brochure from 1997 stated at page 5 that HPMC was a widely used excipient in pharmaceuticals food and cosmetic formulations and was described in the GRAS List (Generally Recognised as Safe) and the United States Pharmacopoeia. The capsule sizes referred to in this brochure were correctly pointed out by Professor Birchall as being for oral use as the capsules for inhalation would be commonly size 2 or 3. For clarification purposes, a further brochure was handed into court after lunch on that day. This brochure was also a Capsugel Vcaps brochure but from 1999 and clearly stated that the capsules were available in size 3 (i.e. suitable for inhalation purposes on Professor Birchall's own evidence)."

88. Professor Buckton gave no evidence on the Capsugel capsules, a perhaps surprising omission. The Capsugel material shown to Professor Birchall was never proved in evidence (so it is not known that it ever saw the light of day or, if it did, when and where). There is no suggestion in Teva's submissions that there was any pre-priority use of HPMC capsules for inhalation purposes. There is only one pre-priority date suggestion that such a use might be made and that is in the Ogura article. (Professor Buckton in his evidence, at Day 3: 121, 21–22, describes the Ogura article as "*the only bits of paper that I know of*" that mention HPMC capsules for inhalation use before the priority date). There is no acknowledgement in Professor Birchall's evidence that the Capsugel capsules themselves were suitable for inhalation purposes. Though he acknowledged in his pre-lunchtime testimony on Day 11 that size 3 capsules were a type of capsule that is now used for inhalation purposes, when the second brochure was unexpectedly put to him after lunch, his quite proper response was to decline to comment on what he had not read; thus, he stated: "*It's still obviously a capsule focused on, well I haven't read it....I don't know what it is focused on because I haven't read it so I won't say anything about it*." (Day 11: 108, 10–13).

h. Some Conclusions.
89. What conclusions can be reached by the court by reference to the foregoing and in addition to any conclusions identified elsewhere herein?

90. First, Ogura, which is focused on HPMC capsules for oral use makes only the slightest reference to the potential for HPMC capsules in the inhalation context, gives no information relevant to inhalation use, is undoubtedly an article but one that is also something in the nature of a promotional piece for oral-use capsules by the manufacturers of same, and appears not to have been a peer-reviewed article.

91. Second, Quali-V-I capsules for inhalation use did not become commercially available until 2003.

92. Third, Aulton was not published until after the priority date, the chapter sought to be relied upon by Professor Buckton was written by the very capsule specialist who was working for Shionogi developing the HPMC capsules, it makes only a passing reference to HPMC capsules and not in connection with their use for inhalation.

93. Fourth, the Aulton chapter on pulmonary drug delivery, written by a DPI formulator and so by someone in the same field as the notional skilled person (though, per Professor Birchall, rather more skilled than the notional skilled person) makes no mention at all of HPMC capsules for inhalation purposes.

94. Fifth, the content of the unpublished patent applications given to Professor Buckton by the Norwegian lawyers was not in the public domain, never mind part of the common general knowledge of the notional skilled person.

95. Sixth, it appears to the court that the implications of (a) the absence of any pre-priority date reference to the use of HPMC capsules for inhalation in any conference, textbook or article (except the Ogura article/promotional), (b) the evidence of Professor Birchall who, from 1994 onwards, was working in a laboratory on the delivery of medicines to the lung using different types of inhaler devices (and was working specifically on DPIs and pMDIs from 2000), that he had not encountered any suggestion for the use of HPMC capsules for inhalation purposes, should prevail over the opinion of Professor Buckton, it having been established that (i) Professor Buckton was not working with capsules for inhalation at the time, (ii) Professor Buckton's opinion what was common general knowledge by the priority date was based on materials that were given to him by this legal team, which materials, the court is satisfied, (I) are insufficient to support the proposition that HPMC was common general knowledge in 2001 and (II) had not otherwise come to Professor Buckton's attention at any point since 2005 when he started working with DPIs.

96. Seventh, the only capsule material used by the priority date for inhalation use was gelatin; the fact that HPMC capsules for inhalation use did not become commercially available until 2003 has particular significance, given the observation of Luxmoore J. in British Acoustic Films, at 250, that "'*It is certainly difficult to appreciate how the use of something which has in fact never been used in a particular art can ever be held to be common general knowledge in the art*".

X. Identifying the Inventive Concept of the Claim at Issue

97. It will be recalled that the *Windsurfing/Pozzoli* methodology contemplates a court, when looking to inventive step/obviousness, identifying the notional person skilled in the art, identifying the relevant common general knowledge of that person and then proceeding, per Jacob L.J. in *Pozzoli*, at para. [23], to "[i]*dentify the inventive concept of the claim in question or if that cannot readily be done, construe it*". Having sought to identify the notional skilled person and her relevant common general knowledge, the court proceeds now to the just-quoted step.

98. In *Conor Medsystems Inc. v. Angiotech Pharmaceuticals Inc.* [2008] R.P.C. 28, Lord Hoffmann indicates, at para. 19, that "[T]*he invention is the product specified in a claim and the patentee is entitled to have the question of obviousness determined by reference to his claim and not to some vague paraphrase based upon the extent of his disclosure in the description*." The 220 Patent identifies the inventive concept of its subject-matter in the first paragraph, the English translation of which states as follows:

> "The invention relates to capsules for inhalation (inhalettes) consisting of specific capsule materials with a reduced moisture content, which contain the active substance tiotropium in the form of powdered preparations and are characterised by increased stability."

99. The invention is identified in the patent as conferring the benefits of increased/sufficient stability, high metering accuracy, efficient emptying of the capsule, and good perforation qualities with good stability and low brittleness. A key element of the inventive concept is the use of reduced-moisture HPMC capsules for a formulation of tiotropium powder for inhalation.

100. A notable feature of the within proceedings is that Teva has consistently sought to characterise, in truth mischaracterise, Boehringer's invention as (i) the use of capsules for inhalation purposes, with (ii) scant reference to the fact that it is a formulation of the active substance tiotropium in the form of powdered preparations, and (iii) no reference to the fact that it comprises such a formulation in a HPMC capsule of reduced moisture-content. What Teva seems to want the court to do is essentially (a) to proceed on the basis of the mischaracterisation aforesaid, and (b) find obviousness to present by reference to (I) Ogura and the passing reference therein to HPMC, (II) the notion that the notional skilled person (A) was dissatisfied with gelatin because of water-based issues and (B) would usually seek to keep the formulation dry enough to ensure physical and chemical stability. But all of the foregoing, it seems to the court, elides one of the fundamental elements of the invention, being that the capsules comprised in the invention are not only HPMC capsules but reduced-moisture HPMC capsules.

XI. Differences Between State of the Art and Inventive Concept; Obviousness

(i) Overview.

101. The court proceeds next to apply steps 3 and 4 of the *Windsurfing/Pozzoli* methodology. Step 3, it will be recalled, involves the court identifying 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. Step 4, requires the court, viewing matters without any knowledge of the alleged invention as claimed, to assess whether those differences constitute steps which would not have been obvious to the person skilled in the art or require any degree of invention. Having gone through the various steps of the *Windsurfing/Pozzoli* methodology, it seems to the court that the critical issue that arises for determination in the within proceedings is whether the development of a formulation tiotropium powder for inhalation in reduced-moisture HPMC capsules would have been obvious by the priority date to the notional skilled formulation scientist who was reading Ogura in the light of her common general knowledge.

(ii) Reduction of moisture; alleged problems with gelatin capsules.

102. The court has already touched at some length above on the propositions, rejected by the court by reference to the evidence before it, that (i) it was part of the common general knowledge to start out on a DPI formulation by reducing moisture content, and (ii) that gelatin capsules were viewed as problematic containers for DPI formulations. The evidence of Professor Birchall, preferred by the court to that of Professor Buckton for the reasons outlined previously above, is that Professor Buckton's posited *ex ante* prescription of moisture-content limits was not the point of departure for formulations; rather, matters were dealt with by equilibrating the respective moisture limits of the (gelatin) capsule and the drug/powder mix to be contained therein, which approach was taken for formulations unless the drug/powder mix turned out to be unstable at its equilibrated level, in which case other options would be reviewed – though a reduction in capsule moisture (with the consequent brittleness of gelatin) would not have been opted for.

(iii) Water.

a. Tiotropium and water.

I. General.

103. Teva sought to show that the notional skilled person would have thought that tiotropium was too water-sensitive to be formulated as normal at the priority date. Teva initially sought support for the notion that tiotropium was water-sensitive in the opinion of Professor Buckton that Experiments 1 and 3 involving tiotropium powder in HPMC capsules and showing a 1% degradation (at accelerated temperature and relative humidity) showed a marked sensitivity of tiotropium to hydrolysis. However, this was an approach that seemed to the court to disregard the implications of Experiment 2, being that where tiotropium bromide was kept at conditions of accelerated relative humidity and temperature it showed no degradation after two weeks. It also appeared to the court to ignore the implication of Barnes and Maesen (considered later below) that tiotropium bromide was formulated into gelatin capsules for DPI use in successful phase II and III trials. In his supplemental report concerning the supplemental experiments put in by Boehringer, Professor Buckton then adduced the European Public Assessment Report of 21st May, 2002, on the SPIRIVA® product, in support of the contention that the notional skilled person would have been concerned in 2001 as to the water. The court would make a number of points as to why it rejects these various contentions of Teva.

104. First, as outlined by Professor Birchall in his evidence, as considered above, even if tiotropium would have been considered by a formulator in 2001 to be water-sensitive, she (the formulator) would not have turned to HPMC capsules and would not have started drying them to achieve a formulation. Instead she would have engaged in what the court has referred to as the 'equilibration process' described by Professor Birchall in his evidence. If she then encountered persistent problems, she would have tried the kind of adjustments that were customary in the field or considered other kinds of formulations if those adjustments did not work.

105. Second, it appears from the evidence that the notional skilled person would have assumed in 2001 that water was in fact unlikely to be an issue. In this regard, it is useful to recall the evidence of Professor Birchall, at paras. 85 and 150 of his first written statement, where he observes as follows:

> "85….Tiotropium had been formulated as both a lactose-based dry powder inhaler and a water-based nebulised formulation by 2001 and so the skilled person in 2001, if given this information, would be likely to assume that water was unlikely to be an issue in terms of stability when the powder was filled into a capsule at an equilibrated water content and in ambient conditions. The formulator should anyway have useful information in relation to the chemical and physical stability of the active ingredient from the preformulation stage….
>
> 150. Professor Buckton [at para. 3.25 of his first written statement]…goes on to attribute an inference to the skilled person from the [220] Patent that 'given that the whole scope of the [220] Patent is directed to reducing the water content of the capsules for tiotropium bromide (or other salts) one can infer that tiotropium bromide is susceptible to these issues in the presence of water as well.' I am not sure how such an inference could be attributed to the skilled person in circumstances where, as I have outlined previously…the reaction of a skilled person to an active that was unstable in the presence of water would never have been to reduce the water content of the capsule. In any event, if the skilled person had common general knowledge of tiotropium as Professor Buckton asserts then the skilled person would have known that tiotropium had been formulated in an aqueous (water based) formulation during early clinical testing. Boeringher Ingelheim's Experiment 2 shows that tiotropium alone does not degrade when stored for two weeks at accelerated (40°C/75%RH) temperature and humidity conditions….This is the kind of information that a skilled person may have gained from preformulation tests and would be armed with when considering his or her formulation choices."

106. *Professor Buckton agreed to the extent of saying that when he first read of an aqueous product of tiotropium "my response to that, without having known about it, was either it's stable or some measures have been taken in order to stabilise it."* (Day 7: 89, 18–21). He also agreed that when it came to a skilled person reading of the phase III information studies in Barnes and Maesen "*You would know for sure that because there are Phase III studies out there…that there is a formulation which is stable….*[Y]*ou know for certain the Phase III study is stable and stable enough to make a product out of….You don't know what it is just yet but you know that there is one to be had"* (Day 7: 93, 25–94, 5).

> 107. As to the reference to the SPIRIVA® report, this is a post-priority date document and appears only belatedly to have come to the attention of Professor Buckton, being exhibited to his second witness statement in the within proceedings. In his assessment of Experiment 6, Professor Buckton observed, *inter alia*, as follows:
>
> "2.8 It is now known that tiotropium bromide is liable to hydrolysis. The majority of drugs degrade over the shelf life of the product, the key issues are that the extent of degradation must not be so great that the drug no longer achieves the necessary therapeutic effect and also that any degradation products are not toxic at the concentrations that they reach during shelf life. The two most common degradation mechanisms are hydrolysis and oxidation, these being reactions involving water (from the atmosphere or the formulation) or oxygen, respectively. Hydrolysis would have been discovered during preformulation.
>
> 2.9 One of the early stages in preformulation is to assess key properties of the drug substance, especially its solubility and chemical stability (tendency to react with water and/or oxygen for example). In order to optimise the drug substance it is usual to select a salt form. In this case the bromide salt has been selected. Salts can be formed by a simple reaction between tiotropium and many pharmaceutically acceptable acids. While the details of salt selection are beyond the scope of this case, it should be understood that the preferred salt will be a material that crystallises readily and which has the best physical properties and chemical stability. This means that the process of salt selection (i.e. picking the bromide) will inevitably have involved the assessment of chemical stability.
>
> 2.10 Having selected a salt (the bromide in this case), the issue of stability will have been optimized to some extent (in as much as the selected salt will most probably be more stable than other salts which were considered). However, even for the selected form the extent to which hydrolysis (which would be well understood by this stage) would be a problem for the formulation would then be assessed. Indeed, this proved to be the case as can be seen from the European Public Assessment Report of Spiriva (the commercial tiotropium bromide DPI marketed by the Respondent), where it is reported that 'The active substance can be hydrolysed due to the presence of an ester bond' followed by discussion regarding minimizing water content in the capsule….
>
> 2.11 These assessment reports are obviously not from the prior art, but I refer to them simply to show that the skilled formulator would carry out preformulation and, indeed, Boehringer Ingelheim did so in this case."

108. A number of points might be made regarding the SPIRIVA® report. First, it is describing an authorised product that had an acceptable shelf-life when properly packaged from environmental conditions in accordance with the practice on which Professor Birchall gave evidence. Second, the report is based on a review of all data and tests submitted in connection with the regulatory

approval of a product; it is not reflective of what would have been found on pre-formulation testing. Third, as to what the pre-formulation tests would be, Professor Buckton gave evidence that appeared difficult to reconcile, if it did not in fact entirely conflict, with Aulton (1988) which, states, *inter alia*, as follows, at 245, under the heading "*Solid-state stability*":

> "Because of the differences observed in the behaviour of drugs in the solid state or in contact with limited amounts of water, such as adsorbed moisture films, when compared with their reaction in solution, studies in dilute solution can often be quite meaningless and should not be extrapolated glibly to the solid state."

109. Professor Buckton's reading of this was that one would nevertheless test solution state degradation behaviour, even though it would not reflect useful information on degradation behaviour in the solid state. In respect of the above-quoted text from Aulton, Professor Buckton observed, at Day 7: 119, 28–120, 3 that "[Aulton] *is saying that the data from solution is something you would generate, it will give you interesting information about the tendency to degrade, but what really matters is the kinetics that links to the solid state, and that is different to the others*." That, with respect, is not a reading that sits easily with the text of Aulton. Neither does it sit easily with the evidence of Professor Birchall; his evidence was that the solution state behaviour of a drug has little or nothing to tell about its behaviour in the solid state. Thus, he observed, at Day 9: 105, 11-16:

> "[I]t has no relevance to dry powder formulation because if your drug is breaking down in solution your dry powder formulation is in solid state. So the solid state experiments are going to be a lot more relevant to you, aren't they? When it might come in is knowing something about -- I think this came up, you need to understand a little bit about what will happen in solution because you are measuring these dry powder inhaler formulations you might have to put the drug into solution to measure it. So you want to do that. Just check it is not going to be broken down because that will affect the measurement."

110. As regards the tests that would be carried out in pre-formulation studies, Professor Birchall's evidence, at Day 9: 108, 15-109, 8, was as follows:

> *"Q….[I]f the person is formulating, against what background is that person looking for physical and chemical stability? What would be the conditions under which that person carries out that exercise?*
>
> *A. So if you wanted to understand physical and chemical stability of your dry powder inhaler product - is that what you are saying?*
>
> *Q. Yes.*
>
> *A. Of your formulation. So there's a number of things you might want to do. So you might want to assess the chemical stability. So look at the break down of any drug or excipient within the product, in the solid state. And you could do that and raise humidity, stress conditions to accelerate that process. So raise the temperature, raise the humidity and have a look to see if you get break down of your drug, the chemical. Is that –*
>
> *Q. Yes.*
>
> *A. And so, the physical stability, this is more about the performance of the powder from the inhaler. So you do the assessments we spoke about, delivered dose, fine particle dose, fine particle fraction."*

111. So Experiment 2, under which tiotropium bromide was subjected to accelerated conditions of temperature and stress appears to be precisely the kind of pre-formulation test that would be carried out, and it showed no degradation after two weeks. Professor Birchall's evidence on re-examination was in effect that the Experiment 2 test was precisely the test that would be done for the purposes of making decisions on pre-formulation, observing as follows, at Day 12: 106, 26 –107, 27:

> *"Q….[Y]ou made reference to Experiment 2 in your answer.*
>
> *A. Yes.*
>
> *Q. And I think the Court has already got the evidence about that; it was material -- tiotropium was on its own, isn't that correct?*
>
> *A. Tiotropium on its own, yes.*
>
> *Q. And what was the result of the experiment with tiotropium on its own, first of all?*
>
> *A. So for two weeks at 40 degrees centigrade and 75% relative humidity, there was no degradation of tiotropium alone.*
>
> *Q….You said in your evidence when you were suggesting that that would have been relied upon by the formulator at the time, at the accelerated conditions to make those early decisions?*
>
> *A. Yes.*
>
> *Q. And it was suggested to you that, in fact, you should have -- or these tests should have been done for longer or repeated, or whatever, or weren't reliable for that purpose. And in the course of that exchange, you said something to the Court along the lines that if you were to follow the FDA guidance at the early stage in relation to the six months and four repeats, and so on, that you would never develop a product. Can you just explain what you mean by that?*
>
> *A. So the nature of the experiment is one to determine chemical degradation at an early stage, so the experiment as a whole looked at capsule materials with tiotropium and tiotropium alone. So tiotropium alone would be the sort of experiment to determine hydrolysis within the solid state, so you would be doing lots and lots of experiments at the early phase, and that would be the nature of the experiment, just to show whether there is any issues of chemical degradation. Now, you would go from those studies, which would be of a limited duration, to bigger studies when you actually start to develop your product, and that's the nature of accelerated stability testing; you have got through the formulation stage, you have a formulation you are looking to use in patients and so you have to address issues of shelf life and storage."*

112. Professor Buckton said that the experiment had not been done for long enough. To this the court would but observe that it was always open to Teva to conduct the experiment and to do it for longer, but it elected, for whatever reason, not so to do. But the critical problem for Teva, it seems to the court, is that the test did not reveal what it would have liked it to reveal, a fact which was made crystal-clear in the following exchange between Professor Birchall when under cross-examination, at Day 12: 47, 20–29:

> *"Q….I think it is common ground that the pre-formulator would carry out solid state stability tests.*
>
> *A. Yes, they would.*
>
> *Q. And I suggest to you that if they had carried out solid state tests on tiotropium bromide monohydrate as of the priority date they would absolutely certainly have revealed that it had significant moisture sensitivity issues?*
>
> *A. So the experiment we have seen did not show that."*

113. As to the Boehringer patents (in truth they were patents that had been assigned to Boehringer) referring to water sensitivity in tiotropium, it became clear as the evidence proceeded that the water sensitivity to which reference was made in same, insofar as it went, was in respect of the finished, authorised and used SPIRIVA® product, and so not information that would have been available to the notional skilled person at the priority date.

II. Some Conclusions.
114. As of the priority date: (1) when it comes to the concern, or want of concern, on the part of the notional skilled person as to the sensitivity of tiotropium to moistiure, she (the notional skilled person) would have taken it that tiotropium had already been formulated in gelatin capsules for phase III clinical trials; (2) ipratropium and oxitropium (related compounds to tiotropium) had been successfully formulated in DPIs in gelatin capsules. Teva seems to ignore the fact that no degradation of tiotropium was shown after two weeks' testing at accelerated conditions of temperature and humidity (75%RH/40°C), and relies instead (and erroneously for the reasons adverted to previously above) on the SPIRIVA® report.

b. 'Natural' water content of HPMC.

I. General.
115. As considered previously above, the inventive concept of the impugned development is the formulation of tiotropium in prescribed reduced-moisture HPMC capsules, being HPMC capsules with =5% water-content, <4% water-content and <2% water-content. Boehringer carried out Experiment 5 to show the water-content of HPMC capsules at normal manufacturing conditions (20°C/40-60%RH) was above 5%. Professor Birchall explains what was done as follows in his first written statement, at paras. 203-217:

> **"Protocol 5 experiments**
>
> 203. The experiments described in Protocol 5 aim to show the water content of HPMC capsules when the atmospheric relative humidity is adjusted and the temperature kept at 20°C. To do this a combination of loss on drying (the 'LOD method') and dynamic vapour sorption methods (the 'DVS method') are employed.
>
> 204. The DVS method is used to determine the change in weight of materials at different relative humidities from very low to very high humidity and vice versa. The change in weight of the material is a result of water absorption into the material or desorption of water from the material into the atmosphere.
>
> 205. DVS dats cannot however be used as a definitive measure of moisture content of the material as the material may not be at 0% moisture content when the relative humidity is set to 0% - as mentioned previously water can be bound to a material and does not leave freely under drying conditions alone, it can only be removed upon heating the material so the water vaporises.
>
> 206. The LOD method in Protocol 5 is therefore used to equilibrate (correct) the DVS data so that the DVS data can be used to measure moisture content. This involves conditioning a sample of the material to a known humidity (in this case 20%RH) and then performing the LOD method.
>
> 207. The LOD test works by heating the sample to 105 under a halogen lamp and so any water present is vaporised into the atmosphere. The water content of the sample is simply derived by subtracting the weight of the sample after heating from the weight of the sample before heating. The result will therefore determine definitively how much water is in the sample (which in the case of Protocol 5 had been conditioned at 20%RH). Having performed a DVS study the DVS plot can then be adjusted so at 20%RH the plot provides a value at the same moisture content value derived from the LOD test. The DVS data should then provide the moisture content of the material across a wide range of humidities (essentially any increase or decrease in weight at humidities above or below the 20% RH value is added or subtracted from the moisture value derived from the LOD test).
>
> 208. My conclusions from the experiments conducted under Protocol 5 are as follows:
>
> Table 1
>
> (I) The moisture contents of HPMC capsules at 20 C/20% RH is 3.9% as determined by a standard LOD method.
>
> Figure 1
>
> (II) The normalised DVS isotherm shows how changes in humidity can affect the moisture content of HPMC capsule at 20 C.

209. Professor Buckton notes the difference between the results yielded by the DVS method and the LOD method in the experiment and appears to conclude that this must be owing to error or unreliable data. However the two methods measure different things – the DVS method measures weight change and the LOD method measures water content; it is not therefore surprising that they are different. That is the point of using both methods, so the difference can be

accounted for. As I have explained, the LOD measurement was carried out by Boehringer Ingelheim in this experiment in order to calibrate the DVS figures to allow conversion of the data on percentage change in mass (obtained from the DVS methodology) to data on water content.

210. In regard of Professor Buckton's comment that this was not a usual correction to do. The correction is not required if the DVS data is used to show the change in weight of a material as a result of a change in humidity (as is normally and correctly the case). A correction is however needed if the DVS data is being used to show absolute moisture content as samples may not need to be dried to 0% moisture content at 0%RH. It is actually very different to ensure conditions of 0%RH and these conditions would not ensure removal of all the contained water, particularly water that is bound into the material structure. Perhaps this is what Professor Buckton is inferring when he states that if the sample had been taken up to 0% RH 'the water would have had the chance to be removed from the sample.'

211. Professor Buckton argues that the Nagata paper he relies upon [Nagata, S., "Cellulose Capsules – An Alternative to Gelatin" in Chiellini, E., ed. Biomedical polymers and polymer therapeutics (2001)]…is more relevant to the question of different water contents at different conditions of temperature and relative humidity. It is perhaps important to consider whether the Nagata data is more robust or accurate. Nagata's experiment reports the chamge in weight of 'cut' capsules under different relative humidity conditions. As previously mentioned, this cannot be related to % moisture content of the 'cut' material unless it is demonstrated, though complete loss on drying, that the moisture content is reduced to zero at 0%RH. This is actually practically quite difficult to achieve and it is not clear in Nagata how this was done and demonstrated. It is perhaps for this reason that Nagata does not actually use the isotherm data when providing definitive values of moisture content for gelatin and HPMC capsules, he uses a completely different 'Karl-Fischer' method for this purpose. It is also interesting to note that Nagata provides the moisture contents of the capsules at 40% –60%RH – these being the accepted standard manufacturing and filling conditions for capsules.

212. With reference to the data in Nagata (notwithstanding the potential limitations I have discussed) it is also important to point out that HPMC capsules are manufactured from a solution of HPMC and so the first dynamic will be one of desorption. Capsules are always stripped from the mould pins at higher water content than their final specification as it helps them to be removed from the pins (they are more flexible at this increased moisture content). For example, gelatin capsules are removed from the pins at 15–18% moisture content and HPMC capsules would be removed at over 7% moisture content. After removal from the pins at high moisture levels the capsules would most likely be stored between 40-60 %RH (the Nagata paper actually supports this), the standard conditions for capsule filling and this would result in a lowering of the moisture content of the capsules. Looking at the desorption of moisture from the capsules the moisture content of the capsules would therefore be above 5%, even according to Nagata.

213. Professor Buckton goes on to say at paragraph 5.52 of his report that 'There are numerous reports of water content of HPMC capsules that are in keeping with the values reported by Nagata and Ogura.' The references he uses to support this statement…are both by Brian Jones who as I already mentioned is and was a consultant to Shionogi/Qualicaps at the time. Both of the articles simply refer to HPMC water content data provided by Ogura or Nagata (both Shionogi/Qualicaps employees) rather than independently confirm or even attempt to replicate the data.

214. In order to check the data adjustment value used in Protocol 5 I performed my own analyses, reviewing some of my own previously published data performed in collaboration with Brian Jones and without any knowledge of this case….

215. In the experiments yielding these data, the water content of HPMC capsules was measured using a LOD method after conditioning the HPMC capsules at known humidities:

Birchall et al. 2008: 2.7% moisture content at approximately 11%RH; 4.7% moisture content at approximately 33%RH.

Torrisi et al. 2013: 3.2% moisture content at approximately 11%RH; 5% moisture content at approximately 33%RH.

Plotting this data provides the following relationship between moisture content and relative humidity (as determined using the LOD method).

[Graph at this point not replicated in the within judgment.]

216. The graph shows that HPMC capsules at 20%RH would be expected to have a water content in the region of 3.5 to 4%. This is in line with the adjustment figure of 3.9% derived from Boehringer Ingelheim's LOD test. I can therefore conclude that this value is not an error or unreliable. I also do not agree with Professor Buckton's suggestion in the footnote that the LOD method is flawed in this instance as other materials may be lost on heating and therefore an inflated value for water content may be derived. Whilst this may be a concern for a sample that contain volatile components, HPMC capsules are a relatively simple formulation of HPMC and gelling agents in water. I do not see why there would be any other material that would be vaporised during the LOD test.

217. My conclusions from Protocol 5 is that the method used to assess water content against humidity is reasonable given the LOD result at 20%RH and that the values presented in the results of the experiment may be useful to determine the water content of HPMC capsules when stored at different humidities." [*Emphases in original*].

II. Nagata.

116. Teva has adduced evidence from Professor Buckton to the effect that the water-content figures set out in Nagata were correct and that the Boehringer figures were incorrect. Professor Buckton's evidence in effect was that the data set out in the Nagata article (though post-priority) was more contemporaneous with the priority date. A number of points might be made concerning the Nagata article.

117. First, the Nagata article gives three different sets of figures which do not correlate with each other (3–7% water content for HPMC capsules, 4-6% using the Karl-Fischer method, and a DVS isotherm showing results of 3.4-5.2, depending on the curve used (sorption or desorption)).

118. Second, the DVS graph done by Boehringer was normalised by LOD but there is nothing to indicate that the Nagata DVS was normalised against an absolute measurement.

119. Third, when it comes to the Karl-Fischer method, although Professor Buckton pointed to the Karl-Fischer method as the standard method used to measure total water content in a wide variety of materials, Professor Birchall, whose evidence has generally been preferred throughout this judgment over that of Professor Buckton for the reasons stated elsewhere above, observed, at Day 10: 31, 7–11, that "[I]*n the industry, in the capsule industry it's loss on drying that's used, it's loss on drying when you heat the sample, vapour of all of the water, it's the reliable method for capsules. It is used as the routine method*."

120. Fourth, there is no information in any event as to how the authors of Nagata carried out the Karl Fischer method.

121. Fifth, as regards the notion, posited by Professor Buckton, that the difference between the Boehringer results and certain of the Nagata results might be accounted for by the boiling off of mass other than water, the court understands Professor Birchall's evidence to be that none of the constituents of HPMC capsules apart from water would be boiled off by an LOD process.

122. Sixth, as regards the notion that the difference could be accounted for by usage of a different material, Professor Birchall normalised the Nagata isotherm against the absolute LOD water-content value obtained by Boehringer and superimposed the Nagata isotherm and the Boehringer isotherm so as precisely to check the material values of each. The results of that exercise were presented in a graph that shows almost identical sorption and desorption curves, which points to the conclusion that the materials must be the same or very similar.

123. Seventh, it emerged from the evidence that Boehringer's experiments had been carried out on Quali-V-I capsules (with a specification of 4.5-6.5% water content) as opposed to Quali-V capsules (with a specification of 4-6% water content), the Quali- V-I capsule being, per Professor Buckton at Day 3: 134, 21-27, "*a line-extension product that came along later in the life of the product. I don't think it's reasonable to represent the original ones as not being intended for both uses because…that was the original intention. Subsequently, they were refined into an inhalation grade and a normal grade*." In his oral evidence, Professor Birchall explained why the usage of the V-I capsules rather than the V capsules would not explain the difference in water-content reflected in the isotherms; the quoted text below takes up Professor Birchall's evidence, at Day 10: 39, 23-42, 2, from the point where he considers the graph mentioned in the last point through to the just-mentioned conclusion:

> *"Q….[W]hat conclusions were you in a position to draw from that graph therefore, professor?*
>
> *A. Well, I have already said, and I said within my report that I had concerns that the DVS data in Nagata had not been normalised and we still don't know whether it was normalised or not. What is interesting is, if you do normalise it against a known water content for HPMC capsules you get a different set of results and you get different values for the moisture content at different relative humidities. And the second point is, if you superimpose the graphs, and this is just considering the shape of the graphs, it shows that the materials used have the same properties in their ability to take up and release water.*
>
> *Q. Therefore what, if any, conclusions were you in a position to draw having done that exercise from the statement in Nagata that the HPMC capsules were measured as having 4-6% moisture content?*
>
> *A. So well the conclusions I draw, the reason for the exercise was to try and explain this concern about me not knowing why we are getting different results. That was the reason for it. Now, going back to what was presented in the Nagata, it gives you the Karl Fischer and a DVS measure of water content, this now gives us a water content measurement which has been adjusted to a known water content. So it allows us to think about why there might be differences between the data. But the Nagata data, I obviously can't comment on how it was performed, the Boehringer data I know how it was performed, so I can compare the two and see if one of the reasons why they are different is because there was no normalisation of the data at the time.*
>
> *Q. And what view did you form about the reason for the difference, because you know Prof. Buckton suggested there was an error?*
>
> *A. So I don't agree there was an error in any of the adjustment through loss on drying but the reason for the difference would not be due totally, let's put it that way, to any change in material. Because if there was a difference to the change in material then if it was to do with different capsules being used and different moisture contents in those capsules you'd expect differences in the shapes of the isotherm. Now one point to raise is that the capsules used for the Boehringer adjustment were Quali-V-I capsules, the Nagata capsules were HPMC capsules at the time and we don't know what those were but the expectation is they were more like the Quali-V capsules. Now, there is a slight difference in the moisture content of those capsules. And so, it's absolutely fair to say that if the adjustment had been done on those capsules you might see a small percentage drop of the data. So the Nagata data might be slightly lower than this but it is going to be in the region of 0.1 to 0.5% moisture. So it is about the thickness of one of these little symbols.*
>
> *Q. And, therefore, Professor, can I ask you, if you wouldn't mind, to comment on do you accept Prof. Buckton's statement that the difference can be explained because there was different, as he suggested, materials because it was Quali-V-I versus Quali-V and, therefore, what you have done isn't reliable?*
>
> *A. So the scale of the difference cannot be explained by that. Because, as I mentioned, the difference between Quali-V and Quali-V-I from a moisture content perspective is very small and it wouldn't explain the size of the difference we're seeing."*

124. In passing, the court notes that while the specification mentioned in the Quali-V brochures is 4-6% water content and 4.5-6.5% water content for Quali-V and Quali-V-I capsules respectively, the capsules are within specification once they are within that range and the weight of the evidence shows that, as delivered and in standard manufacturing conditions, they are above 5% water content, i.e. within specification but above 5%.

125. Eighth, the correctness of the Boehringer values is borne out by Professor Birchall's experiments on HPMC capsules done before any involvement in these proceedings and on which he gave evidence in his first written statement (quoted above), and again in his examination-in-chief, substantiating the absolute LOD figure of 3.9% water content at 20% RH which was used to normalise Boehringer's DVS graphs.

(iv) HPMC capsules and inhalation use.

126. The court has explained its rationale for concluding by reference to the evidence before it that HPMC capsules were not part of the common general knowledge in 2001. It turns now to explain why it considers that (i) their use for inhalation purposes in

connection with tiotropium preparations would not have been obvious to the notional skilled person who was given the Ogura article to read, and (ii) the use of reduced-moisture HPMC capsules for such an application is inventive. It is useful before proceeding to recall the substance of the Ogura article. Professor Birchall's consideration of same in his first written statement, at paras. 219-241, is respectfully adopted by the court, albeit that it is so comprehensive that it runs the danger of making Ogura sound like a longer, more comprehensive and less promotional read than it is. Per Professor Birchall:

> "219….Ogura is an article published in Pharmaceutical Technology Europe in 1998. The article was written by authors from Shionogi/Qualicaps. At the time the company was owned by the Shionogi group but it later had a change in stockholder and became Qualicaps. The article introduces and seeks to promote HPMC capsules as a potential alternative to gelatin.
>
> 220. I do not believe that I saw the Ogura article when it was published (or before the priority date). Ogura was later cited in a paper which I published together with Brian Jones (who had been acting as a consultant for Qualicaps for a number of years at that stage) in 2008 and I believe that it would be around that time that I first came across Ogura.
>
> 221….Pharmaceutical Technology Europe is considered to be a 'soft' publication in that it is a trade or industry magazine featuring many advertisements. I do not think articles published in this journal would have been peer-reviewed (if they had been it would not have been rigorous) and this would affect the way that the articles would be perceived by the skilled person.
>
> 222. After an introduction which mentions some drawbacks with gelatin capsules: they may not be suitable for readily hydrolysable drugs; some drugs may react with the gelatin, causing discolouration or retarding capsule dissolution; and religious or vegetarian objections, the article references recent work by the authors and colleagues on HPMC capsules. The three main sections of Ogura address physical characteristics of HPMC capsules, biopharmaceutical characteristics and application to formulations. I consider each in turn…but first make the following points.
>
> 223. Ogura focuses on capsules for oral use, and is seeking to promote HPMC capsules for that purpose.
>
> 224. Ogura also makes no reference to tiotropium or any excipients that are suitable for use with tiotropium and/or HPMC. As I have already stated, I do not believe that tiotropium would have been part of the common general knowledge of the skilled person. I therefore do not believe that the skilled person would have had tiotropium in mind when reading Ogura.
>
> 225. However, even if the skilled person reading Ogura was interested in formulating tiotropium, he or she would be aware from preformulation/formulation work that it does not, in and of itself, have any moisture sensitivity issues (as shown by Boehringer Ingelheim's experiment in Protocol 2). Therefore, the statements made in Ogura relating to the benefits of HPMC for use with moisture sensitive drugs would not be of any special interest to a skilled person who had the task of formulating tiotropium. The skilled person interested in inhalation formulation may be interested to see whether the article discussed matters touching on the physical stability of the drug/powder blend within the capsule.
>
> **Physical Characteristics**
>
> 226. Ogura starts this section by saying that 'The HPMC capsule is odourless and flexible, and exhibits similar dissolution behaviour to the gelatin capsule'. It continues by referring to Table 1 which lists 'The physical properties of both HPMC and gelatin capsule shells that may affect stability and dissolution, and therefore their suitability for use with various formulations and intended use'.
>
> 227. In this section Ogura focuses on the suitability of capsules for use on automated filling machines (Table II shows defect rates on various machines) and the tendency of capsules to become brittle and therefore subject to breakage during transport and storage. Ogura reports tests for brittleness and tolerance to deformation of gelatin and HPMC capsules at various moisture levels. Figure 1 shows the 'Hardness tester for capsules' used for both types of test – in essence, a weight is dropped on the capsule. For brittleness, a 50g weight is dropped from a height of 10cm and the percentage of broken capsulat es is measured. For tolerance to deformation, a 7g weight is dropped and the height required to deform 50% os the capsules is determined.
>
> 228. The skilled person would consider the methods described for the testing of brittleness and tolerance to deformation as fairly crude and would treat the results and findings from such a test with caution. Regarding the robustness of the tests, the tests rely on dropping a weight on capsules and how the weight impacted upon the capsules and the subsequent damage to the capsules would depend on the alignment of the capsules and the angle of the dropped weight. This could lead to irreproducibility of the results. There is no information in the paper on how robust or reproducible the test is. Regarding relevance of the tests, the dropping of a weight onto capsules does not re-create the conditions the test aims to challenge, i.e. stability of capsules to filling, transport and storage. Others in the field had adapted more refined motorised compression tests for determining the physical robustness of capsules but Ogura does not describe any such tests.
>
> 229. The results of the tests are shown as a factor of moisture content in Figure 2. Ogura states…that 'no brittleness was observed in HPMC capsule shells even at a moisture level of only 2%' and…that gelatin and HPMC showed 'equivalent tolerance to deformation at their average moisture content levels – 2.5% for HPMC capsules and 13-15% for gelatin capsules'. The skilled person would not know, and Ogura does not disclose, under what conditions the HPMC capsules were maintained to arrive at these moisture content levels….
>
> **Biopharmaceutical characteristics**
>
> 230. This section of the Ogura article aims to demonstrate that dissolution and absorption from HPMC capsules is equivalent to that from gelatin capsules. This is important to support the claim of Ogura that HPMC capsules are an alternative to gelatin. Cephalexin (which is an orally administered antibiotic absorbed from the duodenum) is used as a model system. The article first reports the results of an in vitro dissolution tests using standard pharmacopeial techniques….It then reports on in vivo studies in human volunteers, showing plasma concentration profiles….No significant differences between the dissolution or absorption profiles of cephalexin encapsulated within HPMC and gelatin capsules were observed. Of course, this section of the Ogura article is focused entirely on capsules for oral use.
>
> **Application to formulations**

231. Ogura starts this section by saying 'Some drugs react with gelatin, which may prolong dissolution or result in discolouration of the capsule shell during storage. Other drugs become hydrolysed by the moisture contained in the gelatin capsule shell. HPMC is not only chemically inert, but has a lower moisture content (2–5%), permitting maintenance of a low humidity environment within the HPMC capsule shell'.

232. Ogura then addresses, in turn, potential prolonged dissolution problems, potential discolouration problems and potential problems with readily hydrolysable drugs. It explains that prolonged dissolution problems can result from aldehyde-containing drugs cross-linking the gelatin to form a thin insoluble membrane which can delay dissolution, and claims that this can be solved by the use of HPMC capsules….It says that aldehyde-containing drugs can also cause discolouration of gelatin capsules, and that this can be prevented by using HPMC capsules….

233. In relation to potential problems with readily hydrolysable drugs, Ogura reports some studies on aspirin, which appears to have been more readily hydrolysed at 60°C in gelatin capsules than in HPMC capsules. It also reports that hydrolysis could be reduced by adding excipients that absorb moisture. It then states..:

> 'Although HPMC capsules have a naturally low water content, the HPMC film does contain some adsorbed water that is readily released. For drugs that are extremely moisture sensitive, it may still be desirable to add water absorbent excipients to the formulation and dessicants to the container to enhance stability.'

HPMC capsules and inhalation products

234. The focus of the Ogura article is on the potential use of HPMC capsules for oral pharmaceutical products. All of the data are relevant to oral capsules, with Figures 3 and 4 and Table III only being relevant to oral capsules.

235. There is only one reference in Ogura to the potential use of HPMC in inhalation products. This reference is found under the heading 'Other applications'…(which also deals with potential use in the health food industry (again presumably for oral use) and the agricultural sector (application of chemicals to paddy fields)). The text reads as follows:

> 'Capsules have also been used as unit-dose containers to administer finely divided powders with specially designed inhalation devices. In the past, such delivery systems have encountered problems, including adherence of the powder to the gelatin capsule because of static electricity and capsule breakage because of the brittleness that results from storage under very low humidity. The HPMC capsule avoids these problems and would be appropriate for use in these situations'.

236….[T]he skilled person would not have, as part of his or her common general knowledge, any awareness of HPMC capsules for potential use in inhalation devices. In my view, this brief reference in Ogura would not be enough to persuade a formulation scientist to use HPMC capsules in a dry powder inhaler formulation of tiotropium. It is not clear from this passage in Ogura whether the authors have any real experience with capsules for inhalation use. They refer to a problem of adherence of the powder to the gelatin capsule because of static electricity. But, as I have said, this was not usually a significant problem in practice. They also refer to a problem of a capsule breakage because of brittleness resulting from storage under very low humidity. Whilst it is not clear whether this refers to capsule breakage during storage, transport or use, as I have said, formulation scientists knew about this issue and took steps to avoid storage under very low humidity conditions (including, if necessary, by storing the capsules in blister packs or by avoiding use of a capsule-based DPI).

237. Conversely, Ogura does not discuss the major issues which concerned a formulation scientist considering formulating a drug for delivery by a DPI, including issues of physical stability and drug delivery to the lung. There is nothing in Ogura to suggest that the authors were considering these issues.

238. Further, the bitterness and tolerance to deformation data in Ogura would not be sufficient for the skilled person to know whether HPMC capsules would perform efficiently and reproducibility in a DPI. These tests would not tell the skilled person how these capsules would perform in an inhalation device where single capsules are punctured with sharp pins or sheared with blades to permit powder emission.

239. Nor does Ogura contain any data showing drug deposition performance following loading of the HPMC capsule into a DPI, priming it through pin puncturing or shearing and inhaling the exposed powder again meaning that the skilled person would not know whether HPMC capsules would perform efficiently and reproducibly in a DPI. These data could include the aforementioned delivered dose, fine particle dose and fine particle fraction measurements following established laboratory cascade impaction and/or liquid impinge studies or clinical data. In essence these studies would be the equivalent, for the skilled person interested in lung delivery, to the capsule disintegration, drug dissolution and drug absorption studies presented in Ogura, for someone interested in oral delivery.

240. The passage in Ogura…which refers to the possible use of HPMC capsules in inhalation devices does not mention transfer or physical and chemical stability issues. However…Ogura mentions that: 'Although HPMC capsules have a naturally low water content, the HPMC film does contain some adsorbed water that is readily released'. That statement would cause concern to a formulation scientist considering the suggestion by Ogura that HPMC capsules could be used for inhalation purposes. If adsorbed water was readily released from the HPMC capsule shell, then such a moisture transfer could cause a problem of chemical degradation or affect the flow and delivery properties of the powder. Ogura does not even consider the impact that such a release of water could have on the flow and delivery properties in the powder, an issue which applies only in the case of DPIs and not to drugs delivered by the oral route, which is what Ogura is really concerned with.

241. The behaviour of gelatin capsules with respect to moisture transfer was well understood by formulation scientists and they were experienced in formulating DPIs in a way that took account of those properties. By contrast Ogura says very little about the comparable properties of HPMC. Ogura says that HPMC has a lower average water content. But all it says about the moisture transfer properties is that the adsorbed water is readily released. That, as I have said, would have been a significant concern to a formulation scientist who was interested in formulating a drug delivery by a DPI."

127. Having regard to the foregoing, the following points can be made as regards the alleged obviousness of the invention over Ogura.

128. First, the starting-point for the notional skilled person would have been what was tried and tested for relevant existing products, being gelatin capsules in all of the DPIs on the market, gelatin capsules and glucose as an excipient in the existing anti-cholinergics on the market, and the natural and correct assumption that tiotropium had already been formulated for a DPI for clinical trials in a gelatin capsule.

129. Second, HPMC capsules for inhalation were not part of the common general knowledge or the starting-point for such a formulation, let alone reduced-moisture HPMC capsules; there were no HPMC capsules on the market for DPIs; the chapter on DPIs in the relevant textbook (Aulton) makes no mention of HPMC capsules for DPIs; and Ogura teaches nothing to encourage the idea that the aerosolisation performance of inhaled medicines would be acceptable with a HPMC capsule, let alone a reduced-moisture HPMC capsule.

130. Third, the skilled person approaching a formulation for inhalation of tiotropium would be aware from pre-formulation enquiries that tiotropium bromide had been formulated in a DPI for phase II clinical trials and would assume that formulation had been in gelatin capsules (Maesen) and that tiotropium bromide had been formulated for nebuliser use (*i.e.* in an aqueous formulation) for phase II trials and in a DPI with (again presumed) gelatin capsule containers for the phase III trials (Barnes).

131. Fourth, pre-formulation tests showing that tiotropium bromide was not sensitive to water would have been carried out (as demonstrated by the control of tiotropium bromide in Experiment 2 exposed to conditions of accelerated humidity (75% relative humidity) and temperature (40°C) which showed no degradation whatsoever after two weeks).

132. Fifth, there would be no impetus to embark on a new, untried, untested capsule material.

133. Sixth, the notional skilled person would take it that she would obtain perfectly satisfactory results from the existing methodologies and materials.

134. Seventh, not only would there be no impetus/incentive towards HPMC capsules as the choice of container for a formulation of powdered tiotropium for inhalation, but in the unlikely event that the notional skilled person would consider HPMC capsules as an alternative, the impetus and incentive would be entirely in the opposite direction once pre-formulation tests of tiotropium in contact with gelatin on the one hand and in contact with HPMC on the other (along the lines of the tests conducted under accelerated conditions of temperature and humidity in Experiment 2) already showed degradation in HPMC at more than twice the rate of gelatin in those conditions after two weeks.

135. Eighth, the steps that the skilled person would have to take to arrive at the invention from Ogura are set out in detail at p.58 of Professor Birchall's first written statement and replicated below:

> "246….[I]f asked to develop a DPI capsule for tiotropium bromide in June 2001 the skilled person would have considered as a sensible starting point the existing DPIs for the same class of medicines namely oxitropium and ipratropium, that is the active ingredient with glucose, a gelatin capsule and no alteration of the gelatin capsule's moisture content level. As such, to arrive at the combination in Boehringer Ingelheim's patent claims the skilled person would have had to take these steps:
>
> > 1. To move away from glucose as the excipient (as I explain above I would have considered either glucose or lactose as potentially suitable excipients).
> >
> > 2. To exhaust his or her options as regards optimising the active ingredient and excipient mixture and the usual gelatin capsule material.
> >
> > 3. Perceive there to be an issue with the water level of the gelatin capsule material.
> >
> > 4. Revert to packing the formulation into a multi-dose reservoir, foil blister or revert to an MDI ingaler to overcome the perceived gelatin capsule water level issues.
> >
> > 5. If these solutions did not suffice, to consider changing the capsule material, despite not being aware of any other established capsule material and knowing that significant time and money would have to be spent in developing one…and altering the manufacturing process for a new capsule material.
> >
> > 6. Choose to go for HPMC on the back of the Ogura paper as the new capsule material.
> >
> > 7. Check the as yet unknown puncturing and powder release properties of the HPMC capsules and carry out the necessary development work to arrive at an HPMC capsule that could be manufactured and used for inhalation.
> >
> > 8. Exhaust his or her options as regards optimising the active ingredient and excipient mixture in the HPMC capsule material.
> >
> > 9. Perceive there to be an issue with the water content of the HPMC capsule material.
> >
> > 10. Decide to lower the water content of the HPMC capsule material below specified thresholds."

136. The court considers, on the basis of all of the evidence before it, that these steps could not have been taken in connection with tiotropium without inventiveness.

137. Taking the multi-factorial approach contemplated by Kitchin J., as he then was, in *Generics (UK) Ltd v. H. Lundbeck A/S* (considered previously above) and the majority of the case-law of the neighbouring jurisdiction on obviousness, the invention of tiotropium preparations for inhalation in reduced-moisture HPMC capsules would not be obvious.

138. Even leaving aside the multi-factorial approach and assuming (contrary to what the court has found) that the formulation of tiotropium in HPMC capsules would have been obvious over Ogura in 2001, there is nothing in Ogura or in the prior art more generally, howsoever taken, that could lead to the formulation of tiotropium in reduced-moisture HPMC capsules without invention.

139. Taking the 'obvious to try' approach, there would be no reason for the notional skilled person to try reducing the moisture content of HPMC capsules and using them in a tiotropium formulation.

(v) Summary as to Certain Points Arising.
140. The court has sought in the preceding pages to analyse comprehensively the various issues presenting in the context of the application of steps 3 and 4 of the *Windsurfing/Pozzoli* methodology. Without prejudice to that analysis, it may assist for the court to note that when it comes to this aspect of matters, it seems to it that Teva's case in this regard rests on six key contentions: (1) the first step in DPI formulations in 2001 was to prescribe moisture limits for the formulation (and this was part of the common general knowledge in the field); (2) this had problematic consequences for gelatin containers; (3) the notional skilled person would have been concerned about water-related issues with tiotropium; (4) HPMC capsules for inhalation use were part of the common general knowledge in 2001, particularly in connection with facilitating lower moisture content; (5) alternatively, if HPMC was not part of the common general knowledge, the use of HPMC capsules for a tiotropium formulation would have been obvious to the notional skilled person who was given the article to read; and (6) the moisture content limits identified in the patent claims make no technical contribution to the art and are arbitrary or it was not plausible from the 220 Patent that they would make the technical contribution claimed.

141. As should by now be clear, the court's assessment of these six points is that: (1) it was not part of the common general knowledge to start out on a DPI formulation by reducing moisture content; (2) gelatin capsules were not problematic for DPI formulations; (3) water-related issues in tiotropium would not have been a concern of the skilled formulator; (4) HPMC capsules for inhalation were not part of the common general knowledge; (5) (a) the use of HPMC capsules for inhalation purposes in connection with tiotropium preparations would not have been obvious to the notional skilled person who was given the Ogura article, (b) the use of reduced-moisture HPMC capsules for inhalation purposes in connection with tiotropium preparations is inventive; and (6) each of the moisture content limits in the 220 Patent claims does not just make a technical contribution to the art in itself; rather the inventive concept that they embody, viz. tiotropium preparations in reduced-moisture HPMC capsules, makes a technical contribution.

XII. Regulatory Matters
142. If a development is obvious (the development at issue in the within proceedings is not), it cannot be saved from a finding of obviousness on the basis that regulatory approval might not have been forthcoming. A point of contention between the parties, was whether a notional skilled person's understanding of regulatory constraints is a part of the notional skilled person's mind-set when it comes to the issue of obviousness. It was in this context that Boehringer proffered Mr Graham C. Higson, an expert in pharmaceutical regulatory applications, to show that the advice that a notional skilled person would get from a regulatory expert would have been that the more that was known about a product and its component parts the better, and that in terms of a smooth regulatory application process it is helpful to seek to avoid uncertainty.

143. The court respectfully does not accept, as was contended by Boehringer, that the multi-factorial approach to obviousness identified at first instance in *Generics (UK) Ltd v. H. Lundbeck A/S* has the result that the notional skilled person's understanding of how regulatory constraints may effect one option over another is a part of her mind-set. Jacob J., as he then was, is rightly clear as to this point in *Richardson-Vick's Patent* [1995] R.P.C. 568 when he states, at 579, that:

> "Even if it were true that…the regulatory pathway would have been seen as difficult, perhaps impossible…I cannot see that is has anything to do with obviousness. All the argument amounts to is that it would have been impossible or difficult to get permission lawfully to sell the mixtures of the alleged invention."

144. Closer in time, Lewison J., in *Ivax Pharamceuticals UK Ltd v. Akzo Nobel BV (No. 2)* [2006] EWHC 1089 observes as follows, at para. 43:

> "[*O*]bstacles to regulatory approval of pharmaceutical products are not relevant obstacles to an obviousness attack. It is also worth drawing attention to the clear distinction drawn by Aldous L.J. between obstacles to manufacture on the one hand, and obstacles to lawful sale on the other. Obstacles to lawful sale are not relevant to obviousness."

145. The judgment of Alduous L.J. was delivered in *Richardson-Vick's Inc.'s Patent* [1997] R.P.C. 888, when that matter went to the Court of Appeal. There, he states as follows at 896–7:

> "Richardson-Vicks sought to avoid the conclusion that the patent was obvious by relying upon the difficulties of obtaining regulatory approval. That was an obstacle in the path along the road to the conclusion that the patent was obvious which, they submitted, meant that, even though it was obvious to consider substitution of ibuprofen for aspirin, a skilled addressee would have realised that it was not worth trying. They were the first to perceive that it was obvious to try the substitution and therefore, relying upon cases such as Johns-Manville Corporation's Patent ([1967] R.P.C. 479), there was invention.
>
> That submission fails for four reasons. First the alleged obstacle in the path of the skilled addressee did not form part of his common general knowledge and therefore was not an obstacle in fact. Second, claim 1 of the patent purports to monopolise the manufacture of the combination of ibuprofen and a decongestant. The alleged obstacle was not an obstacle to manufacture. It was an obstacle to marketing the combination. Thus the alleged obstacle did not prevent the manufacture of the combination being obvious. Once it was conceded that it was obvious to consider the claimed combination and the way to manufacture the combination was well-known, the conclusion that the invention was obvious was inevitable. Third the alleged obstacle only prevents commercialisation being obvious. That is not relevant to the issue of obviousness. As stated by Slade L.J. in Hallen Co. v. Brabantia (UK) Ltd. ([1991] R.P.C. 195 at page 213):
>
> 'As cases such as Technograph and Beecham show, he (the skilled man) is not to be expected to take steps or try processes which he would not regard as worthwhile. In using the word 'worthwhile', we mean worthwhile as a possible means of achieving or assisting in practice the objective which he has in view. This, we infer, was what the judge had in mind in saying that the word 'obvious' in section 3 is directed to whether or not an advance is 'technically or practically obvious'. We do not think that the hypothetical technician must also be taken as applying his mind to the commercial consequences which might follow if the step or process in question were found in practice to achieve or assist the objective which he had in view. As Oliver L.J. said in the *Windsurfing case* [1985] R.P.C. 59 at 72, 'What has to be determined is whether what is now claimed as invention would have been obvious, not whether it would have appeared commercially worthwhile to exploit it.' We thus agree with the judge that the word 'obvious' in section 3 is not directed to whether an advance is 'commercially obvious."

Fourth, the cases such as Johns-Mansville have no application. They were all concerned with patents where it was alleged that there was a technical difficulty in perceiving the result. In this case there was no such technical difficulty."

146. As can be seen from the foregoing, there is a uniformity of approach among the English courts. Obstacles to regulatory approval

are not relevant to obviousness. Obstacles to lawful sale are not relevant to obviousness. Obstacles to manufacture can be relevant to obviousness. Among the impermissible is the deployment of supposed concerns regarding the obtaining of regulatory approval as a counter-balance to obviousness, which is what Boehringer has sought in the within proceedings to do.

147. In passing, the court notes that, notwithstanding vigorous cross-examination of Mr Higson on the point, it is clear and certain that, as of the priority date, gelatin was on the GRAS List and HPMC was not. The GRAS ('Generally Recognized as Safe') List is maintained by the FDA. Under ss. 201 and 409 of the US Federal Food, Drug, and Cosmetic Act 1938, as amended, any substance that is added to food or which is a food additive is subject to approval by the FDA unless the substance is designated as GRAS. A GRAS listing means that qualified experts are satisfied that a substance is safe under the conditions of its intended use. HPMC was added to this list in 2007. It was, however, listed in the Merck Index, described by Mr Higson in his written evidence as "*the definitive reference work for scientists and professionals looking for authoritative information on chemicals, drug and biologicals….the leading source of information on chemical compounds for generations of scientists and professionals since its publication in 1989*". But it was listed there as, *inter alia*, a stabiliser, suspending agent or thickener in foods, tablet excipient and ophthalmic lubricant which, per Mr Higson (and no expert in pharmaceutical regulatory applications was proffered as a witness by Teva), meant, and he persevered in this view, that it would be considered safe to use in food and for lubricating the eye, but not for use in the respiratory tract, which last use would require toxicology evidence.

XIII. Statistical Evidence

148. Mr Hans-Joachim Delzeit, a professional statistician and head of the Non-Clinical Statistics team at Boehringer, provided a statistical analysis of certain of the experiments that were the subjects of the notices of experiments. His analyses showed that the degradation comparison results between HPMC capsules with lower moisture content versus those with higher moisture content are very consistent, with degradation proving consistently higher, in all comparison scenarios, for capsules with higher moisture content.

149. The substance of the experiments and aspects of the evidence pertaining thereto are considered when and as relevant throughout this judgment. As to the arguments made by Teva in its closing submissions regarding what it styles as 'Statistical Considerations', these are contentions by counsel learned in the law which concern statistical matters and are not grounded by reference to any testimony before the court other than that of Mr Delzeit, which it is sought to flaw. Faced on the one hand with a professional statistician giving expert evidence as to matters statistical and on the other hand with counsel learned in the law making submissions, on bases uncertain, which seek to flaw that expert evidence, the court prefers the evidence of the professional statistician.

XIV. Plausibility

(i) Overview.

150. Plausibility finds no basis in the Act of 1992 as a ground upon which to challenge a patent. It is a concept which has been developed in the United Kingdom and at the European Patent Office in certain cases so as to prevent speculative patents, *i.e.* patents whereby a patentee claims an invention before it has any real basis for believing that it works, with the result that others in the field are prevented from carrying out work that they should properly be allowed to do. The court turns to consider some of the relevant case-law below. Before doing so, it would make a few preliminary comments as to plausibility:

> – first, plausibility is a 'threshold test' in respect of the requirements of patentability such as technical contribution and sufficiency. (That this is so is apparent, *inter alia*, from the judgments of Floyd L.J. in *Warner-Lambert Company LLC v. Generics (UK) Ltd (trading as Mylan) and ors*, as approved by Kitchin L.J. in *Idenix* (considered hereafter)).
>
> – second, "*the test of plausibility is a threshold test which is satisfied by a disclosure which is 'credible', as opposed to speculative." (Actavis Group v. Eli Lilly & Co* [2016] R.P.C. 12, para. 177).
>
> – third, in the main, the circumstances in which plausibility has justifiably been raised are cases involving early-stage science in high-technology fields such as the identification of genes and proteins and possible uses therefor, which is the factual background to *e.g., Johns Hopkins and Idenix*, both of which are touched upon in a little more detail later below. These are cases concerned with the potential for a large area of scientific research effectively to be cordoned off without proper basis by a single industry player at an early stage. As the learned authors of Terrell on Patents (18th ed., 2016) observe, at para. 13-55:
>
> > "The problem of speculative claiming may arise in various contexts but is particularly notable where claims to classes of chemical compounds are filed as Markush formulae.[1] In medicinal chemistry rival applicants may be tempted, at an early stage of research, to file broad claims to classes of novel chemicals in the anticipation that within those classes there may be compounds with particularly useful properties but without, at that point, having shown which compounds will be useful."
> >
> > [1] A 'Markush claim' seeks to create an expression for one class of individual compounds which have common characteristics or similar chemical and physical properties or which have some other equivalent basis for classification in the same group and can often be readily identified by the use of language such as '…a member selected from the group consisting of…'.
>
> The within proceedings are starkly different to the types of context referred to above. Here, Teva is seeking to invalidate, on the basis of plausibility, a patent whose notably discrete subject-matter comprises a new formulation approach to a medicine comprised of a single active substance (tiotropium) and its salts and forms for two identified conditions, being asthma and COPD. The circumstances in *Johns Hopkins* and *Idenix* and those which present here could not be more different.
>
> > – fourth, in approaching the issue of plausibility and seeking to identify general legal principles applicable, it seems to the court also to be sensible to bear in mind the following observation of Birss J. in the infringement/validity proceedings of *Merck Sharp & Dohme Ltd v. Ono Pharmaceutical Co. Ltd* [2016] R.P.C. 10, para. 137:
>
> "Whenever one is considering plausibility it must be done in the context of the invention determined by properly construing the claim and one must keep in mind the particular legal objection which is under consideration. Moreover it is worth reminding oneself that 'plausible' is not a term found in the relevant parts of either the EPC or the 1977 Patents Act

. It has proved to be a useful concept in various factual situations but just because that has proved to be true in one case does not mean that everything said in that context applies in a very different context. There is no law of plausibility as such."

(ii) Some Case-Law.

a. Plausibility and Obviousness.

151. In *Generics (UK) Ltd (t/a Mylan) v. Yeda Research & Development Co. Ltd* [2013] EWCA Civ. 925, Floyd L.J., under the heading "*Lack of technical contribution: legal issues*", describes the evolution of the notion of plausibility in the following terms, at paras. 37 and 39:

> "37 Neither the European Patent Convention ('EPC') nor the Patents Act 1977 includes amongst the available grounds of invalidity of a granted patent an objection that the patent does not make a technical contribution to the art. However the 'problem and solution' approach adopted by the EPO under the EPC to the ground of lack of inventive step necessarily involves isolating from the patent (in comparison with the prior art) some technical contribution or effect. The EPO adopt this approach in order to formulate a technical problem which is solved by the patent – achieving that technical effect – as a precursor to asking whether the patent solves that problem in an obvious or non-obvious way….

[Floyd L.J. briefly describes the PSA, then continues as set out hereafter.]

> 39 As with any consideration of obviousness, the technical results or effects must be shared by everything falling within the claim under attack. This follows from the fundamental principle of patent law, which underpins many of the grounds of objection to validity, that the extent of the monopoly conferred by a patent must be justified by the technical contribution to the art. If some of the products covered by a claim demonstrate a particular property, but others do not, then the technical problem cannot be formulated by reference to that property. Either the products which do not exhibit the property must be excised from the claim by amendment, or the problem must be formulated by reference to some other, perhaps more mundane, technical contribution common to the whole claim."

152. These principles emerge from the decision of a Board of Appeal of the *European Patent Office in AgrEvo*. Floyd L.J. considers that case, another decision of a Board of Appeal in *Johns Hopkins*, and certain decisions of the courts of the neighbouring jurisdiction, before summarising the position at law as follows, at para. 49:

> "(i) Article 56 of the EPC is in part based on the underlying principle that the scope of the patent monopoly must be justified by the patentee's contribution to the art;
>
> (ii) If the alleged contribution is a technical effect which is not common to substantially everything covered by a claim, it cannot be used to formulate the question for the purposes of judging obviousness;
>
> (iii) In such circumstances the claim must either be restricted to the subject matter which makes good the technical contribution, or a different technical solution common to the whole claim must be found;
>
> (iv) A selection from the prior art which is purely arbitrary and cannot be justified by some useful technical property is likely to be held to be obvious because it does not make a real technical advance;
>
> (v) A technical effect which is not rendered plausible by the patent specification may not be taken into account in assessing inventive step;
>
> (vi) Later evidence may be adduced to support a technical effect made plausible by the specification;
>
> (vii) Provided the technical effect is made plausible, no further proof of the existence of the effect is to be demanded of the specification before judging obviousness by reference to the technical effect propounded."

153. Clearly the specification is critical. It must provide enough information to show that a technical contribution has been made and that there is an inventive step. In *Sandvik Intellectual Property AB v. Kennametal UK Ltd* [2012] R.P.C 23, Arnold J. observes as follows, at para. 185:

> "[T]he principles to be applied in determining whether a claimed invention is obvious are the same regardless of the field of the invention, but…the application of those principles can vary according to the circumstances of the case, including the field of the invention. An arbitrary selection from the prior art is not inventive, regardless of the field. Nevertheless this is a problem which is more likely to arise with claims to classes of chemical compounds for the reasons explained by the Board of Appeal in Agrevo. Where it is suggested that a claimed invention is obvious as being an arbitrary selection, the key question is whether the specification 'passes the threshold test of disclosing enough to make the invention plausible' as Lord Hoffmann put it in Conor…that is to say, to make it plausible that the selection has the technical significance claimed for it."

154. In *Idenix Pharmaceuticals Inc. v. Gilead Sciences Inc.* [2016] EWCA Civ. 1089, Kitchin L.J. had occasion to consider what might be styled the plausibility threshold, stating at paras. 111–114:

> "111 What then is meant by plausible in this context? I believe that helpful guidance was given by the Supreme Court in Human Genome Sciences, Inc. v. Eli Lilly & Co. [2011] UKSC 51, in explaining the way in which the requirement of industrial applicability in Articles 52 and 57 of the EPC extends to a patent for biological material. Lord Neuberger, with whom the other members of the court agreed, summarised (at [107]) the principles to be derived from the decisions of the Boards of Appeal of the EPO and which should, he held, be taken as the law. As he there explained, the patent must disclose a practical application for the claimed product and that a plausible or reasonably credible claimed use or even an educated guess as to such a use could be sufficient for that purpose. On the other hand, a merely speculative use does not suffice.
>
> 112 Lord Hope, with whom Lord Walker, Lord Hope and Lord Clarke agreed, provided this further guidance at [149]:

> '149 In paras.6–8 of its judgment in ZymoGenetics [T 0898/05] the TBA contrasted a product whose structure was given but whose function was undetermined or obscure or only vaguely indicated with one which was "definitely described and plausibly shown to be usable'. In the former case, the granting of a patent might give the patentee unjustified control over others who were actively investigating in that area and who might eventually find ways to exploit it. In the latter, because it was plausibly shown to be 'usable', it might be considered to display concrete benefits. As these benefits are assumed not yet to have been confirmed by research, the exercise that these passages indicate is necessarily one of prediction. That is why the Board used the word 'plausibly'. I would not quarrel with Jacob L.J.'s comment, after consulting the Shorter Oxford English Dictionary, that the sense that word conveys is that there must be some real reason for supposing that the statement is true: para.111. The important point, however, is that the standard is not any higher than that. Further experiments are not needed if sufficient information is provided in the description, when common general knowledge is taken into account, to show that a positive answer can be given to the question whether a profitable use can readily be identified: ZymoGenetics, para.20.'

113 This question was also examined in the recent decision of the Court of Appeal in Warner-*Lambert Company LLC v Generics (UK) Ltd* (trading as Mylan) and ors [2016] EWCA Civ 1006 in the context of an appeal against a finding that Swiss claims (claims to the use of a product to make a medicine for a particular therapeutic purpose) were insufficient. Floyd LJ referred to the decisions of the Boards of Appeal of the EPO in T 0609/02 Salk Institute for Biological Studies, Johns Hopkins and AgrEvo/Triazoles , the decision of the House of Lords in Conor and the decision of the Supreme Court in Human Genome Sciences before summarising the position in this way at [46] to [47]:

> '46. The EPO and domestic cases do, however, indicate that the requirement of plausibility is a low, threshold test. It is designed to prohibit speculative claiming, which would otherwise allow the armchair inventor a monopoly over a field of endeavour to which he has made no contribution. It is not designed to prohibit patents for good faith predictions which have some, albeit manifestly incomplete, basis. Such claims may turn out to be insufficient nonetheless if the prediction turns out to be untrue. A patent which accurately predicts that an invention will work is, however, not lightly to be revoked on the ground that the prediction was based on the slimmest of evidence. Thus, the claims will easily be seen not to be speculative where the inventor provides a reasonably credible theory as to why the invention will or might work. The same is true where the data in the specification is such that the reader is encouraged to try the invention.
>
> 47. We heard argument as to whether the invention is only to be treated as plausible if the reader of the specification would be encouraged to try the invention with a reasonable prospect of success, thereby bringing the test for plausibility into line with that sometimes used in the context of obviousness. I do not accept that there is any reason to align the tests in this way. A test designed to prevent speculative claiming need go no further than requiring the patentee to show that the claim is not speculative: the specification does not need to provide the reader with any greater degree of confidence in the patentee's prediction than that.'

114 In my judgment the same approach should be adopted in considering obviousness and whether a technical effect is plausible in the light of the teaching in the specification and the common general knowledge. There must be a real reason for supposing that the claimed invention will indeed have the promised technical effect."

155. It is worth dwelling for a moment on the detail of what Floyd L.J. has to say in the above-quoted text. He states that the test for plausibility is merely that (para. 46) "*the reader is encouraged to try the invention*". There is no requirement that she (the reader) would be encouraged to try the invention with a reasonable prospect of success. All that the patentee need show is (para. 47) that "*the claim is not speculative: the specification does not need to provide the reader with any greater degree of confidence in the patentee's prediction than that*." Again, it is clear, as the court noted in its preliminary comments above, that the policy which underpins the law in this regard is (para. 46) "*to prohibit speculative claiming, which would otherwise allow the armchair inventor a monopoly over a field of endeavour to which he has made no contribution*." And again, the court would note that, for the reasons stated previously above, the within case is not a case that comes within the ambit of the last-quoted text.

156. One last point that arose in this context is whether post-published evidence can be relied upon to establish a claimed technical effect. Again, as mentioned above, the specification is clearly critical: it must provide enough information to show that a technical contribution has been made and that there is an inventive step. However, as is clear from the judgment of Floyd L.J. in *Generics (UK) Ltd v. Yeda*, para. 49, "*Later evidence may be adduced to support a technical effect made plausible by the specification*". Contrary to what is contended by counsel for Teva in their submissions, *Idenix* is not authority for the proposition that post-published evidence cannot be relied upon when it comes to establishing the claimed technical effect. Kitchin L.J. is quite explicit on this point in his judgment in *Idenix*, stating, at para. 109, "*The claimed technical effect must…be plausible in light of the teaching of the specification*." This is undoubtedly so. But Kitchin L.J. immediately and rightly then continues: "*The claimed technical effect cannot be established solely by post-published evidence*", so not "*solely*" but (without prejudice to his immediately preceding observation) there can be regard to same. Counsel for Teva's reliance on the judgment of Floyd L.J. in *Warner-Lambert* in this regard likewise fails. Floyd L.J. is equally explicit on the point, stating at para. 39, following a review of then-applicable case-law that later published data are not admissible "*if they alone render the invention plausible*".

b. Plausibility and Sufficiency.

157. It will be recalled that s.58 of the Act of 1992 provides that an application for revocation of a patent may be made on the grounds that, inter alia, "*(b) the specification of the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*". In *Novartis AG v. Johnson & Johnson Medical Ltd* [2011] E.C.C. 10, Jacob L.J., at para. 74, summarised the requirements as to a patent in terms of sufficiency in the following terms: "*Can the skilled person readily perform the invention over the whole area claimed without undue burden and without needing inventive skill?*", so from a reading of the specification and claims of the patent, and with the benefit of the notional skilled person's common general knowledge.

158. Teva has made no traditional case based on insufficiency, so, for example, by performing experiments in accordance with the 220 Parent to show that the invention cannot in fact be achieved by the notional skilled person by following the instructions of the 220 Patent. What it has done is launched a sufficiency broadside on the basis that it is not plausible that the impugned invention could be obtained across the range of salts and tiotropium. In this regard it has referred the court, in particular, to the decision of the Court of Appeal of England and Wales in *Regeneron Pharmaceuticals Inc. and another v. Genentech Inc.* [2013] R.P.C. 28, where Kitchin L.J. observes as follows, at paras. 100–1:

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

159. Additionally, the Court of Appeal of England and Wales made clear in *Idenix* that the threshold test for plausibility is the same for obviousness and insufficiency. Likewise the same precepts as regards post-published evidence considered under the heading 'Plausibility and Obviousness' above apply.

(iii) The Substance of Teva's Claims as to Plausibility.

160. There are effectively two limbs to Teva's claims as to plausibility. The first rests on certain observations made by Professor Buckton in his oral testimony that were themselves prompted by the following observations made by Professor Birchall in his first written statement, at paras. 133–134:

> "133. I have been asked to consider, in connection with considering the [220] Patent generally, whether the skilled person would, when he or she reads the [220] Patent, regard it as plausible that an HPMC capsule designed for use in a DPI for administering tiotropium (in admixture with lactose, where the HPMC capsule has a moisture content of =or <2%) would achieve the aims set out on page 2 of the [220] Patent.
>
> 134. In my view the skilled person would regard it as plausible that the claimed HPMC capsules could achieve sufficient stability of the active substance contained within them to enable the active substance to be released with a high metering accuracy, allow for efficient emptying of the capsule and have good perforation qualities of the capsule with good stability and low brittleness. While the wording of the [220] Patent expresses these aims in absolute terms and while it is never possible to empty a capsule completely so that words indicating that such an outcome was 'guaranteed' or 'ensured' 'without any problems' could be regarded as somewhat overstated, the skilled person has no reason when reading the [220] Patent to think that he or she would not see such benefits upon making (and then using) the capsules in accordance with the instructions set out therein."

161. During the course of direct examination, Professor Buckton had the just-quoted paragraphs put to him and was asked "*Do you agree with that answer…to the question phrased* [by Professor Birchall]?" responded as follows, at Day 4: 26, 1–13:

> "The first part is the overarching thing that I was struggling with my words on earlier, which is that reducing water content you would expect to have benefits in terms of less hydrolysis and better physical delivery. That's a reasonable overarching concept. That doesn't lead you to the second part which is the numbers which are in the Patent, is it plausible that for any one particular formulation that those numbers will have significance in relation to that chemical stability and physical stability? I don't think there's any reason to believe those numbers have any significance. There is nothing here to convince me those numbers have significance."

162. The court considers Teva's contentions as to plausibility in greater detail hereafter. However, it would but note in passing that (1) it would have found the just-quoted text, on which Teva has placed no little reliance, to be rather more persuasive had Professor Buckton not indicated in an answer but two minutes previously that there was real substance to the [220] Patent, stating, at Day 4: 24: 15–21, that "*I think there is no doubt that significant work will have been carried out on that work that was in clinical studies, that specific one….So some of this information on dose and the blend will have come from that information*", and (2) Professor Buckton appeared subsequently to contradict himself as to the significance of the absence of test results when the following exchange occurred between counsel for Boehringer and Professor Buckton, at Day 8: 116: 11-23:

> "Q….I suggest to you, professor, likewise the reader of a patent knowing its Boehringer Ingelheim, or any other multinational pharmaceutical company, can trust that the testing has been done and you can replicate it through working up the examples?
>
> A. I don't think you can say that the testing has been done if the testing isn't there. I think the testing will be there if it had been done. But I do accept, and I have done already, that if you already have a trial which is in late stage, and phase 3, you will have done a lot of testing on that particular product but that doesn't mean that you have tested any of the others that are put forward here."

163. It is perhaps just worth recalling at this juncture that it is clear from the above-considered case-law on plausibility that no particular information or test data is required of a patent, so long as the claim is plausible, i.e. credible, as opposed to speculative.

164. Teva's second complaint on plausibility grounds involves the assertion that it is not plausible that the patented invention would work (plausibility as to technical contribution) or could be obtained (plausibility as to sufficiency) across the range of salts and forms of tiotropium.

(iv) Some Aspects of the Plausibility Contentions.

a. The First Limb of the Teva Contentions.

165. The absence of test data was a repeated theme of Teva's questioning of witnesses. However, as touched upon in the consideration of some of Professor Buckton's oral testimony immediately above, it is clear from the case-law on plausibility that no particular information or test data is required of a patent, so long as the disclosure is plausible, *i.e.* credible, as opposed to speculative. As Carr J. observes in the revocation proceedings of *Actavis Group v. Eli Lilly & Co.* [2016] R.P.C. 12, para. 175: *"175 There is no requirement in the EPC that a patent should contain data or experimental proof to support its claims. The reference in* Salk *[*Case T609/02 *Salk Institute for Biological Studies/AP-I complex* (EPO Tech. BoA, 27th October 2004)*] to the provision of experimental tests to support the claimed therapeutic use was by way of example. In respect of claims to therapeutic applications which are of wide scope, such experimental tests may well be required. In the case of narrow claims, they may not be."*

166. It is also clear from Professor Birchall's evidence that the benefits to be obtained at the water-content thresholds of the 220 Patent are plausible. Under cross-examination, for example, the following exchange occurred at Day12: 38, 178–39, 12:

> *"Q….I know we have looked at the experiments, we have talked about what that may or may not show, but that boundary of less than or equal to 5%, there's nothing in the patent that would inform the skilled formulator to say well, I see all that is in here and it is plausible to me that if I go below 5% I will achieve the technical aims of the patent, whereas above 5% I would not?*
>
> *A. Clearly that's something you're going to have to test, is to see –*
>
> *Q. Sure.*
>
> *A. – which is the best moisture content with regard to stability.*
>
> *Q. Okay. But we don't see that testing in the –*
>
> *A. The data isn't there.*
>
> *Q. The data isn't there. And even your assumptions on Boehringer having made the thing, you're not assuming that they have done that test on that particular boundary, are you?*
>
> *A. Well, I would have thought they have done tests because they have come up with a boundary. And, as I explained before, you do your test first, you establish your boundary, you do your test and you demonstrate whether that boundary makes a difference or not."*

167. A few questions later, dealing with claim 8 where the water threshold is < 2%, and a suggestion from counsel for Teva that claim 8 really added nothing by way of additional information save that one of the examples had a moisture content in the range of < 2%, the following exchange occurred with Professor Birchall, at Day 12: 43, 18–44, 4:

> *"Q. The only additional information is of course that one of the examples has a moisture content in that range of under 2% –*
>
> *A. Right.*
>
> *A. – so one would think, to have got down to that as an example though might be one of the ones that is working particularly well. That is all you take from that.*
>
> *Q. But that would only work in that – you're supporting that with the example, your inference from the example, that would only work in respect of tiotropium bromide monohydrate, which is the subject of the example –*
>
> *A. Yes.*
>
> *Q. – not any of the multitudinous of other tiotropium things we have looked at?*
>
> *A. Yes, I think in that particular sample it must be quite good, otherwise why would it be an example?"*

168. Professor Buckton, at Day 8: 115, 7–116, 6, also accepted that the skilled person could readily do measurements to check the technical benefits from the patent in the following exchange with counsel for Boehringer:

> *"Q [Counsel for Teva].. brought you through a number of patents asking you to comment is it usual to have this sort of experimental data and clinical results and so on in a patent, and you remember I brought you to other formulation patents, I think particularly one by your own client, or a related company of your own client, where there was no such data? Do you remember that?*
>
> *A. There was no clinical data.*
>
> *Q. Yes. About the technical benefit of that invention. And I just want to make sure, professor, that we're not at cross purposes here, you understand that the patent doesn't have to contain that type of data?*
>
> *A. I understand patents don't have to contain data. They have to give you a clear indication of the benefits you would achieve at those particular levels, I would have said, and I don't see that as being clear in the patent at all.*
>
> *Q. No, because you can find out, you can work up the examples, you can go to the pharmacopoeia that I directed you to, you can test for deliver dose and fine particle dose, you can calculate the fine particle fraction and you can assess for yourself the extent of the benefit that you are going to get as a result of the teaching of the patent, from your common general knowledge?*
>
> *A. Well, you can do measurements for sure. So you certainly can do measurements. There's no doubt about that."*

b. The Second Limb of the Teva Contentions.

169. As mentioned above, the second limb of Teva's plausibility contentions involves the assertion that it is not plausible that the patented invention would work (plausibility as to technical contribution) or could be obtained (plausibility as to sufficiency) across the range of salts and forms of tiotropium. In this regard Professor Buckton observed, *inter alia*, as follows, at Day 4: 26, 23–28, 8:

> *"Q….If you go to page 10 of the Patent.*
>
> *A. The bottom of page 10?*
>
> *Q. Yes.*

A. It says:

> 'The material of tiotropium can be used in its salts which could be chloride, bromide, iodide, methanesulfonate, para-toluenesulfonate and methylsulfate.'

So those are a range of salts from page 13, reading down. We talked yesterday about the fact that salts will have different physico-chemical properties. They will have different chemical stabilities, different physical properties. They will have different crystal morphologies, the shape and properties of the crystal externally will be different. All of those things from those salts will give rise to differences in performance which means that the numbers in the Patent, even if plausible for one thing, which I don't think they are, are completely implausible for a whole range of salts. Then we move on down that paragraph to say that it relates to tiotropium bromide and it also relates to hydrates. Amorphous in crystalline forms and those which have solvent in their crystal structure so that's sulphates, hydrates, amorphous and crystalline forms of the tiotropium bromide. They all have very different physicochemical properties. The specific numbers can't make any sense in relation to all of that wide remit of potential physicochemical properties.

Q. How does that impact on plausibility?

A. As I said, it's implausible that just the one preferred example will get those numbers because there's nothing to suggest those numbers are relevant for that one preferred example, tiotropium bromide monohydrate and completely implausible that the whole remit, they're included in the claims as well as, this isn't just in the specification, this is included in the claims, they can't possibly hit all of the -- they can't hit the same number for each of those particular forms because they're very different physical and chemical forms."

170. It does not appear to the court that the foregoing involves an assertion that it is implausible that an effective formulation of tiotropium can be made that achieves the aims of the invention across the salts and forms of tiotropium within the water-content thresholds of the 220 Patent. Rather, it seems to the court to involve the assertion that it is implausible that the technical effect achieved for each salt or form will "*hit the same number*" across the salts and forms. This is an assertion that goes beyond what patent law requires: as indicated in the above consideration of case-law what is required at law is that the invention as claimed works, *i.e.* that the claims lead to the benefits described, not that different salts and forms "*hit the same number*" across the various salts and forms.

171. The following exchange between counsel for Teva and Professor Birchall, at Day 12: 30, 10-31, 29, appears to the court to capture accurately the thrust of Professor Birchall's testimony on the issue of physical and chemical stability across salts and forms:

> *"Q… Chemical degradation for this guarantee of sufficient stability of the active in terms of chemical degradation, the skilled addressee certainly couldn't assume that all those different forms of salts would equally guarantee sufficient stability of the active?*
>
> *A. Well, you use the word would, and you wouldn't guarantee. So one of the things about salt form, which hasn't been discussed, salt form isn't just about chemical stability and pre-formulation, salt form is about what happens when it gets into the body of course.*
>
> *Q. Yes.*
>
> *A. Where it disassociates, whether it gets through cell membranes, whether it has an effect on the body.*
>
> *Q. Right, okay.*
>
> *A. So, when we think about salt form, if the patent had said that it would have the same therapeutic effect at the target site then that adds an additional layer of complexity, yeah.*
>
> *Q. Sure. So we're certain, you're saying that you would certainly not assume, couldn't safely assume, the skilled addressee at the priority date, that the different salts would have the same therapeutic effect?*
>
> *A. Yes.*
>
> *Q. Okay. But also, I think you're not disagreeing with me when I say that you couldn't, the skilled addressee could not assume across all these different salts that they would have, they would each guarantee sufficient stability of the active to meet the aims of the formulator?*
>
> *A. What I have said is that there is a formulation which is delivering tiotropium bromide monohydrate. If testing has been done on that –*
>
> *Q. Yeah?*
>
> *A. – and demonstrates that to be having sufficient stability –*
>
> *Q. Yeah?*
>
> *A. – then that could apply across the salt forms from a physical stability perspective.*
>
> *Q. Yes?*
>
> *A. You would have more concerns about stability, that is what I am agreeing with.*
>
> *Q. So, for chemical stability you would have concerns, yeah?*
>
> *A. You would always have concerns.*
>
> *Q. You would not assume that it would work?*

A. Unless you tested it you would always have concerns.

Q. Unless you tested it would be speculation?

A. Well, you would have concerns."

172. As mentioned above, what is required at law is that the invention as claimed works, *i.e.* that the claims lead to the benefits described, not that different salts and forms, to borrow from Professor Buckton's phraseology "*hit the same number*" across the various salts and forms. To the extent that counsel for Teva can be read in the above line of questions to be suggesting that something further is required under patent law, that suggestion is not accepted by the court to be correct. As for the closing round of questions, the fact that "*you would have concerns*" does not suffice to make a claim speculative, and Professor Birchall's evidence, it seems to the court, seeks to make precisely that distinction. All a patentee need show is that a claim is not speculative; a specification does not need to provide the reader with any greater degree of confidence in the patentee's prediction than that, and it seems to the court to be a reasonable and proper reading of Professor Birchall's evidence that Boehringer has crossed that threshold in its 220 Patent. It is also useful again to recall that the policy which underpins the law as to plausibility is to prohibit speculative claiming, what counsel for Boehringer have colourfully described in their written submissions as "*a kind of speculative land grab*" (or property-rights grab), that would yield an a monopoly over a field of endeavour to which a putative inventor has made no contribution: for the reasons stated previously above, the Boehringer patent is simply not, to use a colloquialism 'in that space'.

(v) Some Conclusions.

173. What conclusions can be reached by the court as to plausibility in addition to any conclusions elsewhere identified?

174. First, for what it is worth, Teva's assertion that the technical contribution of the invention would not have been plausible to the notional skilled person in 2001 cannot be reconciled with the alternative proposition advanced by Teva that the notional skilled person would, because of the expected technical benefits, have been trying to make the formulation within the ambit of the claims. But, of course, parties may argue alternative propositions; that is a legitimate, logical and long-recognised approach to the manner in which cases at court are argued.

175. Second, Teva's argument as to plausibility is inconsistent with the experimental evidence. As discussed previously above, Teva has mistakenly suggested that evidence generated subsequent to the priority date cannot be adduced to support plausibility. In fact, the correct position at law is that later evidence may be adduced to support a technical effect made plausible by the specification, and the court accepts that the invention in issue was rendered plausible by the 220 Patent.

176. Third, as outlined in the court's description of the substance of the 220 Patent above, the 220 Patent identifies the benefits to be obtained from the invention, and then gives the reader of the patent information necessary to make the products claimed. As Professor Birchall indicates in his first written statement, following on his observations as to plausibility, at paras. 134-5 of same (considered previously above), in evidence accepted by the court as correct:

> "135….[A]s I indicated above, there is enough information in the [220] Patent to suggest to the skilled person that the claimed capsules work for the purposes of administering a tiotropium/lactose formulation by DPI, and have been made, tested and administered by DPI by a company with expertise in formulating DPIs.
>
> 136. The Patent therefore provides the skilled person with everything he or she needs to make the claimed capsules for use in a DPI. There is nothing in the [220] Patent that would put the skilled person off doing so."

177. Fourth, it seems to the court that an objection as to plausibility is misplaced in a challenge to a patent such as the 220 Patent. In the main, the circumstances in which plausibility has justifiably been raised are cases involving early-stage science in high-technology fields such as the identification of genes and proteins and possible uses therefore. The within proceedings are starkly different. Here Teva is seeking to invalidate, on the basis of plausibility, a patent the notably discrete subject-matter of which comprises a new formulation approach to a medicine comprised of a single active substance (tiotropium) and its salts and forms for two identified conditions, being asthma and COPD.

178. Fifth, the test of plausibility is a threshold test which is satisfied by a disclosure which is credible, as opposed to speculative. It appears to the court that there is ample in the 220 Patent by way of worked-out instructions as to the making of embodiments of the invention to demonstrate to the notional skilled person that it is not speculative.

179. Sixth, in truth what Teva has sought in the within proceedings to achieve under the heading plausibility is to establish a ground of challenge, unrecognised at law, whereby Boehringer is not entitled to its patent if it does not provide the proof of the effectiveness of the invention of the patent itself. This is a basis of challenge that was rejected by Lord Hoffmann in *Conor*. There Conor Medsystems did not plead lack of plausibility but sought instead to establish that the technical effect had not been demonstrated sufficiently in the specification of the patent. When it came to this approach, Lord Hoffmann made the following observation, at para. 37 of his speech, which observation, it seems to the court applies equally to the case as to plausibility that Teva now seeks to make, *viz.* "[T]*here is in my opinion no reason as a matter of principle why, if a specification passes the threshold test of disclosing enough to make the invention plausible, the question of obviousness should be subject to a different test according to the amount of evidence which the patentee presents to justify a conclusion that his patent will work.*"

180. Seventh, were Teva to succeed in its efforts to have the 220 Patent invalidated by reference to plausibility and on the basis that examples for every salt and form of tiotropium are not set out in the 220 Patent, such a finding, it seems to the court, would have the effect of preventing patentees from claiming the plausible scope of their inventions and would favour 'free-loaders' wishing to profit off the work of others and seeking to do so by evading the scope of a patent through minor modification to a salt or the form of the active substance.

181. Eighth, and this is more observation than conclusion, it is a feature of the within proceedings that Teva, although admittedly it was under no obligation to do so, has not sought to prove its case in the within proceedings by experimenting with a few salts and forms and then coming to court with the results of such experiments so as to demonstrate the substance of its attack on the validity of the 220 Patent. Boehringer has suggested that Teva has not done so because Teva is aware that any such tests would show the benefits of the impugned development for the other salts and forms of the active. Why Teva did not so proceed is a matter best known to Teva and the court reaches no conclusion, it cannot safely reach any conclusion, in this regard. But one overriding conclusion is clear: the second to the sixth points mentioned above (inclusive) and the various other considerations and conclusions of the court in the context of plausibility offer abundant reason as to why Teva's line of attack by reference to plausibility must and does fail.

XV. Barnes, Maesen, and Casaburi

(i) Overview.
182. As mentioned above, Teva asserts that the claims are invalid on the basis that the invention protected by them is obvious in light of three prior publications, Barnes, Maesen and Ogura, the full citations of which were given previously above, all of which were cited as prior art, and the last of which has been considered previously above, received the bulk of the attention at hearing, and is not considered further here. There was also some mention of Casaburi, though this was not cited as prior art. Having regard to the evidence before the court concerning Barnes, Maesen and Casaburi, the court would make the below observations.

(ii) Barnes and Maesen.
(Barnes, P., "Tiotropium bromide" (2001) 10(4) Exp. Opin. Invest. Drugs *733; Maesen, F.P.V., "Tiotropium bromide, a new long-acting anti-muscarinic bronchodilator: pharmacodynamic study in patients with chronic obstructive pulmonary disease (COPD) (1995) 8 Eur. Respir. J. 1506)*

183. First, the Barnes article is in a journal which is not routinely read by formulation scientists and, further, is not directed to the formulation of tiotropium bromide. In this regard, the court notes the evidence of Professor Birchall, whose evidence is generally preferred by the court for the reasons stated above, not least because of the 'at the coalface' nature of his experience, states as follows at para. 257 of his first written statement:

> "Until my instructions in the parallel UK proceedings, I do not recall having seen this article and, like Maesen, I doubt that it would have come to the attention of many formulation scientists and is not directed to the formulation of tiotropium bromide."

184. Second, even assuming that the notional skilled person would have come across Maesen before the priority date and read it with interest, the following observations are made by the court, having regard especially to the evidence of Professor Birchall in his first written statement:

> (1) Barnes does not itself provide any information about the formulation of tiotropium bromide used in any of the clinical trials (other than that it is given using a DPI).
>
> (2) The notional skilled person would know that the tiotropium bromide must have been formulated in such a manner as to provide suitable chemical and physical stability for delivery characteristics for use in clinical trials. To find out how it had been formulated she could check the references in Barnes to the clinical trials. She would then find out that for the phase II trials, tiotropium bromide had been formulated with lactose in a capsule delivered from the Inhalator Ingelheim (though she would note that one of the trials had involved the use of a nebuliser). For the phase III trials, the skilled person would see that tiotropium bromide had again been formulated with lactose in a capsule, this time delivered from a different kind of dry powder inhaler called the HandiHaler). She (the notional skilled person) would assume that the capsule used in each case was a gelatin capsule, as that was the then standard material used for DPI capsules. She would not see the mention in Barnes of the potential for inadvertent delivery into the eye as a major challenge to overcome.
>
> (3) It seems to the court that the obvious thing for a formulation scientist to do, having read Barnes would be to formulate tiotropium with lactose in a gelatin capsule., *i.e.* it was not obvious, whether based on Maesen or indeed on common general knowledge (the level of common general knowledge of the notional skilled person having been considered previously above), for the skilled person (i) to try any capsule material other than gelatin, never mind a HPMC capsule or (ii) to think of reducing the moisture content in the capsule material (the skilled person would have approached water issues in the 'normal' way, considered previously above).

185. Third, the Maesen article is in a journal which is not routinely read by formulation scientists and, further, is not directed to the formulation of tiotropium bromide. In this regard, the court notes the evidence of Professor Birchall, whose evidence is generally preferred by the court for the reasons stated above, states as follows, at para. 249 of his first written statement:

> "I do not recall having seen this article before I was instructed in the parallel UK proceedings and doubt that it would have come to the attention of many formulation scientists. As a formulation scientist, if you are looking at product development literature what you are interested in is improvements to formulations. You are rarely interested in the characteristics of a drug itself, but instead whether there is anything interesting in the way in which it is formulated and/or delivered (e.g. whether a novel device is being used to deliver the product."

186. Fourth, even assuming that the notional skilled person would have come across Maesen before the priority date and read it with interest, the following observations are made by the court, having regard especially to the evidence of Professor Birchall in his first written statement:

> (1) there are only two statements in the paper which refer to the formulation that was tested. The first reference is in the abstract, at 1506, and states that "In a randomized, double-blind, placebo-controlled, crossover design, patients inhaled single doses of 10-80ìg tiotropium bromide and placebo, formulated in lactose powder capsules". The second reference is in the "*Procedure*" section, at 1508, and states "*On the five study days, tiotropium bromide 10, 20, 40, 80 ìg or placebo, as a lactose powder, were inhaled using the Inhalator Ingelheim (FO2)*."
>
> (2) (i) The notional skilled person would know that the Inhalator Ingelheim was a DPI which employed capsules. (ii) Although the capsule material is not specified, the skilled person would assume it was gelatin as that was the then standard material used for DPI capsules. (iii) The skilled person reading these passages would understand that the tiotropium bromide had been formulated as a dry powder with a lactose carrier;
>
> (3) when reading Maesen, the notional skilled person (i) would have a basic understanding of (a) the timeline for development of a product and (b) the clinical trials to which a product would be submitted in order to obtain regulatory approval, (ii) would know that phase II trials, such as those referred to in Maesen, are relatively early results in the development of a product and are targeted primarily at tolerability and dose response, (iii) would expect a practical level of stability and performance from the product at this stage in the development of same;
>
> (4) it seems to the court that the obvious thing for a formulation scientist to do, having read Maesen, would be to formulate tiotropium with lactose in a gelatin capsule., *i.e.* it was not obvious, whether based on Maesen or indeed on common general knowledge (the level of common general knowledge of the notional skilled person having been considered

previously above), for the skilled person (i) to try any capsule material other than gelatin, never mind a HPMC capsule or (ii) to think of reducing the moisture content in the capsule material (the skilled person would have approached water issues in the 'normal' way, considered previously above).

187. Fifth, there is in general nothing in Barnes and Maesen, cited as prior art, that could have led to the development of a formulation of tiotropium powder in HPMC capsules of reduced and specific moisture content since they (Barnes and Maesen) contain very little formulation information and were not directed at formulation scientists.

188. Sixth, in relation to Barnes, the information that tiotropium bromide had been through phase I, II and III clinical trials and that it had been formulated with lactose in a capsule and administered in the Inhalator Ingelheim® and HandiHaler® devices would merely confirm the idea that the capsule container was a gelatin container (an idea that would be further buttressed by regard to Maesen), which at the time was the only capsule material in use for inhaled products, and that the formulation had achieved the stability and performance necessary for the clinical trials in question.

189. Seventh, in relation to Maesen, insofar as it reported a phase II clinical trial of tiotropium bromide which was described as a potentially longer-acting alternative to ipratropium bromide (which was already on the market formulated in admixture with glucose in a gelatin capsule) and insofar as it referred to the administration via the Inhalator Ingelheim® of tiotropium bromide formulated in lactose powder capsules, it appears to the court that the notional skilled person when shown Maesen would assume that the medication had been formulated in gelatin capsules and that they delivered at least the basic stability and performance required for phase II clinical trials.

(iii) Casaburi.
(Casaburi, R., "The Spirometric Efficacy of Once-Daily Dosing with Tiotropium in Stable COPD" (2000) 118(5) *CHEST* 1294)

190. Casaburi has not been cited as prior art. It describes a three-month, randomised, double-blind, placebo-controlled, multicentre clinical trial of 470 patients with COPD. The patients either received tiotropium or placebo treatment and the measurable efficacy outcomes were COPD symptom severity scores, lung function tests and requirements for additional 'as needed' albuterol therapy to relieve their symptoms. Analyses of these outcomes demonstrated that tiotropium was significantly more effective than placebo at reducing pulmonary symptoms of COPD. As far as specific information of interest to a skilled formulator is concerned, the Casaburi paper only refers to the tiotropium formulation as being a lactose-based, dry-powder inhaler device delivered by identically appearing lactose-based inhalers whereby a single capsule in the device was used by the study participants. Professor Birchall notes in his first written statement that, at the time of the Casaburi paper, it would have been assumed that the capsules used in the clinical study were gelatin capsules, being the only capsules that had previously been used in DPI products, and there being nothing in the paper to suggest the use of any new, previously untested excipients. One final observation might be made in this regard: the information that successful clinical trials of a tiotropium preparation formulated with lactose had been carried out via the HandiHaler® device, with no mention of the capsule material, would seem to reinforce the point that at that time it was taken for granted that the capsule material was not considered part of the formulation.

XVI. Expert Witnesses
191. Before proceeding to its conclusion the court would like to acknowledge the kind assistance of the various expert witnesses who prepared expert witness reports and gave evidence at the trial of the within application. It is the nature of court proceedings that a court will, inevitably and properly, favour the evidence of some witness over another, as this Court has. However, all of the expert witnesses who participated in the within proceedings were and remain notably accomplished individuals in their chosen fields of expertise.

XVII. Conclusion
192. By petition of 23rd October, 2014, Teva seeks an order revoking Irish Patent Number EP (IE) 1379220 with a filing date of 27th May, 2002, as granted to Boehringer. Teva asserts that the claims in issue are invalid on the basis that (1) the invention protected by them is obvious in light of three prior publications, being the Barnes, Maesen and Ogura publications (the obviousness challenge), (2) insofar as the invention covered by the relevant claims is not obvious in light of those publications, it is obvious for lack of technical contribution to the art (the *AgrEvo* challenge), and (3) the specification of the 220 Patent does not disclose the invention clearly and completely enough for it to be performed by a person skilled in the art (the insufficiency challenge). As should be clear from the foregoing text, and the Appendix that follows, none of these grounds of challenge is accepted by the court. It follows as a consequence that the court must respectfully decline to grant the order now sought by Teva.

Appendix

The Clinical Evidence

(i) Introduction.
193. Mindful that the within judgment might yet proceed to appeal, it seems appropriate that, not least for the benefit of any (if any) court that might yet hear such appeal, and without any prejudice to the court's finding that the addressee of the 220 Patent is a formulation scientist, a finding which the court is entirely satisfied for the reasons stated previously above is correct, it should nonetheless treat with the clinical evidence as to whether in 2001 tiotropium would have been comprised in the general knowledge of a clinician involved in the development of an inhaled medicine for asthma and COPD. In this regard the court would make the points set out hereafter. For the avoidance of doubt, this Appendix forms a part of the court's judgment.

(ii) Who is the addressee of the 220 Patent?
194. The issue as to who is the addressee of the 220 Patent has been considered previously above by the court. However, it also arose in the context of the expert evidence of Professors Costello and Geddes and in the broader 'clinical' context and thus the issue is treated with here also.

195. First, it became clear in the following exchange through the cross-examination of Professor Geddes, at Day 2: 95, 5–14, having being brought in laborious detail though the description and claims in the patent, that he did not believe the teaching of the 220 Patent to be addressed to a clinician:

> *"Q….[T]hat is essentially the end of the substantive teaching of the Patent?*
>
> *A. Right.*
>
> *Q. So I think you have agreed, Professor, that everything from the description of the invention to the claims, is about*

formulation essentially.

A. Everything you have taken me through, yes."

196. If there is an implicit suggestion in the last-quoted answer that counsel for Boehringer had somehow been selective in the elements of the 220 Patent of which consideration was made, this is not borne out by the transcript of the hearings. The description and claims were considered in detail and Professor Geddes' answer in effect was that everything in the 220 Patent from the description to the claims is essentially about formulation.

197. Second, on a related note, Professor Geddes also confirmed the implications of the evidence just considered, in an exchange with counsel for Boehringer, which commenced with counsel putting to Professor Geddes his observations as to the concept of the notional skilled person, at para. 4.1 of his written statement, *viz*:

> "The concept of the 'skilled person' in the UK has been explained to me by [*a firm of solicitors in the United Kingdom*]….I understand that the Court has to consider the position of a person or team which is skilled in the relevant art and has a practical interest in putting into effect the technical subject matter of the Patent but who has no capacity for invention. [*A firm of solicitors in Ireland has*]… explained to me that this concept is broadly given the same meaning in Ireland".

198. The legal error comprised within the above-quoted text is considered later below. Suffice it, at this point, to note that after Professor Geddes was brought to the just-quoted text, the following exchange then ensued between counsel and Professor Geddes, at Day 2: 97, 6–27:

> *"Q. Now, from what you have just said, the substantive teaching of the [220] Patent is to do with formulation?*
>
> *A. Right.*
>
> *Q. It's the province of a formulation scientist?*
>
> *A. Right.*
>
> *Q. And at least claims 1 to 11 are the province of a formulation scientist?*
>
> *A. Yes.*
>
> *Q. So, I am taking it, really, that when talking about this [220] Patent, the respiratory clinician isn't really the skilled person when looking at what this [220] Patent actually deals with, which is formulation?*
>
> *A. Apart from the last two paragraphs where - the only part of my expertise or my understanding of the skilled person would be in the use rather than the formulation.*
>
> *Q. Very well. And, Professor, so, when you discussed, then, the attributes of the skilled respiratory clinician, you are discussing those attributes in the context of, say, a wider project, of the wide project of bringing forward a medical product rather than the narrow formulation aspects?*
>
> *A. Yes."*

199. Third, Professor Costello was likewise clear that the 220 Patent is not addressed to a clinician, observing, at para. 10 of his witness statement: "*It appears to me that the main substance of the* [220] *Patent is addressed to the formulation of capsules containing tiotropium for inhalation*."

200. Fourth, Teva makes the point in its closing written submissions that during the cross-examination of Professor Geddes, "*despite Counsel for the Respondent's attempts to exclude the relevance of Claims 12 and 13 of the* [220] *Patent*", Professor Geddes confirmed that the claims contained the word "*use*" and are therefore directly relevant to the expertise of the notional skilled person. However, the court understands the point that is sought to made by Boehringer in this regard is the (correct) legal argument that claims 12 and 13 claim the use of the formulation that results from the teaching of the 220 Patent and thus are not relevant to the issue of assessing what is the teaching of the 220 Patent for the purposes of identifying its addressee.

201. Fifth, while Professors Buckton and Geddes, both witnesses called by Teva, each indicated in their respective witness statements that the notional skilled person would be a team that included both a formulation scientist and a clinician, it can be seen from the foregoing that Professor Geddes accepted under cross-examination that the substantive teaching of the 220 Patent is directed towards a formulation scientist and not a clinician (and that his views about the skilled team including a clinician referred to the broader project of developing a pharmaceutical product for inhalation. Professor Buckton adhered to the position that the notional skilled team for the 220 Patent would have included a clinician. However, it is, with respect, clear from his answers that that interest of clinicians to which he referred is an interest not in the teachings of the 220 Patent *per se*, but rather in working on the development of the formulation resulting from the 220 Patent. The fact that Professor Buckton was thinking about this wider project and not the addressee of the 220 Patent is evident, *inter alia*, from the following exchange between Professor Buckton and counsel for Boehringer, at Day 3: 18, 2–17:

> *"Q….[W]ho do you think or what do you think constitutes the skilled team for the purpose of this Patent?*
>
> *A…. I think the key part is that the skilled team or person has a practical interest in putting…into effect the technical subject of the Patent. So the team really involved in putting into effect the technical subject of the Patent would be a team that would be formulating and subsequently testing, clinically, the - an inhalation product for tiotropium, and that team would certainly include a formulator, would certainly include a clinician and would include others, and the number of the other people it would include would depend on which company you were in, but it would certainly have advice, if not team members, who had regulatory input and commercial input as well."*

202. The court notes in passing that the clinical effects of the formulation form no part of the teaching of the 220 Patent; accordingly, the notional skilled team, were it the addressee of the 220 Patent and it is not, would not include someone involved in the testing of those effects.

(iii) Common general knowledge of clinician involved in development of an inhaled medicine for asthma and COPD.
203. Sixth, Professor Geddes expressed the view that tiotropium would have been common general knowledge at the priority date. As will be seen later below, Professor Costello disagrees. There are a number of issues with the evidence of Professor Geddes that leads the court to prefer the evidence of Professor Costello in this regard:

– first, it will be recalled that at para. 4.1 of his written statement Professor Geddes indicated as follows:

> "The concept of the 'skilled person' in the UK has been explained to me by [*a firm of solicitors in the United Kingdom*]….I understand that the Court has to consider the position of a person or team which is skilled in the relevant art and has a practical interest in putting into effect the technical subject matter of the Patent but who has no capacity for invention. [*A firm of solicitors in Ireland has*]… explained to me that this concept is broadly given the same meaning in Ireland".

This quote is, with respect, reflective of a tendency on the part of Professor Geddes to treat common general knowledge as everything that could reasonably have been found out by the skilled person. However, as a matter of law, common general knowledge extends only to things the skilled person would find if she knew of their existence and went to find them as a matter of course. As Laddie J. observes in *Raychem Corp.'s Patents* [1998] R.P.C. 31, 40:

> "The common general knowledge is the technical background of the notional man in the art against which the prior art must be considered. This is not limited to material he has memorised and has at the front of his mind. In includes all that material in the field he is working in which he knows exists, which he would refer to as a matter of course if he cannot remember it and which he understands is generally regarded as sufficiently reliable to use as a foundation for further work or to help understand the pleaded prior art. This does not mean that everything on the shelf which is capable of being referred to without difficulty is common general knowledge nor does it mean that every word in a common text book is either."

– second, there is a regrettable aspect to the manner in which Professor Geddes was directed to the Casaburi paper that is reflective in part of the 'brown tempera' point made by the court previously above in respect of the evidence of Professor Buckton. Thus after Professor Geddes was asked by Teva's solicitors in the United Kingdom to find out what was known about COPD in 2001 and what the treatments and developments then were, he undertook a comprehensive exercise and a degree of to-ing and fro-ing with the English firm of solicitors acting for Teva, a process that was well described by him both in his written statement, at para 3.1 and also when giving his evidence under examination on Day 2, both of which are quoted hereafter.

Para 3.1 of Professor Geddes' written statement reads as follows:

> "3.1 In preparing my report in the UK proceedings, I was asked by…[t*he English firm of solicitors*] to do the following tasks:
>
> 3.1.1 I was asked by [*the English firm of solicitors*]…to consider what was known about COPD as at June 2001, how it was treated and what the developments in treatment at that time were. I also discussed with PM what was known about the treatment of asthma as of that date. I was told to put out of my mind any information or knowledge which I acquired after June 2001. In order to do this I identified and reviewed some of the contemporaneous medical literature so as to ensure that I had the right time frame in mind. A particular piece of literature, Chest 2000 Nov; 118(5): 1294–302 was identified and provided to me by [*the English firm of solicitors*] Through this I confirmed the various treatments available at the time, as well as the fact that tiotropium bromide was a drug that was well known to be in late phase development at the time.
>
> 3.1.2 [*The English firm of solicitors*]…then asked me to consider in more detail what would have been known by the skilled person as part of their CGK [*common general knowledge*] about tiotropium bromide at June 2001. For this I asked [t*he English firm of solicitors*]…to conduct literature searches for me on Pubmed using search terms that I chose, and supply me with the resulting articles. These search terms were 'tiotropium' and a combination of 'tiotropium' with either 'pharmacology', 'treatment'. 'asthma' or 'COPD'. At the same time as this, I also requested [*the English firm of solicitors*]… to provide me with seven review articles relating to tiotropium published from 2002-2004 in order to be able to get back to the source articles more easily. I was subsequently provided with these articles.
>
> 3.1.3 I then reviewed the results of the PubMed searches, and further articles which I identified during the review, to assist me in my recollection of exactly what would have been known about tiotropium by the skilled person at June 2001. It is this issue which [*the English firm of solicitors*]…has asked me to concentrate on in this report.
>
> 3.1.4 Where I refer to articles below, unless I state otherwise, they are articles which were identified during my searches and review.
>
> 3.1.5 I was then sent a copy of EP 1327220 B1 ('the Patent') and the proposed amended claims, and a copy of an item of prior art [the Ogura article]…for my consideration. I was further informed that two of the articles I had already identified in my searches above, were also cited as prior art, being Maesen…and Barnes. Ogura is a document that is directed at detailed formulation issues, and is outside my area of expertise. I have therefore not been asked to comment on it in this report…".

The transcript account of Professor Geddes' oral evidence under examination, at Day 2: 49, 23 –52, 10, reads as follows:

> *"Q [C]an I ask you then to deal with the preparation for the evidence that you are giving in these proceedings? You say at paragraph 3.1 [of Professor Geddes' written statement] that, in preparing your report for the United Kingdom proceedings, certain things were done. Do you see that?*
>
> *A. Yes.*
>
> *Q. Yes. If we can just go through those. Firstly, you refer to the original instructions given to you by [the English firm of solicitors]…to consider what was known about COPD as of June 2001, how it was treated and what the development treatments at that time were. At that point in time were you made aware of the Patent in these proceedings or made aware of the relevance of tiotropium to these proceedings?*

A. No, very specifically not. I was left in the dark as to what they wanted me to focus on, which, in fact, made my job rather difficult, because it's a very wide field, and to be asked to give my opinion on the whole of treatment of COPD, gave me an extremely wide angle of vision.

Q. And you were told to put out of your mind the information and knowledge you acquired after June 2001, I think, is that right?

A. That's right.

Q. And what did you do, just in practical terms, what did you do at that point in time in your consideration of the issues identified to you?

A. I then went to the main medical textbooks as a starting position and then decided upon a number of different ways of trying to assemble summary information as to what was going on at that date. So it's starting from textbooks. I then went to the national guidelines and international guidelines for the management of the condition, partly to – for their own content, but also, importantly, in order to get references to original papers that supported those guidelines. I then went to search for review articles from the date 2000/2001 and later, because they also were useful sources of references looking backwards. So just to be clear on that, I was not going to those papers for their content but I was going for the references within them. I also did a limited literature search from PubMed, but the difficulties with doing that is that if the question you are asking is so broad, you end up getting tens of thousands of references to look at, so it's not a very efficient way of doing it. I also went to my hospital pharmacy and asked them for information about drugs that were in development at the time, and I had, by this stage, identified tiotropium as one of the likely candidates for drugs being developed at the time. So I asked the pharmacy if they could give me more information about that particular drug. At that point, they advised me to contact the manufacturers of the drug as a good source of that information, which I did, and the manufacturers sent me a letter with some references in it, which was, as it turned out, not particularly useful because most of them were after the date of 2001.

Q. And there is a reference at 3.1.1, if you just look at that, to a particular piece of literature chest that was provided to you. I think that is the Casaburi piece, is that right?

A. That is the Casaburi paper yes.

Q. And we will come back to that. Was that provided to you before or after tiotropium was identified to you as an ingredient of interest to…[the English solicitors]?

A. Well, the way it was went was, I was asked for my preliminary trawl of the information of the state of the art at the time. Then, there was a meeting at the offices of Pinsent Masons, in which I discussed what I had discovered to date, including the fact that I had identified tiotropium as one of the treatments of interest. And at that point, they then handed me the Casaburi paper, to say was this the drug I was talking about?"

Notably, Professor Geddes did not give his opinion about treatments and potential new treatments that were common general knowledge after his own trawling exercise, but rather after the solicitors engaged by Teva in the United Kingdom gave Professor the Casaburi article, told him that tiotropium was of interest, and conducted a search and provided the materials from that search, from which articles Professor Geddes then selected the articles relied upon for his opinion. Asked by counsel for Teva whether he had already identified tiotropium in his general search before he was given the Casaburi article, Professor Geddes, in the last-quoted answer above, indicated that he had, though he did not indicate the source by reference to which he had so done. The court must admit to scepticism as to whether, at the very least, Professor Geddes' evidence was as helpful as it might have been had Teva's legal advisers in the United Kingdom not furnished him with the text of Casaburi, an article that featured in the within proceedings (though not as cited prior art), for the purposes of asking him whether the subject-matter of that article (tiotropium) was the same tiotropium being referred to by Professor Geddes. But even putting that aspect of matters to one side, it seems to the court that Professor Geddes ought preferably to have been asked to give his opinion about the treatments and developments that he believed could have been properly described as common general knowledge in June 2001. In this regard the court recalls, again, the observations of Luxmoore, J. in *British Acoustic Films*, at 250:

> 'In my judgment it is not sufficient to prove common general knowledge that a particular disclosure is made in an article, or series of articles, in a scientific journal, no matter how wide the circulation of that journal may be, in the absence of any evidence that the disclosure is accepted generally by those who are engaged in the art to which the disclosure relates. A piece of particular knowledge as disclosed in a scientific paper does not become common general knowledge merely because it is widely read, and still less because it is widely circulated. Such a piece of knowledge only becomes general knowledge when it is generally known and accepted without question by the bulk of those who are engaged in the particular art; in other words when it becomes part of their common stock of knowledge relating to the art….It is certainly difficult to appreciate how the use of something which has in fact never been used in a particular art can ever be held to be common general knowledge in the art'.

The question that remains disappointingly unanswered from Professor Geddes' evidence is whether, absent Teva's solicitors telling him that the target of the evidence was tiotropium and before conducting a focused search solely for materials to tiotropium, he would have regarded tiotropium as having been assimilated into the stock of usable knowledge of clinicians of ordinary skill in the field on the basis of his general search and what materials he would have relied on for that opinion.

204. Seventh, by contrast Professor Costello designed and carried out, his own searches against COPD and asthma, which searches were conducted in the same database used by Teva's solicitors for their targeted searches. In his written statement, Professor Costello indicates that of 5,140 articles returned on COPD, but 14 were concerned with tiotropium. A real question therefore arises as to whether the few articles in question would have been noticed by persons operating in the field, let alone assimilated to the common general knowledge. In passing, the court does not accept the somewhat fanciful contention by Teva that Professor Costello set out to hide or minimise the significance of tiotropium. Indeed, Professor Geddes' evidence in this regard was of some interest. He noted as follows, at Day 2: 122, 28–123, 6:

> "I think it's a curious form of logic that because there is a lot - a large number of other papers being published, means that you would not notice the ones that were of a particular interest. Just to be absurd, it would sort of imply that if there was twice as many irrelevant papers published, that would make it even less likely they would be noticed."

205. Professor Geddes, it seems to the court, does himself an injustice in the above-quoted text: he is neither being absurd nor posing an absurdity. He has, in truth, hit upon the very crux of matters. How would the notional skilled person know that tiotropium was of particular interest? Unless she proceeded on the basis that the significance of tiotropium was a given, then if she searched, as Professor Costello rightly did, against such terms as 'COPD' and 'asthma', she would have come up with 5,140 articles, of which a mere 14 were concerned with tiotropium. There is no reason to think that she would, to use a colloquialism, have 'zoomed in' on those 14 articles. And yes, to borrow from the wording of Professor Geddes' just-quoted oral evidence, if there were twice as many "*irrelevant papers*" yielded from the search, it would be even less likely that the 14 articles would be noticed in the proverbial 'haystack' of materials encountered. In his oral evidence, Professor Geddes suggested that the number of articles to be consulted from that 'haystack' would be fewer because a clinician would focus on the leading journals. It is to be regretted that Professor Geddes did not himself undertake a hindsight-free exercise of the type undertaken by Professor Costello in order that he could himself have given more useful evidence in this regard.

206. Eighth, all of the items relied on by Professor Geddes pursuant to the search that he conducted were written by persons concerned with the development of tiotropium, as opposed to commentary or review. When it was put to Professor Geddes that the materials relied upon by him did not comprise commentary by those working in the field generally but comprised reports or comment from the developer or co-workers, Professor Geddes, under cross-examination, suggested, at Day 2: 143, 10–15, that "*that all of those studies are done in collaboration with the drug company but that has to be the case because they're the people who have the drug. It couldn't be done any other way if the drug is not available to anybody else*." In truth, however, it does not seem to the court that this explains the absence of commentary by others, especially if the court were to believe that tiotropium was an eagerly-awaited new drug. And Professor Geddes in any event went on to indicate when being re-examined, at Day 2: 171: 14, 22, that non-proprietary knowledge, in the form of published clinical trials, was available for independent comment, yet such independent comment still was not forthcoming:

> *"Q….[W]ould anybody else, apart from persons connected with Boehringer, have access to the drug to write about it?*
>
> *A. Access to?*
>
> *Q. The clinical trials to write about them?*
>
> *A. Yes. I mean ones that have been published, yes. The ones that were not yet published but from which some preliminary data was coming out, would have been privileged to information."*

207. Ninth, it is notable that, as discovered by Professor Costello when he did a focused search in this regard, among the post-priority date experts on tiotropium there was no pre-priority commentary by them on tiotropium.

208. Tenth, it appears from the evidence that the anti-cholinergics available for prescription in 2001 were oxitropium and ipratopium which each required dosage a few times a day. But as to the notion that tiotropium was an eagerly awaited, long-acting drug, Professor Geddes' evidence as to the long duration of action of tiotropium being its particular attraction (i) sits uneasily with the fact that a through-the-night drug (oxitropium) was in fact withdrawn from the market, and (ii) appears, from the below-quoted extract from Day 2: 152, 25–153, 11, to be informed by hindsight:

> *"Q. Why was oxitropium a bit of a bust then, Professor?*
>
> *A. Oxitropium was not long-acting enough. It didn't last long enough. One treatment a day was not enough.*
>
> *Q. It doesn't seem to make sense to me, that a treatment in oxitropium, which cuts in half, essentially gives you protection doses through the night, would not be a success and something that comes along, because it extends it a bit further, would be a success?*
>
> *A. Well that, that, I mean that's a perfectly respectable theoretical position to take. I disagree with it and subsequent events would suggest that a longer acting drug has been a great deal more successful. Oxitropium never really took off and was withdrawn.*
>
> *Q. My point, and I think Professor Costello's evidence will be that actually nobody expected a new anticholinergic to be as good as tiotropium is."*

209. Eleventh, Professor Geddes' failure to put tiotropium in the context of other impending and developing treatments at the time, and the resultant limitations to his evidence, seemed to the court to be borne out by his response to the questions asked in respect of Dr Peter Barnes' New England journal article (Barnes, P., "Chronic Obstructive Pulmonary Disease" (2000) 343(4) *The New England Journal of Medicine* 269). That article referred to numerous treatments and approaches to COPD, including (i) drugs to assist smoking cessation, (ii) the re-purposing and (surprising) anti-bacterial effects of long-acting beta-antagonists in the treatment of COPD, (iii) antibiotics, (iv) oxygen therapy, (v) systemic corticosteroids, (vi) non-pharmacological interventions such as lung volume reduction surgery, (vii) non-invasive ventilation, (viii) pulmonary rehabilitation, and (ix) some 36 new chemical materials under investigation for the treatment of COPD. Professor Geddes, at Day 2: 138, 25–139, 11, accepted that since he had not carried out a targeted search, such as the one he carried out in respect of tiotropium, in relation to any of the existing and new treatments discussed in the just-mentioned Barnes article, he was (regrettably) not in a position to put the tiotropium materials he retrieved in context with all of the other contemporary developments:

> *"Q. Professor, I think we're almost agreeing in the sense that since you didn't carry out searches on any other treatments, leaving aside the drugs even, other treatments that could include lung volume reduction therapy and so on and so forth you just aren't in a position to weigh up what you got from a targeted search on tiotropium with what you would have got on a targeted search with anything else at the time? You're not in a position to weigh that up?*
>
> *A. I don't know what I would have got if I had done a targeted search on -- I would have ended up with 20,000 papers which is not a way to do a search.*
>
> *Q. Which is the point I'm trying to make, Professor, which is that people who are specialised in COPD and asthma had a lot of information coming at them?*
>
> *A. Yes."*

210. Twelfth, and in truth a development of the last point, in an exchange, at Day 2: 169, 25–170, 21, between counsel for Teva and Professor Geddes, when the latter was re-examined, concerning the above-mentioned Barnes article, (i) Professor Geddes accepted that he had not been aware, when carrying out his search, of some of the treatments mentioned in the article (and of those general areas of interest and development of which he had been aware, he would not have known the details), but that (ii) of those treatments of which he had been aware, he was aware that they were promising at the time but used hindsight to discount them:

> *"Q Are any of those potential interventions in respect of COPD ones that you were unaware of when you carried out your search, the initial search to identify what the new promising treatments were for COPD?*
>
> *A. Yes. Some ….*
>
> *Q. Yes.*
>
> *A. I was aware that mediator antagonists, protease inhibitors and anti-inflammatory drugs were being researched but the details of each one mentioned I would not have known about.*
>
> *Q. Indeed. And after you carried out that preliminary search, before you were told that tiotropium was the focus of your engagement at all, what view had you come to about the range of promising avenues for intervention for COPD?*
>
> *A. I think I'd come to the view that there were a number of avenues of interest at the time, but that it was unlikely that most of them would be the subject of interest because many of these you never heard about again. So I'm struggling at the moment because inevitably there is some hindsight coming in here. The fact that in 2015 I knew that nothing else had come through the pipeline in the subsequent 14 years, I can't pretend that I didn't know that."*

211. It seems to the court, with respect, that it is this flawed, hindsight-driven approach that prompted, on the part of Professor Geddes, the mistaken opinion that (a) the next iteration of an anti-cholinergic which (i) did not provoke any pre-priority comment on the part of anyone other than the developer and co-workers, (ii) represented but the next iteration, in terms of duration of action, of the commercially failed oxitropium, (b) had, at the priority date, not only (I) become common general knowledge in the field of those interested in asthma and COPD but (II) was anxiously awaited.

212. The court does not accept Teva's contention that Professor Costello's evidence as to the attitude at the priority date in the field of anti-cholinergics (relevant to the issue of whether or not the few pre-priority mentions sought to be relied upon by Teva would have resonated with the notional skilled person) as the application by Professor Costello of undue pessimism. Indeed, given, *inter alia*, the results of Professor Costello's literature search, *viz*. that of 5,140 articles returned on COPD only 14 were concerned with tiotropium, it seems to the court that to reach any other conclusion in this regard would be for it to err.

213. The court does not accept Teva's contention that when Professor Costello referred to the factors going into his opinion as the 'evidence' that he considered, that he thereby arrogated to himself the function of weighing evidence which properly belongs to the court. In truth, it would have been a concern if Professor Costello had not considered relevant matters before offering his opinion to the court, and that, it seems to the court, is all that occurred.

214. The court does not accept Teva's contention that Professor Costello sought to advocate against the notion that tiotropium was a part of the common general knowledge at the priority date. The court found his evidence as to common general knowledge to be dispassionate, informed and, for the reasons stated previously above, has preferred it to the evidence of Professor Geddes in this regard.

215. The court does not accept Teva's contention that Professor Costello could not offer any direct evidence as to tiotropium bromide not being generally known at the priority date. This assertion seems to rest on the following exchange between counsel for Teva and Professor Costello, at Day 13: 86, 8–9:

> *"Q. [Y]ou're not giving opinion evidence based on your expertise at the time, are you?*
>
> *A. No."*

216. In truth, the court would have been concerned had the answer to the just-quoted question been 'yes' as Professor Costello's expertise at the priority date was much in advance of the person of ordinary skill in the field.

217. The court does not accept Teva's contention, in circumstances where Professor Costello openly accepted that he himself knew about tiotropium at the priority date, that there is any ground for disquiet in the fact that Professor Costello did not expressly mention in his written statement that tiotropium had been mentioned by him in a pre-priority date article written to overcome prejudice against anti-cholinergics.

218. The court does not accept that, in the particular circumstances presenting (and considered hereafter), the insertion of footnotes by Boehringer's lawyers into Professor Costello's statement offers a ground for objection by reference to Lord Wilberforce's comments as to the proper role of experts and legal advisors in *Whitehouse v. Jordan* [1981] 1 W.L.R. 246, 250, a professional negligence case that arose after a child was tragically born with brain-damage following a difficult forceps delivery. Although Lord Wilberforce expresses "*some concern as to the manner in which part of the expert evidence called for the plaintiff came to be organised*", he refers the reader to the discussion of this aspect of matters by Lord Denning, M.R. when the case was before the Court of Appeal (reported at [1980] 1 All E.R. 650). It is worth recalling the exact nature of the concerns expressed by Lord Denning, at 655, under the heading "*The evidence of the medical men*":

> "This case has been considered by some of the most eminent men in the country. They have studied the hospital notes and seen both child and mother. The great preponderance of opinion is that neither Mr Jordan nor the hospital were guilty of any negligence. Professor L B Strang (London), Professor J P M Tizard (Oxford), Dame Josephine Barnes (Charing Cross Hospital) and Professor Sir John Dewhurst (London) all say so. I would summarise their view by quoting the concluding three paragraphs of Sir John Dewhurst's report:
>
> > 'How hard one should pull on the forceps and how many times one should pull in this kind of case is again a matter of clinical judgment based on experience. Force of pull on a pair of obstetric forceps is not measured but is judged by the operator in the light of his previous experience. Mr. Jordan says that he exerted traction 5 or 6 times co-incidental with the uterine contractions and that he relaxed the lock of the forceps between these pulls. He then

> concluded **not** that delivery was not possible but that **safe** delivery was not possible and proceeded to Caesarean section. I see nothing improper in this course of action nor in the manner of implementing it. One cannot argue that because the child **probably** suffered some intracranial damage (although even this is uncertain) he pulled too hard. Children have sustained intracranial damage from a normal delivery; the hardness of all babies heads is not the same and they are not all similarly resistant to pressure. I find no evidence to support an allegation of negligence on Mr. Jordan's part and I recommend that he be strongly defended.' (Emphasis mine.)
>
> In addition I may say that Professor Sir John Stallworthy (Oxford, now retired) at first made a report saying that Mr Jordan was not negligent. He said that he had dealt with the case 'with courage and skill'. But afterwards Sir John Stallworthy joined with Sir John Peel (also Oxford, retired) in holding that Mr Jordan was negligent. Their joint report was the justification for the continuance of this action to trial. But their joint report has been subjected to severe criticism and has been shown to be mistaken on some very important points.
>
> In the first place, their joint report suffers to my mind from the way it was prepared. It was the result of long conferences between the two professors and counsel in London and it was actually 'settled' by counsel. In short, it wears the colour of special pleading rather than an impartial report. Whenever counsel 'settle' a document, we know how it goes. 'We had better put this in', 'We had better leave this out', and so forth. A striking instance is the way in which Professor Tizard's report was 'doctored'. The lawyers blacked out a couple of lines in which he agreed with Professor Strang that there was no negligence.
>
> There is also evidence of serious mistakes in the joint report itself. The two professors said that the baby's head was 'not engaged', whereas the hospital notes made it clear that those on the spot had found that it was 'engaged'. And the judge so found.
>
> The two professors also said that the pulling was so hard that Mrs Whitehouse was 'lifted from the bed' which they explained as meaning that she was pulled down off the bed and lifted back on to it again. That was contrary to all the evidence in the case, including that of Mrs Whitehouse herself. The two professors did not have the benefit of the evidence of Dr Skinner. He said that nothing of the kind took place.
>
> The two professors also criticised the hospital for not having made a pelvic assessment: without paying sufficient regard to the fact that Mrs Whitehouse was so tense that it could not be done: and she refused an X-ray.
>
> The defects in the joint report of the two professors are so great that, to my mind, it cannot stand up against the reports of the other distinguished men in the case."

219. These were clearly the most serious of defects and it was in this context that Lord Wilberforce noted as follows on appeal, at 256–7:

> "While some degree of consultation between experts and legal advisers is entirely proper, it necessary that expert evidence presented to the court should be, and should be seen to be, the independent product of the expert, uninfluenced as to form or content **by the exigencies of litigation.** To the extent that it is not, the evidence is likely to be not only incorrect but self-defeating." (Emphasis added).

Nothing of a like situation presents here. There are ten footnotes in the main body of Professor Costello's written statement, all of which footnotes are one sentence long, four of which give journal citations, five of which identify a relevant exhibit to the statement, and the last of which, referring to a sentence in the text of the report which reads, so far as relevant, "[T]*he number of patients that took part in the Phase III studies referred to in Littner et al. was 252*", states "*We note that only 169 of the 252 screened subject[s] participated in the study*". It emerged in Professor Costello's cross-examination that the footnote had been inserted by the solicitors for Boehringer; hence the "*We*". However, Professor Costello maintained, and the court accepts, that he authored and stood over the body of the report. And although two wrongs do not make a right, and again the court sees no wrong in the just-described occurrence, the court cannot but recall that Professor Buckton, a witness called by Teva, when making the minor corrections to the text of his first written statement that are so often a part of the introductory segment of the hearing of an expert witness' oral evidence, had to make one of these corrections because, it emerged in cross-examination, at Day 4: 111, 1–14, there had been some cutting and pasting, it seems by Teva's lawyers, so as to revise, for the purpose of the Norwegian proceedings, the report that Professor Buckton gave in London, with the result that the text before this Court was not to Professor Buckton's satisfaction. Lawyers can and do provide ancillary assistance to expert witnesses when the latter prepare their written reports, and can do so in a manner that, as here, does not contravene the observations of Lord Wilberforce in *Whitehouse v. Jordan*, and neither approaches nor even begins to approach the egregious type of behaviour to which both Lords Wilberforce and Denning expressed such objection as the different appellate stages of the last-mentioned proceedings unfolded.