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Case Nos: HP-2020-000048 and HP-2021-000009

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

Rolls Building, Fetter Lane, London, EC4A 1NL
15 July 2022

Before : **MR JUSTICE MEADE**
Between :

SANDOZ LIMITED	**Claimant/Pt 20 Defendant in HP-2020-000048**
TEVA PHARMACEUTICAL INDUSTRIES LIMITED	**Claimant in HP-2021-000009**
-and-	
(1) BRISTOL-MYERS SQUIBB HOLDINGS IRELAND UNLIMITED COMPANY **(2) PFIZER INC.**	**Defendants/ Pt 20 Claimants in HP-2020-000048 & HP-2021-000009**
-and-	
TEVA UK LIMITED	**Part 20 Defendant in HP-2021-000009**

- -

Andrew Lykiardopoulos QC and Adam Gamsa (instructed by Bristows LLP) for **Sandoz**
Justin Turner QC and Katherine Moggridge (instructed by Pinsent Masons LLP) for **Teva**
Piers Acland QC and Anna Edwards-Stuart (instructed by Hogan Lovells LLP) for **Bristol-Myers Squibb and Pfizer**
Hearing dates: 28-29 April, 4 and 9 May, 10 and 13 June 2022

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APPROVED JUDGMENT

I direct that no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic. This Judgment was handed down remotely by email circulation to the parties' representatives and release to the National Archives. Deemed date for hand-down: 15 July 2022.

Mr Justice Meade:

INTRODUCTION

1. Apixaban, trade name ELIQUIS, is a successful drug for treating thromboembolic disorders. In a judgment of 7 April 2022, [2022] EWHC 822 (Pat), I held that a patent covering apixaban as such, and which also claimed apixaban for use in treating a thromboembolic disorder, was invalid. As a result, an associated SPC was also invalid. I will refer to that as "the First Judgment", and to the trial which led to it as "the First Trial".

2. The patent in issue at the First Trial had a priority date of 21 September 2001.

3. This trial concerned four further patents relating to apixaban ("the Patents"), all from the same family as one another and all having priority dates of 25 February 2010. They cover formulations of apixaban.

4. In the Introduction to the First Judgment I explained the parties. The situation was the same at this trial, except that Pfizer as well as BMS is a patentee. Nothing turns on that and I will refer to BMS and Pfizer collectively as "BMS".

5. As was the case at the First Trial, infringement is admitted if the Patents are valid.

6. The Patents are:

   i) EP(UK) 3 246 021;

   ii) EP(UK) 3 017 811;

   iii) EP(UK) 3 251 660;

   iv) EP(UK) 3 257 500.

7. Sandoz reached a settlement with BMS so that only the first Patent (which I will refer to as "`021") remained in issue so far as it was concerned, and from that Patent, only claims 1-6 (it was these claims that Sandoz admitted were infringed if valid). That, however, is now only of historical interest (and possibly of relevance to costs) because the independently valid claims in issue dwindled over time, and by the start of the trial, only claim 1 of `021 needed to be addressed. All the other Patents and claims stand or fall with it.

8. When this trial began, `021 and the second Patent (ending `811) had been revoked by the Opposition Division of the European Patent Office. During this trial, which was prolonged for reasons explained below, the third Patent (`660) was revoked by the Opposition Division, and reasons were given on 27 June 2022, when the drafting of this judgment was at an advanced stage. In each case, revocation is stayed pending appeal (though BMS has not yet actually appealed the `660 decision, with time for it still running). Teva submitted that the 27 June 2022 reasons supported its case. BMS submitted that the prior art, arguments and evidence were different. In my view BMS is right about this. Although the reasons are broadly consistent with my conclusions, and I do not in any way criticise them, it would not be right to

put weight on them and I do not do so. I should also mention, if only for completeness, that another related patent has been conclusively revoked by the Technical Board of Appeal for added matter, an issue I am not addressing (the patent was included in these proceedings at an earlier time but dropped out when conclusively revoked).

9. Much as I recorded in the First Judgment, Sandoz and Teva are separately represented but have made common cause, submitting joint skeleton arguments (except for a short supplemental skeleton on dependent claims submitted by Teva alone when such claims were still live) and sharing expert witnesses. Their Counsel again split the oral advocacy. They have run the same arguments with one exception, a prior art citation which only Sandoz ran and which has faded from the case. I will once more refer to Sandoz and Teva together as "the Claimants".

10. BMS has also applied to amend the Patents. All that matters for the purposes of this judgment is that claim 1 of `021 is in proposed amended form. The amendment was to address an insufficiency allegation, which the Claimants accept that it has done (the allegation was of an omission to stipulate test conditions for a claim feature, and by the amendments the conditions were brought into claim 1 from a dependent claim). There is no issue over the amendments other than that the Claimants say they do not cure any invalidity.

11. As with the First Trial, there has been related litigation in two actions in Canada. It is of some, albeit modest, relevance because evidence given there by Prof Davies (BMS's formulation expert) was used to cross-examine him here.

CONDUCT OF THE TRIAL

12. The evidence and argument took place live in Court. Unfortunately, however, Prof Davies contracted COVID and his recovery took a while. It goes without saying that this was no fault of his, and naturally the priority of all concerned was that he should make the fullest possible recovery, unburdened by this case. As a result, the trial started in April and did not end until June, despite being only a few days in Court.

13. I should mention that:

    i) 4 and 9 May, while recorded on the front of this judgment as being sitting days, involved only short hearings to discuss timing in the light of Prof Davies' indisposition.

    ii) Prior to the trial resuming on 10 June I took the opportunity to refresh my memory of the case from materials including the opening skeletons, the experts' reports, and the transcript of the cross-examination of Dr Stott.

    iii) Prof Davies coped well with his cross-examination. He said he was tired at one or two points, but it was an intense day by any standards

and my view was that he was fully in command of what he thought and said.

THE ISSUES

14. When opening skeletons were submitted, the issues were:

    i) Some issues over common general knowledge ("CGK") relevant to obviousness.

    ii) Some minor points about the skilled team.

    iii) Obviousness over a review article by Carreiro and Ansell, "*Apixaban, an oral direct Factor Xa inhibitor: awaiting the verdict*", published in November 2008 in Expert Opinion on Investigational Drugs, ("Carreiro").

    iv) Obviousness over a BMS press release of 10 June 2008 entitled "*Bristol-Myers Squibb and Pfizer Initiate New Study in the Apixaban Phase 3 Clinical Trial Program*", ("the Press Release").

    v) Obviousness over US 2006/0160841 A1, a US patent application by BMS, with inventors Wei and Yang, published in July 2006 ("Wei").

    vi) Obviousness due to arbitrariness/lack of technical contribution of some claim features. These points were really in reinforcement of the obviousness case over Carreiro.

15. However, it seemed unlikely that the Press Release would add anything to the arguments over Carreiro, and so it proved. Wei was covered in the cross-examination of Dr Stott (for the Claimants) but also seemed unlikely to be of separate importance. Both were formally dropped towards the end of the oral evidence.

THE WITNESSES

16. The parties each put in evidence from two experts:

    i) A clinician; and

    ii) A formulator.

17. As I shall explain below, the areas of dispute between the clinicians, never great to begin with, shrank still further during trial and had vanished by the closing arguments.

18. There was no fact evidence.

19. The Claimants' experts were:

    i) Prof Mike Laffan (clinician);

ii) Dr Paul Stott (formulator).

20. BMS's experts were:

i) Dr Jeffrey Weitz (clinician);

ii) Prof Martyn Davies (formulator), to whom I have referred already.

21. Prof Laffan was cross-examined only briefly, and the Claimants decided not to cross-examine Dr Weitz at all.

22. BMS made clear that they had no personal criticisms of Dr Stott. He was well qualified and a good, fair and clear witness.

23. The Claimants attacked Prof Davies in a number of respects:

i) They criticised him for not having dealt with dissolution testing adequately in his first report, and said it was particularly problematic given that he has been an expert in patent litigation about 20 times. I did not think there was much at all in this for a variety of reasons, including that his evidence across his two reports was not incomplete in the respect focused on, and I make clear that I did not find Prof Davies to be remotely a hired gun.

ii) They criticised him for not having acknowledged statements made in written evidence in one of the Canadian cases. I have found that Prof Davies' Canadian evidence does materially support the Claimants' case, but reject any argument that he was at fault in not pointing it out. There was nothing underhand or malicious.

iii) They said that compared with Dr Stott he had a more academic background, with less experience of run-of-the-mill formulation work. I think the comparison was factually accurate, but Prof Davies clearly did have adequate practical experience (indeed, a lot of it) to found opinions about the skilled addressee's thinking. The fact that Dr Stott had more is irrelevant.

iv) They said, and this was called the "central criticism", that there was no basis in any document for his opinion that for BCS Class III drugs the skilled addressee would have such extremely high optimism about dissolution rate that it would not even be tested. I have formed a clear view, for reasons which I deal with in detail below, that the Professor's opinion about the skilled addressee's perspective was wrong. But I do not think the issue was so one-sided, or the documents so free of scope for argument, that the Professor can be criticised for advancing his view, and nor do I doubt that he believed what he was saying. Also, the criticism may have overstated the Professor's position, because it was common ground that dissolution rate would at least be tested at the prototype formulation stage. The dispute seemed to me to be less binary than the Claimants depicted it as being.

OBVIOUSNESS - APPLICABLE LEGAL PRINCIPLES

24. I will start with the basic principles and then identify some other aspects of the law said to be relevant. I will also explain where these points were said to be significant to the arguments.

Basic principles

25. The basic approach is as set out in *Actavis v. ICOS* [2019] UKSC at [52] – [73]. At [63] the Supreme Court endorsed the statement of Kitchin J, as he then was, in *Generics v. Lundbeck* [2007] EWHC 1040 (Pat) at [72]:

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

26. The Claimants relied on *Brugger v. Medicaid* [1996] RPC 635 (at 661), as approved by the Supreme Court in *Actavis v. ICOS* for the proposition that an obvious route is not made less obvious by the existence of other obvious routes. I have commented on it in other recent judgments – it must not be taken too far. In the present case the Claimants do not rely on it to do much work: they merely said that if it was shown that particle size reduction and excipient optimisation were both obvious things to do to improve dissolution rate, the former was no less obvious because of the availability of the latter. In any event, however, I will have such regard as is appropriate on the facts both to the *Brugger* principle and to the caution needed in respect of it.

Obviousness arising from testing

27. BMS relied on what Jacob LJ said in *Leo Pharma v Sandoz* [2009] EWCA Civ 1188 at [9]-[10]:

> 9. So the case is unusual. The ordinary obviousness attack consists of a contention that the skilled person would, using his technical knowledge, discern the invention from the prior art. The case here is that the skilled person would have come upon the invention (the hydrate and its benefit) without any expectation of successfully finding a better product.
>
> 10. That sort of obviousness attack should be scrutinised with great care. I do not say it could not succeed, but one must be very confident that the steps said to lead to the discovery of a new and beneficial product "by accident" as it were, were at the least, really likely, almost mandated. If you need to do research to find an invention then, for a finding of obviousness, that research must be of a kind which a skilled man would do, not which he might do.

28. Picking up on the reference in [10] to the steps leading to the invention having to be "really likely" or "almost mandated", BMS referred to *Actavis v. ICOS* where obviousness arose because although the 5mg dose in the claims could not be predicted, routine research would (BMS's emphasis) have led to its being tested with success.

29. I thought there was a danger that BMS's submissions were really just trying to approximate the facts of the present case to those in *Leo*, and/or to contrast the facts with *Actavis*, rather than identifying legal principles. The former case was an extreme one where the obviousness attack was that something wholly new would emerge in the course of rather blue-sky testing, the testing being done without any particular expectation of success. The latter was a case where the research was routine, and done for a solid reason with the expectation of getting a useful result, albeit one which numerically speaking could not be predicted in advance. Neither really maps onto the present case, where the obviousness case is that dissolution rate testing would be done (as is accepted), knowing that it would either give reassurance that all was well, or show that improvement was needed.

Arbitrary features

30. The Claimants referred to the well-known explanation of Jacob LJ in *Actavis v. Novartis* [2010] EWCA Civ 82 by reference to the 5 ¼ inch plate: arbitrary and non-technical limitations which do not solve a problem are not inventive for that reason. Birss J (as he then was) considered this in *Apple v. Optis* [2020] EWHC 2746 (Pat) and explained that having an arbitrary feature in a claim is not a ground of invalidity but it does mean that the feature cannot be relied on for inventive step.

31. This principle was invoked by the Claimants because claim 1 of `021 contains detailed numeric limitations as to dissolution rate and particle size. As I understood it, the Claimants wanted to head off an argument that for example, while it might be obvious to go for a "small" particle size, they could not show that specifically a D_{90} of 89µm would be achieved. This is perhaps not quite the same as the 5 ¼ inch plate situation, but in any event I did not understand BMS to run a point based on the exact numbers. I have made findings about CGK particle size ranges below; I do not consider that there was any magic to 89µm and had BMS really run such an argument, I would have held that the precise limits in the claims were arbitrary; similarly with dissolution rate.

Lack of technical contribution

32. The Claimants argued that a patent monopoly must be justified by a technical contribution and that a patent which does not solve any problem is not inventive. They referred to *Generics v. Yeda* [2013] EWCA Civ 925 at [49]. I think that case is really more to do with the proper scope of a claim, but I accept the principle as stated by the Claimants. The reason this point mattered, at least potentially, is that the Claimants' obviousness case assumed that the skilled addressee would find a problem with the dissolution rate of apixaban in a prototype formulation. But other than in the figures of the `021

Patent there was no demonstration of such a problem. The Claimants wanted to be able to say that either there was a problem of slow dissolution to be solved (in which case it would be identified routinely with smaller particle size being an obvious solution) or, if there was in fact no problem then there was no inventiveness. This was rather elaborate and I did not understand BMS to argue that there was no problem to be solved. Nonetheless, I consider the application of this principle briefly below.

Common general knowledge alone

33. It is well-established that cases of obviousness over common general knowledge alone have to be scrutinised with care because they may be too abstract and allow a case to be run which is unrealistically and unfairly free of real world problems and details (see e.g. *Ratiopharm v Napp* [2008] EWHC 3070 (Pat)). In the present case, obviousness is alleged over a concrete piece of prior art, Carreiro, but that just provides the clinical jumping off point for what is in substance a formulation invention, and the obviousness of the formulation aspects is indeed based on common general knowledge alone. So in my view I do have to exercise appropriate caution, and I have tried to do so.

THE SKILLED TEAM

34. It was accepted that the skilled team, working from Carreiro, would include a clinician and a formulator. It was also common general knowledge that the clinician would define what was desired and the formulator would seek to put it into effect. For reasons that I come to shortly, the issue of obviousness turned entirely on the formulator's work. There was a trivial dispute about how many years' practical experience the formulator would have. It does not matter. He or she would have a relevant degree or degrees, and practical experience. From here on, if I refer to "the formulator" I just mean the notional "Skilled Formulator" (the term used in the parties' CGK document). This does not mean the addressee is not a team, it is simply that there is in general no need to say anything further about the clinician to decide the issues.

AGREED COMMON GENERAL KNOWLEDGE

35. The parties provided a statement of the Agreed CGK. I have edited it down quite extensively to remove most of the general background clinical material, and some parts of the formulation section. My objective was to preserve the material most central to understanding this judgment while reducing its length and taking out material of limited importance or usefulness. My removing material does not detract from its agreed status.

36. The upshot of the clinical CGK is that apixaban was a promising drug that had reached advanced clinical trials and would be obvious to progress in an appropriate formulation. When I come to Carreiro I will explain that it identifies a number of doses (in particular 2.5mg and 5mg tablets) that BMS

accepted would be obvious for the clinician to recommend to the formulator to make into tablets for twice-daily administration; these would be immediate-release formulations. The clinician would not have to have any further involvement relevant to the issues at this trial.

DOACs

37. For many years before the priority date, warfarin was the main oral anticoagulant in clinical use for treating thromboembolic disorders including deep vein thrombosis, pulmonary embolism, stroke (often caused by atrial fibrillation), and acute coronary syndrome.

38. Limitations with warfarin (including a need for a tailored dose for each patient that was hard to identify) prompted a search for oral anticoagulants that could be given in fixed doses without coagulation monitoring and which were at least as effective and safe as warfarin. This search led to the development of the DOACs. [Weitz 1/7.19]

39. The DOACs were designed to be orally administered and were small molecule inhibitors designed to target components of the coagulation cascade namely either thrombin or Factor Xa alone. [Laffan 1/60; Weitz 1/7.20]

40. By 2010 two DOACs had been licensed for use in the UK - dabigatran, a direct inhibitor of thrombin, and rivaroxaban, a direct inhibitor of Factor Xa. Both had been licensed for use in the UK for the prevention of thromboembolic problems after joint replacements and were in advanced trials for other indications.

Apixaban

41. In 2010, the Skilled Clinician would also have been aware of another DOAC being developed, although not approved: apixaban. They would have been aware of apixaban from the scientific literature and conferences. [Laffan 1/63; Weitz 1/7.23]

42. The Skilled Clinician would have been aware in 2010 that apixaban was a direct acting oral Factor Xa inhibitor and that it was being trialled in a number of clinical trials, several of which were at an advanced stage (Phase III). [Laffan 1/64; Weitz 1/7.23].

Drug development and the formulator's role

43. The Skilled Formulator typically joins a drug development project after the drug discovery team has identified a small number of lead candidate compounds, but before studies in humans have been carried out. [Davies 1/46]

44. In the circumstances of this case, the choice/identification of a lead compound is not of relevance: the Skilled Formulator would be tasked with formulating apixaban specifically.

45. Starting with a lead compound, in this case apixaban, the development phase of the R&D process would initially comprise a series of pre-formulation studies, to gain an understanding of the physicochemical properties of the API. [Stott 1/38; Stott 1/39; Davies 1/49] During pre-formulation there is typically only a small amount of the API available for analysis. [Stott 1/39]

46. The data from the pre-formulation studies feeds into the subsequent formulation development and may highlight any potential difficulties that the Skilled Formulator may encounter in formulating an effective dosage form. [Stott 1/39; Davies 1/51]

47. Before they start work, the formulator will be advised of the proposed dose range and route of administration. [Davies 1/52; Stott 1/38]

The Skilled Formulator's goals

48. The goal is to formulate a dosage form which:

    i) provides an accurate and safe dose of the API; [Davies 1/54]

    ii) is sufficiently stable such that the API is not degraded during the target shelf life of the product and also until it reaches the site of absorption *in vivo*; [Stott 1/43.1; Davies 1/54]

    iii) is suitable for the clinical need such that the API is being released in a manner which can reach the biological target in sufficient quantity to exert its therapeutic effect consistently; [Stott 1/43.4; Davies 1/54]

    iv) is convenient for patients, to help with compliance; [Stott 1/43.2]

    v) is reproducible such that the dosage form is capable of being made on a large scale with consistent properties; and [Stott 1/43.3; Davies 1/54]

    vi) if a tablet formulation is used, has adequate quality attributes (e.g. it does not crumble or chip and does not break apart during the manufacturing process or on packaging and distribution). [Stott 1/45 - 47]

49. The skilled team, including the formulator, will know that should any problem emerge with the API or formulation during later stages of the development phase, a significant delay and reworking of the formulation might be required. The R&D costs to bring a product to market are substantial and hence, any delay or setback will cost time and money and significantly delay the launch of the product. [Davies 1/55]

Passage of the API through the body

50. For a drug exerting its therapeutic effect in the systemic circulation the API must reach the blood / plasma. For the majority of drugs, there are four main processes that take place before the API in a tablet reaches the systemic circulation:

i) Firstly, once taken by the patient the tablet must disintegrate in the stomach releasing the API contained in the tablet. This means that the tablet is no longer a single compressed mass but disperses into smaller particles that are exposed to gastrointestinal ("GI") fluids. This process is termed "disintegration". [Stott 1/51.1; Davies 1/68; Davies 2/24]

ii) Secondly, the API released from the tablet must enter into solution i.e. the API must dissolve into the GI fluids. This generally occurs in the stomach but, if not completed here, the API will continue to dissolve in the small intestine. This process is termed "dissolution". [Stott 1/51.2; Davies 1/68; Davies 2/24]

iii) Thirdly, the API must permeate across tissue membranes at the site of absorption in the GI tract. This process occurs primarily in the small intestine and is termed "permeation" (also referred to as "absorption" in Stott 1). Some permeation may occur in the large intestine but this tends to be much more limited. [Stott 1/51.3; Davies 1/68; Davies 2/24]

iv) Fourthly, the API may be subject to first pass metabolism in the gut wall and in the liver so that it is no longer therapeutically active. The rate of excretion cannot be affected by the design of an immediate release product. Excretion is not of any direct relevance to the issues.

51. The process of drug absorption from oral solutions is different. There are no disintegration or dissolution steps because the medicinal ingredient is pre-dissolved in the solution formulation. [Davies 1/73; Stott 1/165]

52. Bioavailability can sometimes be described as being "dissolution rate limited" or "permeability rate limited", which refers to the slowest step that effectively controls the rate at which the API enters the body. [Stott 1/67; Davies 1/59; Davies 1/69; Davies 2/29].

Appropriate therapeutic effect

53. The amount of API that gets absorbed, among other factors, usually determines the nature and extent of its clinical effect. If not enough is absorbed, the effect may be minimal or insufficient. Too much, on the other hand, can result in unwanted side-effects. Accordingly, absorption is an important consideration in formulation design. The level of API in the blood at a given time is commonly represented as a plasma concentration-time curve, an example of which is shown below: [Stott 1/48; Davies 1/66]

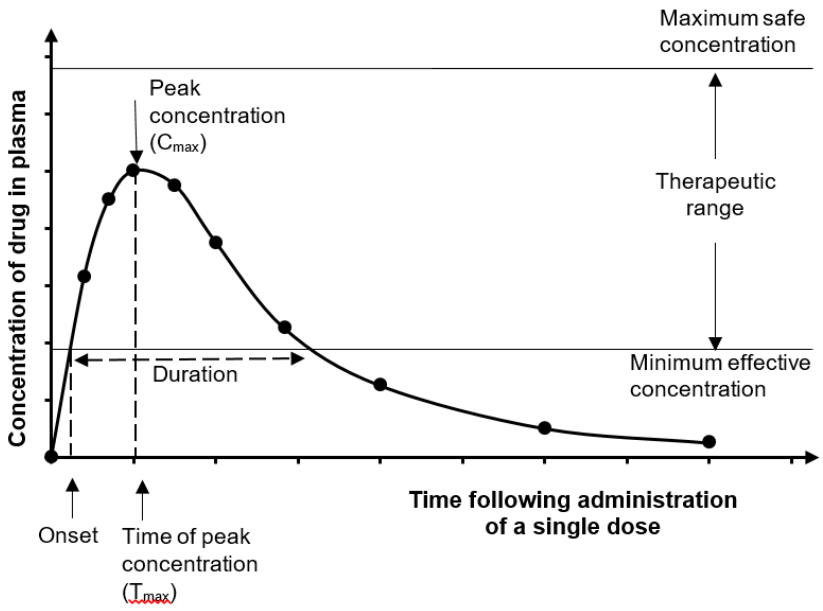


Figure 2 – Example plasma concentration-time curve obtained following administration of a single oral dose of a drug. The figure shows a hypothetical therapeutic range and the maximum safe concentration and minimum effective concentration of the API. The area under the curve (AUC) is the total exposure of the drug [Stott 1/Figure 1]

54. The following terms are used to describe plasma concentrations and would be familiar to the Skilled Formulator:

    i) C_{max} - represents the highest concentration of API achieved in the blood plasma following administration of the dosage form. C_{max} must fall under the maximum safe concentration to avoid toxicity.

    ii) T_{max} is the period of time taken to reach the peak blood plasma concentration of API following administration of the dosage form (i.e. the time at which C_{max} is reached).

    iii) AUC ("area under the curve") is an estimation of the total amount of API absorbed into systemic circulation after administration of the dosage form.

    [Stott 1/49; Davies 1/123; Davies 1/124]

Bioavailability

55. The relative amount of an administered dose of a particular dose of a particular drug that reaches the systemic circulation intact and the rate at which this occurs is known as "bioavailability". [Davies 1/119]

56. If all of the API gets into the bloodstream (like it will for intravenous drugs), then the bioavailability is 100%. If only a portion of the API gets into the bloodstream, the bioavailability will be less than 100%. For oral dosage forms, bioavailability is expected to be below 100% because many diverse

factors can affect how much API is absorbed into the blood stream (e.g. incomplete absorption and first-pass metabolism by the liver and in the gut wall). The bioavailability of orally administered drugs can vary greatly between different drugs and different dosage forms of the same drug. [Stott 1/52; Davies 1/120]

57. Pharmacokinetic studies are used to measure the bioavailability of an API from a dosage form that is under evaluation by assessing the parameters AUC and C_{max} (discussed above). T_{max} may also be assessed. [Davies 1/121] The study of absorption, metabolism, distribution and excretion of an API is known generally as the field of pharmacokinetics. [Davies 1/126] The values of C_{max}, T_{max} and AUC are used in bioavailability studies to assess the rate of systemic absorption (C_{max} and T_{max}) and extent of systemic exposure (AUC) of an API from a pharmaceutical formulation. The value of C_{max} is used to assess the maximum plasma concentration value for the API. [Davies 1/125]

58. The terms "absorption" and "exposure" are often used synonymously when discussing "bioavailability", although strictly speaking, they are each slightly different concepts. Absorption is strictly the process of absorption of the API into the bloodstream from the gastrointestinal tract for an oral dosage form. Exposure is more synonymous with bioavailability as it is a measure of the amount of API that is absorbed into the bloodstream after an API is administered and can be evaluated by considering the rate (C_{max} and T_{max}), and the extent of exposure (AUC) of the API in the bloodstream and the maximum concentration of the API in the bloodstream (C_{max}). [Davies 1/128]

Pre-formulation

59. As noted, in the pre-formulation stage, the physicochemical properties of the API and its stability are tested. It is essential to get an understanding of these properties prior to the formulation of the API into a product. [Stott 1/70; Davies 1/75]

60. Standard pre-formulation tests would include: equilibrium solubility; stability; permeability; investigating alternate forms such as crystal forms, hydrates, solvates and salts; purity; particle size, shape and surface area; particle density, powder flow and compressibility. Excipient-API compatibility studies may also be done. [Davies 1/76; Stott 1/71]

Solubility and Dissolution Rate

61. The equilibrium solubility of an API (i.e. the amount that will make a saturated solution) is typically expressed as a mass of the medicinal ingredient that can be dissolved in a unit of liquid, such as milligrams per millilitre (mg/ml), although it can also be expressed in percentages and sometimes in parts i.e. number of parts of a solute dissolved in a number of parts of a solvent. This is typically determined by suspending an excess amount of the API in the solvent at a fixed temperature and stirring the mixture for a long period of time (usually many hours) until the concentration in solution remains constant. [Stott 1/60.1; Davies 1/80]

62. The equilibrium solubility of an API is typically one of the first properties of a new potential API to be measured in pre-formulation studies following routine protocols. [Davies 1/81]

63. The Skilled Formulator would typically test an API's equilibrium solubility at human physiological temperature (37 ºC) in a range of media across a range of pH to mimic the changing pH of the GI tract, and usually over a time period of at least 24 hours in order to allow equilibrium to be reached. The aqueous equilibrium solubility is of particular interest as the environment in the GI tract is aqueous, but solubility in non-aqueous solvents will also be checked. If an API is an acidic or basic molecule and therefore capable of being ionised, the pH will affect its equilibrium solubility. If the API is non-ionisable, then the Skilled Formulator would expect the pH of the medium to have no effect on the solubility of the API. [Stott 1/73; Davies 1/80-81]

64. The equilibrium solubility is not a measure of how quickly a substance will dissolve. The latter is called the "dissolution rate". The dissolution rate can be shown in the Noyes-Whitney equation below. According to this equation equilibrium solubility and surface area are factors affecting the dissolution rate of an API *in vivo.*

$$\textbf{Dissolution rate} = kA\,(C_s - C_t)$$

Where:

A = surface area of the dissolving API

k = constant relating to diffusion of the dissolved material away from the interface between the solid API and the solvent

C_s = solubility of the API

C_t = concentration of the dissolved API at time (t)

[Stott 1/59; Davies 1/82]

65. Dose is considered by the formulator in terms of the "dose-solubility ratio". The reason for this is that the Skilled Formulator would want to put the equilibrium solubility of the API in context with the amount of API that actually needs to dissolve. [Stott 1/76; Stott 2/8; Davies 1/85-86]

66. The formulator would be told which dose(s) or dose ranges to formulate by the clinician. [Stott 1/38]

Permeability

67. The propensity of an API to cross the intestinal membrane is a function of its permeability. The extent of permeability depends on the chemical structure of the API (including its molecular weight of the API, its lipophilicity and the extent of ionisation), the mechanism of transport of the API across the membrane, the extent to which the API is metabolised within the cells of the intestinal membrane, and any counter-efflux. [Davies 2/14; Stott 1/65]

68. Along with equilibrium solubility, the permeability of a compound is an inherent property of a new API to be considered in pre-formulation studies. [Stott 1/71; Davies 1/84]

69. Permeability is not a characteristic which is particularly easy for the Skilled Formulator to influence. This is because the Skilled Formulator cannot typically add anything to the formulation that changes the inherent properties of the API. There are agents that may modify the barrier properties of the GI membrane (permeation enhancers) but these have very limited applicability and often cause deleterious side effects. [Stott 1/66]

Intrinsic dissolution rate testing ("IDR")

70. IDR testing is a method of looking at the dissolution rate of the API itself. IDR testing employs methods to control factors such as surface area, temperature, agitation or stirring speed, pH and ionic strength of the dissolution medium. The IDR is obtained by exposing a disc of compressed API to the dissolution medium under specified conditions. Dose is not taken into account. [Stott 1/footnote 11; Davies 2/19; Davies 2/20]

Alternative API forms such as crystal forms, hydrates, solvates, salts

71. APIs can exist in different physical forms and these will be investigated at the pre-formulation stage. APIs can be in crystalline or amorphous form (or sometimes an intermediate form, i.e. crystalline with some amorphous content). In crystalline structures, the API molecules will be in a regular and orderly structure, whereas in amorphous APIs the molecules will be arranged in a random manner. The Skilled Formulator would usually select a crystalline form, rather than develop an amorphous form, if it is possible to do so, as crystalline forms are more stable (physically) and therefore less prone to change form during and after product manufacture. [Stott 1/80]

Particle Properties

72. During pre-formulation the Skilled Formulator will investigate the characteristics of the particles of the API such as particle size, shape, and the compressibility of the API. [Stott 1/88; Davies 1/76]

73. Particle size distribution may be presented in the form of a % of particles that have an equivalent diameter of less than, or more than, a particular value, typically given in µm and displayed as $D_{V[\%]}$ (or $D_{[\%]}$). For example, a hypothetical population of particles where 90% of the particles have an equivalent volume diameter less than 200 µm would be described as having a particle size D_{v90} (or D_{90}) of less than 200 µm. [Stott 1/91]

74. The shape of the particles will also be evaluated, usually by microscopy. [Stott 1/93]

Formulation

Dosage form

75. An immediate release dosage form is designed to immediately release the drug that is inside the tablet once it has been swallowed (discussed above). Various well-known excipients like disintegrants are included to aid in the tablet breaking up after it has been ingested. [Stott 1/37; Davies 1/59] By contrast, modified release formulations release the API over a longer time period. [Stott 1/37]

Excipients

76. Pharmaceutical formulations typically contain the API along with excipients. Excipients are usually categorised according to their function and include:

    i) A diluent/filler.

    ii) Binders.

    iii) Disintegrants.

    iv) Surfactants (also referred to as "wetting agents") facilitate the entry of the API into solution. Commonly used surfactants include sodium lauryl sulfate (SLS, also known as sodium dodecyl sulfate, SDS) and polyethylene glycol.

    [Stott 1/95; Davies 1/57]

77. A surfactant reduces the surface tension at the interface between the solvent and solute. [Stott 1/103.2; Stott Supplementary 1/4.9; Davies 1/107; Davies 1/113; Davies 1/137] Details of commonly used surfactants, including recommended amounts to be used in pharmaceutical compositions, would have also been available to the Skilled Formulator in textbooks such as the Handbook of Pharmaceutical Excipients. For instance, some commonly used surfactants at the priority date and recommended ranges for specific applications (as a % concentration in the total pharmaceutical composition) are set out below in Table 1 below:

Compound	**% Concentration**
Docusate sodium (for use as a wetting/dispersing/emulsifying agent)	0.01 – 1%
Poloxamer (for use as a wetting agent)	0.01 – 5%
Sodium lauryl sulfate (for use as a wetting agent)	1 – 2%

Sorbitan esters (for use as a solubilizing agent or wetting agent for poorly soluble / insoluble active constituents in lipophilic bases)	0.1 – 10%

[Stott Supplementary 1/4.10 and Table 1]

Disintegration

78. As noted, the disintegration of a tablet can be influenced by well-known excipients, such as disintegrants. Disintegration can also be influenced by the type of process used to manufacture the tablet, the selected process parameters, and the amount of force used to compress the tablet. [Stott 1/56]

Tablet manufacture

79. A key decision to be made is the manufacturing method to be used and this will be decided early on in the formulation development process. The manufacturing method itself and selected process parameters can affect many of the tablet characteristics, including the disintegration, hardness, friability or dissolution rate of the tablet (and therefore bioavailability of the API). Excipients can be used to try to counter these effects. [Stott 1/96; Davies 1/58]

80. The manufacturing process typically involves mixing the API with the excipients and then compressing the resultant powder blend into a tablet. It may also include an agglomeration or granulation step used to impart favourable properties on the powder blend for subsequent processing steps. The ways in which tablets are made include direct compression, dry granulation and wet granulation. [Stott 1/45; Stott 1/96; Davies 1/58]

81. Direct compression involves compressing the powder blend into a tablet without further manipulation. In granulation primary powder particles are made to adhere to form granules containing multiple particles in order to modify their flow or compression properties or to facilitate the uniform distribution of the API. [Stott 1/96; Davies 1/58]

82. In dry granulation, the API and excipients are mixed and aggregated typically at high pressure to form granules without the use of a liquid. [Stott Supplementary 1/4.12]

83. Wet granulation involves the mixing of the API and excipients with granulating fluids, such as water, ethanol or isopropanol, and the subsequent removal of this liquid by drying. Water is commonly used as a granulating fluid. Binders are added to ensure that the API and other excipient particles aggregate and remain bound together once the granule is dry. [Stott Supplementary 1/4.13]

In vitro dissolution testing procedure

84. The dissolution testing conditions employed can affect the dissolution rate and hence the results obtained on measurement. The USP therefore sets out guidance on the dissolution test conditions that should be used by the Skilled Formulator, in order to ensure standardisation across the pharmaceutical industry. The USP identifies four different apparatus for testing the dissolution rate of solid oral dosage forms. In terms of apparatus selection, Apparatus I (USP I) and Apparatus II (USP II) are used most frequently for solid oral dosage forms, with Apparatus II being preferred for tablets. [Stott 1/99; Davies 1/115]

85. The following factors of dissolution testing are broadly standardised by the pharmacopoeias:

    i) Dissolution media – typical dissolution media include dilute hydrochloric acid (HCl) at a concentration of 0.1 N, buffers in the physiological pH range of approximately 1 to 7.4, simulated gastric or intestinal fluid (with or without enzymes), water and surfactants such as polysorbate 80, sodium lauryl sulfate and bile salts. The USP indicates that for very poorly soluble compounds, the medium used for dissolution testing may contain a surfactant to enhance drug solubility. [Stott 1/100/1]

    ii) Dissolution testing medium volume - usually between 500 mL and 1000 mL, the most commonly used volume is 900 mL. The volume should be large enough that the medium does not approach saturation which can slow down the dissolution process, or stop it altogether. [Stott 1/100.2]

    iii) Temperature - 37 ºC. [Stott 1/100.3]

    iv) Apparatus rotation speed. [Stott 1/100.4; Davies 1/115]

86. The Skilled Formulator will sample the dissolution test. The sample will then be analysed to determine the concentration of API present. [Stott 1/101]

Methods for particle size reduction

87. There are a number of different methods available to the Skilled Formulator to reduce the particle size by compression forces, impact, cutting and/or attrition. The equipment selected depends on, amongst other things, the target particle size (or sizes) and the properties of the material. A common technique is milling. Alternatively, a microniser can be used. Particle size reduction any lower than 1 µm would typically be referred to as "nanosizing" and is not typically used in tablet applications. [Stott 1/103.1; Stott Supplementary 1/4.4]

88. At the priority date, the Skilled Formulator would have been aware of different types of milling / micronizing methods using different types of mills such as cutter mills, hammer mills, pin mills and fluid energy mills can be

used for the milling/ micronizing step. Broadly speaking, each of these mills applies mechanical or kinetic energy to break down particles to a desired level. [Stott Supplementary 1/4.6]

89. The choice of an appropriate method would be dictated by various factors including the target particle sizes required, the physical nature of the particles and cost, and the method chosen would be performed by a person with expertise in particle size reduction techniques. [Stott Supplementary 1/4.8]

Bioequivalence

90. Bioequivalence is a measure of whether two different formulations containing the same amount of the same API are equivalent in terms of their absorption. Bioequivalence studies are typically based on AUC and C_{max} values although T_{max} may also be assessed. [Stott 1/105; Davies 1/129-130]

91. Bioequivalence is achieved when there is no statistically significant difference between the tested pharmacokinetic properties of two products. [Stott 1/106; Davies 1/130] The formulator would have a reasonable understanding of the basic methodology, and would be able to interpret the data generated from bioequivalence studies. [Stott 1/108; Davies 1/131]

The Biopharmaceutics Classification System

92. The Biopharmaceutics Classification System ("BCS") is a well-known method for classifying APIs according to their solubility and permeability. [Stott 1/78] It was originally published by a group of four leading formulation scientists in a well-known 1995 article, "*A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability*", G. Amidon et al., 12 Pharmaceutical Research 413 (1995) 12: 413-429 ("Amidon"). [Davies 1/88] The Skilled Formulator would be aware of this paper and the BCS system. [Stott 1/110; Davies 1/88]

93. In accordance with the BCS, APIs can be classified into four categories:

    i) Class I (high solubility and high permeability);

    ii) Class II (low solubility and high permeability);

    iii) Class III (high solubility and low permeability); and

    iv) Class IV (low solubility and low permeability).

    The classification is based on the API's dose/solubility ratio, and its permeability. [Stott 1/78; Davies 1/91]

94. An API has 'high solubility' under the BCS where the highest dose strength is soluble in 250 mL or less of aqueous media over the physiological pH range (of pH 1-7.5) at 37ºC, calculated using the API's equilibrium solubility value. This can also be described as a "dose-solubility ratio" of less than 250 mL. The 250 mL is supposed to represent the minimum volume anticipated in the

stomach when an oral dosage form is taken with a glass of water by a fasting patient. [Stott 1/111]

95. The other criterion the BCS uses to base its classification is the API's permeability. An API has 'high permeability' if it is at least 90% absorbed or where permeability has been established *in vitro*. [Stott 1/112; Davies 1/94]

96. The BCS was originally developed as a framework for procuring biowaivers. [Davies 1/90] In the context of obtaining a biowaiver, instead of conducting *in vivo* bioequivalence studies to prove bioequivalence to the earlier product, a biowaiver can be applied for to demonstrate bioequivalence by *in vitro* dissolution testing alone. [Stott 1/113]

DISPUTED COMMON GENERAL KNOWLEDGE

97. The parties also prepared a document indicating the disputes about CGK. Regrettably, they could not agree what was not agreed. This may be inevitable to a minor degree in some cases, but one would hope that it would happen only in small measure, and at the periphery.

98. The situation when opening skeletons were put in was that the parties did identify by agreement two disputed issues on the clinicians' CGK; others were not agreed. None of them matters any longer because the obviousness arguments all turn on formulation. So I am not going to resolve them.

99. On the formulation side, one disputed issue was put forward by the Claimants, broken into three sub-issues. BMS put forward ten. The importance of these all changed during the trial and I am going to organise the CGK disputes in the way I think most helpful to identifying the real issues at the end of the trial.

The implications of the BCS system

100. The central arguments on the formulator's CGK concerned the BCS system. There were a number of aspects to this which are interrelated.

101. It is worth reiterating the starting point for these disputes:

    i) It was common ground that the BCS system itself was CGK.

    ii) It was common ground that at an early stage the formulator working on apixaban would assess its equilibrium solubility and that at doses of 2.5mg and 5mg it would be a Class III drug (high solubility, low permeability). It is in fact relatively insoluble as a compound *per se*, but because the BCS system takes dose into account, it would count as "high" solubility. This was not CGK as such, rather something that would be routinely found out once the formulator started work on apixaban, but it forms an important part of understanding why the issues matter.

iii) It was common ground that it was CGK that equilibrium solubility and dissolution rate are different concepts. Higher solubility tends to imply faster dissolution but that is not always so.

iv) It was CGK that in the case of BCS Class III drugs where "high" solubility was accompanied by a fast dissolution rate, the great majority of the drug would dissolve in the stomach, and it would therefore act essentially the same as a solution, with absorption depending only on permeation. This would be the ideal.

v) I believe BMS accepted, but I anyway would find, that it was CGK that, by contrast, it was *possible* that a "high" solubility drug in fact would have a rather slow dissolution rate, slow enough that the dissolution rate would limit bioavailability.

102. A nuance is that even where some drug was not dissolved in the stomach, then permeation might still be slow enough that it was the limiting factor, with the rest of the drug dissolving in the gut.

103. The key disputed matters on this aspect of CGK were:

i) The degree of confidence that the formulator would have in a BCS Class III drug having a sufficiently fast dissolution rate that it would not limit absorption;

ii) Whether the formulator would think that rapid dissolution should be ensured;

iii) If so, what dissolution rates the formulator would have in mind;

iv) Would the formulator want "solution-like" behaviour;

v) The regulatory position and whether having a fast dissolution rate would help secure approval for production changes and the like ("SUPAC") and biowaivers.

104. These points were all explored in the context of a number of contemporaneous documents. I will deal with them in chronological order, save that I group two EMEA documents together.

Amidon

105. Amidon is a 1995 paper entitled "*A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of* in Vitro *Drug Product Dissolution and* in Vivo *Bioavailability*", and which provided the basis for the BCS system. It was clearly CGK, as was common ground before me.

106. Amidon defined the four classes in Table II:

Table II. *In Vitro–in Vivo* (IVIV) Correlation Expectations for Immediate Release Products Based on Biopharmaceutics Class

Class	Solubility	Permeability	IVIV Correlation Expectation*
I	High	High	IVIV correlation if dissolution rate is slower that gastric emptying rate, otherwise limited or no correlation.
II	Low	High	IVIV correlation expected if *in vitro* dissolution rate is similar to *in vivo* dissolution rate, unless dose is very high (see discussion).
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIV correlation with dissolution rate.
IV	Low	Low	Limited or no IVIV correlation expected

* A limited correlation means that the dissolution rate while not rate controlling may be similar to the absorption rate and the extent of correlation will depend on the relative rates.

107. And it contained the following commentary on Case 1 and Case 3 (which correspond to Class I and Class III):

> ***Case 1.*** *High Solubility–High Permeability Drugs*. This is the case where the drug is well absorbed (though its systemic availability may be low due to first pass extraction/metabolism) and the rate limiting step to drug absorption is drug dissolution or gastric emptying if dissolution is very rapid. In this case the dissolution profile must be well defined and reproducible to insure bioavailability. For immediate release dosage forms that dissolve very rapidly, the absorption rate will be controlled by the gastric emptying rate and no correlation with dissolution rate is expected. In the fasted state the gastric emptying rate is both volume and motility phase dependent with a gastric half emptying time of between 5 and 22 min., and an overall average of 12 and 22 min. for administered volumes of 50 and 200 ml respectively, Figure 3 (9). This suggests that a dissolution specification for immediate release (IR) dosage forms of perhaps 85% dissolved in less than 15 min. may insure bioequivalence[9].

…

> ***Case 3.*** *High Solubility–Low Permeability Drugs*. For this class of drugs, permeability is the rate controlling step in drug absorption. While the dissolution profile must be well defined, the simplification in dissolution specification as in Class 1 is applicable for immediate release dosage forms where drug input to the intestine is gastric emptying rate controlled. Both the rate and extent of drug absorption may be highly variable for this class of drugs, but if dissolution is fast i.e. 85% dissolved in less than 15 min., this variation will be due to the variable gastrointestinal transit, luminal contents, and membrane permeability rather than dosage form factors.

FDA Guidance 1997

108. The FDA published a 1997 document entitled "*Guidance for Industry*", subtitle "*Dissolution Testing of Immediate Release Solid Oral Dosage Forms*". The following parts were relied on in particular at trial and the subject of oral evidence:

I. INTRODUCTION

This guidance is developed for immediate release (IR) dosage forms and is intended to provide (1) general recommendations for dissolution testing; (2) approaches for setting dissolution specifications related to the biopharmaceutic characteristics of the drug substance; (3) statistical methods for comparing dissolution profiles; and (4) a process to help determine when dissolution testing is sufficient to grant a waiver for an in vivo bioequivalence study. This document also provides recommendations for dissolution tests to help ensure continuous drug product quality and performance after certain postapproval manufacturing changes. Summary information on dissolution methodology, apparatus, and operating conditions for dissolution testing of IR products is provided in summary form in Appendix A. This guidance is intended to complement the SUPAC - IR guidance for industry: *Immediate Release Solid Oral Dosage Forms: Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*, with specific reference to the generation of dissolution profiles for comparative purposes.

II. BACKGROUND

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolution may be relevant to the prediction of in vivo performance. Based on this general consideration, in vitro dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules, are used to (1) assess the lot-to-lot quality of a drug product; (2) guide development of new formulations;

and (3) ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process.

Current knowledge about the solubility, permeability, dissolution, and pharmacokinetics of a drug product should be considered in defining dissolution test specifications for the drug approval process. This knowledge should also be used to ensure continued equivalence of the product, as well as to ensure the product's *sameness* under certain scale-up and postapproval changes.

New drug applications (NDAs) submitted to the Food and Drug Administration (FDA) contain bioavailability data and in vitro dissolution data, that, together with chemistry, manufacturing, and controls (CMC) data, characterize the quality and performance of the drug product. In vitro dissolution data are generally obtained from batches that have been used in pivotal clinical and/or bioavailability studies and from other human studies conducted during product development. Acceptable bioequivalence data and comparable in vitro dissolution and CMC data are required for approval of abbreviated new drug applications (ANDAs) (21 CFR 314.94). The in vitro specifications for generic products should be established based on a dissolution profile. For new drug applications, as well as generic drug applications, the dissolution specifications should be based on acceptable clinical, bioavailability, and/or bioequivalence batches.

> **III. BIOPHARMACEUTICS CLASSIFICATION SYSTEM**
>
> Based on drug solubility and permeability, the following Biopharmaceutics Classification System (BCS) is recommended in the literature (Amidon 1995):
>
> Case 1: High Solubility - High Permeability Drugs
> Case 2: Low Solubility - High Permeability Drugs
> Case 3: High Solubility - Low Permeability Drugs
> Case 4: Low Solubility - Low Permeability Drugs
>
> This classification can be used as a basis for setting in vitro dissolution specifications and can also provide a basis for predicting the likelihood of achieving a successful in vivo-in vitro correlation (IVIVC). The solubility of a drug is determined by dissolving the highest unit dose of the drug in 250 mL of buffer adjusted between pH 1.0 and 8.0. A drug substance is considered highly soluble when the dose/solubility volume of solution are less than or equal to 250 mL. High-permeability drugs are generally those with an extent of absorption that is greater than 90% in the absence of
>
> documented instability in the gastrointestinal tract or those whose permeability has been determined experimentally. The BCS suggests that for high solubility, high permeability (case 1) drugs and in some instances for high solubility, low permeability (case 3) drugs, 85% dissolution in 0.1N HCl in 15 minutes can ensure that the bioavailability of the drug is not limited by dissolution. In these cases, the rate limiting step for drug absorption is gastric emptying.
>
> The mean T50% gastric residence (emptying) time is 15-20 minutes under fasting conditions. Based on this information, a conservative conclusion is that a drug product undergoing 85% dissolution in 15 minutes under mild dissolution test conditions in 0.1N HCl behaves like a solution and generally should not have any bioavailability problems. If the dissolution is slower than gastric emptying, a dissolution profile with multiple time points in multimedia is recommended.
>
> In the case of low solubility/high permeability drugs (case 2), drug dissolution may be the rate limiting step for drug absorption and an IVIVC may be expected. A dissolution profile in multiple media is recommended for drug products in this category. In the case of high solubility/low permeability drugs (case 3), permeability is the rate controlling step and a limited IVIVC may be possible, depending on the relative rates of dissolution and intestinal transit. Drugs in case 4 (i.e., low solubility/low permeability drugs) present significant problems for oral drug delivery.

109. I need not quote the text, but note that section VI of the document deals with the relevance of dissolution testing and profiles for "SUPAC-IR", which concerns the regulatory requirements surrounding changes to manufacturing site, or scale, and for "biowaivers" for lower strengths of a dosage form.

FDA guidance 2000

110. The FDA issued another guidance document in 2000. It was also entitled "*Guidance for Industry*", but with the subtitle "*Waiver of In Vivo Bioavailability Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*". It had a more intense and detailed focus on biowaivers and the procedures for getting them than did the 1997 document. Its contents relevant to this trial are very similar to the 1997 document and so I will limit how much I quote. The key section the subject of evidence and argument was this:

> **C. Dissolution**
>
> In this guidance, an IR drug product is considered *rapidly dissolving* when no less than 85% of the labeled amount of the drug substance dissolves within 30
>
> minutes, using *U.S. Pharmacopeia* (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

111. So this was a slightly less stringent parameter than the 85% in 15 minutes contained in the 1997 document.

112. I note that both FDA documents cited Amidon.

EMEA guidance 2001 and 2010

113. In Europe there was similar guidance for like reasons. A specific document discussed at trial was an EMEA 2001 "*Note for Guidance on the Investigation of Bioavailability and Bioequivalence*"; it was exhibited to both formulator experts' reports but not the subject of specific cross-examination. I was also taken to a 2010 document called "*Guideline on the Investigation of Bioequivalence";* this was only introduced for the cross-examination and not put in with any expert's report. So the coverage of these in evidence was a little patchy and it was not really clear that the second document would have been CGK by the priority date. Each document refers to biowaivers being potentially available if 85% of the drug is dissolved in 15 minutes. The 2010 document also allows for the possibility of 85% dissolution in 30 minutes, with measurements at more time points being required.

Aulton 2007

114. "*Aulton's Pharmaceutics - The Design and Manufacture of Medicines*" is a standard work and, I find, a source of CGK of the classic kind. I was referred to the 3rd edition, from 2007. Both experts had relied on it.

115. The following text was relied on:

BIOPHARMACEUTICAL CLASSIFICATION SCHEME

As a result of the plethora and variability of biopharmaceutical properties of existing and potential drugs, an attempt has been made to arrange drugs in a small number of groups. A scientific basis for a biopharmaceutical classification scheme has been proposed that classifies drugs into four classes according to their aqueous solubility across the gastrointestinal pH range and their permeability across the gastrointestinal mucosa (Amidon et al 1995). Two of the four potential barriers to absorption (see Fig. 22.1) are thus addressed by the scheme.

The scheme was originally proposed for the identification of immediate-release solid oral products for which in vivo bioequivalence tests may not be necessary. It is also useful to classify drugs and predict bioavailability issues that may arise during the various stages of the development process and is utilized by the regulatory authorities.

The four classes are defined in terms of high and low aqueous solubility and high and low permeability.

- Class I – high solubility/high permeability
- Class II – low solubility/high permeability
- Class III – high solubility/low permeability
- Class IV – low solubility/low permeability.

A drug is considered to be highly soluble where the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range 1–8. The volume is derived from the minimum volume anticipated in the stomach when a dosage form is taken in the fasted state with a glass of water. If the volume of aqueous media needed to dissolve the drug in pH conditions ranging from 1 to 8 is greater than 250 mL then the drug is considered to have low solubility. The classification therefore takes into account the dose of the drug as well as its solubility.

A drug is considered to be highly permeable when the extent of absorption in humans is expected to be greater than 90% of the administered dose. Permeability can be assessed using one of the methods discussed earlier in this chapter that has been calibrated with known standard compounds or by pharmacokinetic studies.

Class I drugs Class I drugs will dissolve rapidly when presented in immediate-release dosage form, and are also rapidly transported across the gut wall. Therefore (unless they form insoluble complexes, are unstable in gastric fluids or undergo presystemic clearance) it is expected that such drugs will be rapidly absorbed and thus show good bioavailability. Examples of class I drugs are the β-blockers propranolol and metoprolol.

Class II drugs In contrast, for drugs in class II, the dissolution rate is liable to be the rate-limiting step in oral absorption. For class II drugs it should therefore be possible to generate a strong correlation between in vitro dissolution and in vivo absorption (discussed earlier in this chapter). Examples of class II drugs are the non-steroidal antiinflammatory drug ketoprofen and the antiepileptic carbamazepine. This class of drug should be amenable to formulation approaches to improve the dissolution rate and hence oral bioavailability.

Class III drugs Class III drugs are those that dissolve rapidly but which are poorly permeable. Examples are the H_2-antagonist ranitidine and the β-blocker atenolol. It is important that dosage forms containing class III drugs release them rapidly in order to maximize the amount of time these drugs, which are slow to permeate the gastrointestinal epithelium, are in contact with it.

Class IV drugs Class IV drugs are those that are classed as poorly soluble and poorly permeable. These drugs are liable to have poor oral bioavailability or the oral absorption may be so low that they cannot be given by the oral route. The diuretics hydrochlorothiazide and frusemide are examples of class IV drugs. Forming prodrugs of class IV compounds or finding an alternative route of delivery are approaches that have to be adopted to significantly improve their absorption into the systemic circulation.

116. This is more general than the other documents; it does not contain any concrete numerical indications of what rate of dissolution should be targeted. BMS relied on it as saying that the BCS system was a way to classify drugs and predict bioavailability and that in relation to Class III drugs the reference to "release" concerned disintegration because sufficiently rapid dissolution could be assumed. The Claimants took the position that "release" included dissolution and that the reader would understand that dissolution needed to be ensured and would not be left to chance. I agree there is some ambiguity; I prefer the Claimants' position but do not think it matters very much. In any event, any ambiguity over this text has to be seen in the overall context of all the documents.

Abrahamsson 2009

117. This was a chapter entitled "*Application of the Biopharmaceutics Classification System Now and in the Future*" in a book entitled "*Drug Bioavailability*". It was put in as an exhibit by Prof Davies.

118. The arguments over Abrahamsson were quite detailed and rather fiddly. As with the slight ambiguity in Aulton, I think the position as to CGK has to be considered in the round in the light of all the documentary sources. I also think that the end point in relation to Abrahamsson is not materially different from the other documents. However, since it was the focus of quite a lot of argument and in case it should matter, I will deal with the points taken.

119. Abrahamsson contains the following:

19.6.2.3 ***In Vitro/In Vivo* Correlation**

In vitro dissolution testing is an important tool in the development of solid drug products as well as in batch quality controls. The aim of the test is to see that the drug is appropriately dissolved in the GI tract and made available for absorption. It is therefore highly desirable that the *in vitro* tests provide data that correlate to the *in vivo* situation. However, attainment of IVIVC has often failed, and the concept of IVIVC has been challenged.

The BCS could be used as a framework for predictions when IVIVC could be expected for solid immediate-release products as summarized in Table 19.5. It is

Table 19.5 Expectations for *in vitro/in vivo* correlations for IR products based on BCS.

Class	IVIVC expectations
I. High *S*/High P_{eff}	No IVIVC until product dissolution becomes slower than gastric emptying
II. Low *S*/High P_{eff}	IVIVC should be possible to establish provided that *in vitro* relevant dissolution test method is used and drug absorption is limited by dissolution rate rather than saturation solubility
III. High *S*/Low P_{eff}	No IVIVC until product dissolution becomes slower than intestinal permeability
IV. Low *S*/Low P_{eff}	Low chance for IVIVC

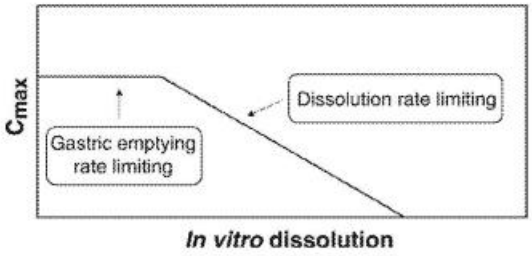


Figure 19.12 Principal level *C in vitro/in vivo* correlation for IR formulation of class I substance.

important to realize that the *in vitro* dissolution test only models the release and dissolution of the active drug substance from the formulation and it is only when these processes are rate limiting in the absorption process that IVIVC can be expected. In the case of class I drugs, the complete dose will be dissolved already in the stomach and, provided that the absorption over the gut wall is negligible, the gastric emptying of the dissolved drug will be the rate-limiting step. This is clearly not a factor that is included in the *in vitro* dissolution test. Thus, no IVIVC should be expected for class I drugs as long as the release of drug is faster than the gastric emptying. The half-life of gastric emptying of fluids in the fasting state is normally about 10 min though this could vary because of several factors such as the timing of drug administration in relation to gastric motility phase and fluid volume [84]. The relationship between *in vitro* dissolution, described as the time to dissolve half of the dose (t50%), and the peak plasma concentration (C_{max}) for a fictive class I drug is exemplified in Figure 19.12. This type of *in vitro/in vivo* relationship should only be expected for variables that are influenced by the absorption rate, whereas variables reflecting the extent of bioavailability, for example, AUC, should be independent of dissolution rate.

120. Thus there is a general introduction of the BCS system and an explanation of IVIVC ("*in vitro in vivo* correlation"). It may be beguiling to think, on first encountering the term, that IVIVC would be an unqualifiedly good thing because it would enable a prediction about the *in vivo* situation to be made from an *in vitro* measurement. In fact the position is very different: for BCS Class I drugs, one wants fast dissolution such that absorption of the drug is *only* affected by gastric emptying. Provided the dissolution rate remains above that level, a change to it will not affect *in vivo* behaviour – there is no correlation - and that is a good thing.

121. The authors seek to illustrate this by reference to Figure 19.12, reproduced above. It is potentially a bit confusing because the x-axis, "*In vitro* dissolution", is time to dissolve 50% of the drug, so dissolution rate is dropping rather than increasing from left to right.

122. There is also a problem in understanding Figure 19.12 because it relates to "a fictive class I drug". It is unclear whether this means a variety of fictive Class I drugs with different dissolution rates, or a single Class I drug whose dissolution rate can be varied, perhaps by changing formulation. Before me, BMS argued that it was a single drug and said that Dr Stott had accepted as much. The Claimants said it was a range of drugs. I do not think Dr Stott did accept that it was a single drug, or at least not clearly so. However, so far as it matters (and I think it does not), my view is that the text is simply not

clear as to whether it is one drug or a number. The authors' intention was to give a very general indication that there would be a range of dissolution rates, represented by the plateau in the left hand side of the figure, over which gastric emptying would be the limiting factor, but then there would be a tipping point, beyond which dissolution rate would increasingly limit absorption.

123. The fact that the authors' intention was as general as this is supported by the fact that there are no values on either axis.

124. Figure 19.12 and the text that I have quoted above concern class I drugs. Class III drugs are addressed on the following page:

> The absorption of class III drugs is limited by their permeability over the intestinal wall. Thus, since this process is not at all modeled by the classical *in vitro* dissolution test, no IVIVC should be expected. When the drug dissolution becomes slower than the gastric emptying, a reduction of the extent of bioavailability will be found in slower dissolution rates because the time when the drug is available for permeation over the gut wall in the small intestine will then be reduced. Thus, the same type of relationship can be expected between bioavailability and *in vitro* dissolution as shown in Figure 19.12 for a class I drug.

125. This is a very condensed explanation seeking to transpose Figure 19.12 to the case of a Class III drug where permeability is low. In my view it would be plain to the reader that Figure 19.12 could not simply be applied without modification for a Class III drug, because the figure does not show permeability or its effect. In my view the authors were just saying, as I think is clear from the text, that for class III drugs there would be a conceptually similar tipping point where the dissolution rate became slow enough that the time for permeation would be reduced, and more so as dissolution became yet slower.

126. None of this is a criticism of the authors of Abrahamsson. Had they been trying to answer exactly the same questions as arise at this trial they no doubt would have gone into more detail and expressed themselves differently. They were just dealing with matters at a rather more general and conceptual level.

Analysis of the implications of the BCS system

127. BMS characterised its position in its written closing submissions as follows (emphasis in the original):

> 38. The dispute therefore concerns whether or not it was CGK that the *dissolution rate* (as distinct from disintegration) of a BCS Class III drug could hinder its rate of absorption. For the avoidance of doubt, it is not necessary to resolve (at least on BMS' case) the issue of whether or not the dissolution rate (as distinct from disintegration) of a BCS Class III drug *could* hinder its rate of absorption, the issue is whether or not this was CGK.

128. Contrary to BMS's position, I think it is useful to start with whether the dissolution rate could in fact hinder absorption. The answer is quite clearly

that it could. It is a basic proposition because if dissolution is too slow then not all the drug is available to permeate the gut wall when, or soon after, it leaves the stomach. This is so basic that in my view it must also be CGK; any formulator would understand it and the expert evidence supported it. To be fair, Counsel for BMS backed away in oral closing submissions from the proposition that the formulator might not understand that slow dissolution could affect absorption. The more realistic line that BMS took, and which Prof Davies had maintained, was that with a Class III there would be a very high degree of confidence that it would dissolve fast enough that it would not hinder absorption. He also said that the degree of confidence would be so high that the formulator would not trouble to test IDR at an early stage – I deal with that below.

129. As I understood it, Counsel for BMS accepted that a drug's being Class III could not guarantee sufficiently rapid dissolution, if only because the classification depends on equilibrium solubility, which tends to be correlated to dissolution rate, but is not the same thing, and so sometimes a soluble drug may be slow to dissolve. In any event, even if not accepted that would be my finding, to the CGK standard.

130. These basic propositions are, in my view, all supported by and consistent with the documents that I have quoted above. They tend to explain matters in terms of having certainty: that if the dissolution rate is in fact established to be fast (whether 85% in 15 minutes or in 30 minutes) that there will not be a problem. But the formulator would understand that this clearly implies that if dissolution gets slower, there is a risk of its limiting absorption.

131. Understood in this light, the disagreement between the experts was more a matter of emphasis than a binary one. Prof Davies' consistent position was that the formulator's confidence for a Class III drug would be high, and so they would not regard 85% in 15 or 30 minutes, or any similar values, as a necessity or as an invariable criterion to be adopted at the start of a project. Adequately fast dissolution, he said, might be achieved with less demanding figures.

132. I agree that if they thought about it, the skilled formulator would accept that such was possible. But based on Dr Stott's evidence, and what I think is a very clear picture that emerges from the documents I have referred to above, I conclude that the CGK was that the safe and natural way to proceed with a Class III drug was to aim and test for a dissolution rate of about either 85% in 15 minutes or in 30 minutes. With an expensive drug development process there would be no incentive to take a chance, and every reason to play it safe. The motivation to play safe would be for regulatory reasons to do with SUPAC and the possibility of a later biowaiver, and more fundamentally simply to have confidence that there would be one less thing to worry about going wrong.

133. I note that this conclusion is fully consistent with what Prof Davies said in his Canadian evidence. For example, in a report of 21 August 2020, in a section dealing with CGK, he wrote:

> 87. For BCS Class III drugs, rapid dissolution (85% in 15 minutes or faster in 0.1N HCI) is the target for solution-like behaviour:
>
> > Case 3. High Solubility-Low Permeability Drugs. For this class of drugs, permeability is the rate controlling step in drug absorption. While the dissolution profile must be well defined, the simplification in dissolution specification as in Class 1 is applicable for immediate release dosage forms where drug input to the intestine is gastric emptying rate controlled. Both the rate and extent of drug absorption may be highly variable for this class of drugs, but if dissolution is fast i.e. 85% dissolved in less than 15 min., this variation will be due to the variable gastrointestinal transit, luminal contents, and membrane permeability rather than dosage form factors.[30]

134. Reference 30 is Amidon. Prof Davies sought to qualify this by saying that it was in response to the other side's experts' reports in that case but I could not see how that would make any difference or qualify the simple meaning of his statement about "target". I also note the reference to "solution-like behaviour" which supports my view that it was a known concept, and desirable.

135. It is convenient at this point to sweep up two other points on the evidence, which are related:

    i) BMS said that "solution like behaviour" had not been raised by Dr Stott in his written evidence.

    ii) BMS said that 85% dissolution in 15 minutes had not been raised by Dr Stott in his written evidence and been sprung on BMS only in the cross-examination of Prof Davies.

136. I reject both of these points. In his first report at e.g. paragraph 114 Dr Stott had referred to Amidon's teaching that "all the API dissolves in the stomach and the rate of absorption is controlled by when the API leaves the stomach". This is talking about solution like behaviour in different words. I also repeat that Prof Davies had no trouble with the concept and had used the expression in his Canadian evidence to which I have referred above.

137. In the same paragraph Dr Stott referred to 85% in 15 minutes and noted in a footnote that the FDA later reduced this to 85% in 30 minutes. There were many other occasions when Dr Stott referred to 85% in 30 minutes but it is wrong to say that he did not also raise 85% in 15 minutes.

What testing and when

138. The technique of IDR testing was part of the agreed CGK, as described above. Prof Davies' evidence was that for a Class III drug he would probably not bother with it, and certainly not at an early stage. It is not an important point given the nature of the obviousness argument as explained below, but I prefer Dr Stott's evidence that IDR testing would be done, including for Class III

drugs, and generally at an early stage. I think this conclusion is also consistent with the somewhat cautious attitude I have described above in relation to dissolution rates.

139. Dr Stott also described something he called "kinetic testing". This was a sort of shortcut in which aliquots would be taken at various time points during equilibrium solubility testing so as to give a rough idea of dissolution rate. It was said by BMS that Dr Stott had not mentioned kinetic testing in his written evidence. I find that he had, albeit rather briefly. More importantly, Prof Davies disputed that it was CGK. On this point, I agree with BMS that the technique was not CGK. I do not doubt that Dr Stott had used it, but that does not mean it was widely used or known. Prof Davies said at one point that he supposed that some industry players might use it, but in context he did not mean that he accepted that it was widely used. There were no documents referring to it as CGK.

140. It was common ground that dissolution rate would have to be tested once the formulator reached the stage of having prototype formulations.

Techniques to address slow dissolution rates

141. There was no dispute that the CGK was that the first thing that the formulator would do if it were found that prototype formulations were too slow to dissolve was to assess and if necessary improve the disintegration of the tablet. This makes sense because, as was common ground, if the drug did not escape the tablet in the first place it would not have the opportunity to dissolve and other tweaks would not help.

142. It was agreed to be CGK that particle size reduction was a way to improve slow dissolution rates. Other ways existed such as changing or improving excipients. BMS said the latter would be preferred to the former. I do not think any such *per se* preference was made out. Both approaches would be in the CGK notional "toolkit" of the formulator.

Typical particle sizes

143. Aulton says that most pharmaceutical powders have crystals in the range of 0.5-300µm, but that distributions are often smaller, such as 0.5-50µm, to help blend homogeneity.

144. The experts agreed that there comes a lower limit where matters such as handling difficulties, aggregation and the like start to pose problems. It is hard to be precise, but I find that the CGK was that that lower limit was at about 10µm.

145. Prof Davies said that the formulator would not reduce particle size so readily with Class III drugs as they would with Class II or Class IV; subject to that limitation he accepted that Aulton's range was CGK. I do not think that the difference in approach with different Classes was soundly based in any document and it may have been a consequence of his attitude that the

formulator would have an overwhelmingly high degree of confidence of the dissolution rate of Class III drugs, which I have rejected.

146. I therefore find that Aulton's suggestion was CGK. Dr Stott's evidence was that 10-100µm was typical. I think this reflected the concern mentioned above about very small particle sizes, and an upper limit which is somewhere between the two values mentioned by Aulton (50µm and 300µm).

147. In any event, and cutting to the chase, the D_{90} value of 89µm in claim 1 of `021 is well within the CGK of the formulator and would be regarded by him or her as completely normal and unsurprising.

THE TEACHING OF `021

148. `021 seeks to explain the invention first of all in paragraphs [0005], [0006], [0011]. [0005] says:

> [0005] The aqueous solubility (40 µg/ml at all physiological pH) of apixaban suggests that the tablets with less than 10 mg apixaban (dose/solubility ratio = 250 mL) should not demonstrate dissolution rate limited absorption since dissolution rate limitations are only expected when the dose/solubility ratio is greater than 250 mL. Based on this dose and solubility consideration, the particle size of the compound should not be critical for achieving consistent plasma profiles, according to the prediction based on the Biopharmaceutics Classification System (BCS; Amidon, G.L. et al ., Pharmaceutical Research, 12: 413-420 (1995)). However, it was determined that formulations that were made using a wet granulation process as well as those using large particles of apixaban drug substance resulted in less than optimal exposures, which can present quality control challenges.

149. The last sentence of [0005] is referring to tables 3 to 5 which were not said to be relevant to my task. [0006] and [0011] are as follows:

> [0006] Surprisingly and unexpectedly, it has been found that compositions for tablets comprising up to 5 mg apixaban particles having a D_{90} (90% of the volume) less than 89 microns (µm) lead to consistent in-vivo dissolution in humans (at physiologic pH), hence, consistent exposure and consistent Factor Xa inhibition that will lead to consistency in therapeutic effect. Consistent exposure is defined as that where in-vivo exposure from tablets is similar to that from a solution and not affected by the differences in dissolution rates. Accordingly, the invention provides a tablet comprising up to 5 mg crystalline apixaban particles having a D_{90} less than 89 µm, as measured by laser light scattering, and a pharmaceutically acceptable diluent or carrier, wherein the formulation exhibits dissolution properties such that an amount of the drug equivalent to at least 77% dissolves within 30 minutes, wherein the dissolution test is performed in an aqueous media buffered to a pH range 1 to 7.4 and controlled at 37° C. It is noted that the notation D_x means that X% of the volume of particles have a

> diameter less than a specified diameter D. Thus a D_{90} of 89 µm means that 90% of the volume of particles in an apixaban composition have a diameter less than 89 µm.
>
> …
>
> [0011] The formulations of this invention are advantageous because, *inter alia*, as noted above, they lead to consistent human in-vivo dissolution. The invention is surprising in this respect, however, in that exposures are variable even though apixaban has adequate aqueous solubility that would allow the drug to dissolve rapidly. That is, one would expect that the dissolution rate for a drug that has high solubility (as defined by the Biopharmaceutical Classification System) would not be limited by the particle size. It has surprisingly been found, however, that the particle size that impacts apixaban absorption rate is about a D_{90} of 89 µm. Thus apixaban can be formulated in a composition having a reasonable particle size using a dry granulation process, to achieve and maintain relatively fine particles to facilitate consistent in vivo dissolution.

150. Prof Davies said that paragraph [0011] contained a mistake and that "dissolution rate" should instead have said "absorption". The Claimants responded that it was unclear. I agree with Prof Davies that the reader would think there was probably a mistake and "absorption" is quite likely what was meant. I agree with the Claimants to the more limited extent that one cannot be entirely sure as to the error or what was intended. I think the overall gist about what is said to be inventive or "surprising" is reasonably clear, but I do not agree that it is surprising.

151. The statements in these paragraphs are consistent with the case advanced by BMS at trial, but that does not mean that they are correct. As I explain in relation to CGK and when I come to obviousness below, the formulator would realise by routine means that apixaban was a Class III drug and would appreciate that that meant it was "high" solubility as the BCS uses that term. But he or she would know that that did not guarantee that the dissolution rate did not affect bioavailability. They would know that it might have an effect if it was too slow. They would not be particularly surprised that apixaban had turned out to be a case of a Class III drug where dissolution rate affected absorption, and they would not be at all surprised that the patentee had tested that experimentally.

152. Of course, how the skilled formulator would react to a patent's teaching is not part of the assessment of obviousness. Obviousness has to be assessed without knowledge of the patent. I am dealing with these paragraphs because of the way that BMS relied on them and sought to characterise the inventive step: as the realisation that for apixaban, dissolution rate does affect bioavailability.

153. Paragraph [0013] gives test conditions for assessing dissolution rate. Nothing turns on the details of this.

154. Paragraphs [0014]-[0017] give various definitions which I need not go into because of the agreed CGK.

155. Paragraphs [0018]-[0020] give details of the synthesis of apixaban and crystallographic parameters of two forms of it. Again, nothing turns on this.

156. Paragraphs [0021]-[0024] give information about granulation processes and refer to the use of a surfactant. This is all consistent with the agreed CGK. Paragraph [0025] says that the apixaban tablets may contain 2.5 or 5 mg of the active substance, usually taken orally twice a day. As will appear below, these are among the dosing parameters disclosed in Carreiro.

157. Paragraphs [0026]-[0029] give some experimental details and reiterate the use of a surfactant.

158. The experimental data begins at [0031] to [0033], which relate to some tests with dry and wet granulated tablets, but as I have already said, the parties' arguments did not focus on this so I pass over it.

159. Paragraph [0034] introduces Table 6 and Table 6a as follows:

> [0034] Table 6 and Table 6a provide the dissolution data from tablets made with different manufacturing processes (comparative wet and dry granulation according to the invention) and drug substance different particle sizes. As shown in Table 6, apixaban tablets that had 77% dissolved in 30 minutes or 86% dissolved in 30 minutes both had AUC values that met bioequivalence criteria (Confidence Interval between 80% to 125%) when compared to the tablets that had 89% dissolved in 30 minutes. Similar rank order of the dissolution rates was observed for these tablets (A, B & C) when tested in 0.1N HCl.

160. The argument before me focused on Table 6 which, by contrast with Table 6a, uses a surfactant (SLS). The role of a surfactant is, as I have said, explained in [0024] and [0028], although the skilled formulator would know it from their CGK in any event.

161. Table 6 is as follows:

Table 6

Time (minutes)	% apixaban dissolved (USP II, 75 rpm, 0.05% SLS in 50mM phosphate, pH 6.8)		
	Wet Granulation 2 x 2.5 mg Tablets (A)	Wet Granulation 2 x 2.5 mg Tablets (B)	Dry Granulation 2 x 2.5 mg Tablets (C)
10	63	42	70
20	79	64	84
30	86	77	89
45	91	87	94
60	94	93	96
Cmax (ng/mL)	101.8 (21)	87.8 (24)	108.3 (24)
AUC(INF) (ng*hr/mL)	1088 (32)	1030 (25)	1153 (26)
Geomean (CV%) are presented for Cmax and AUC(INF)			

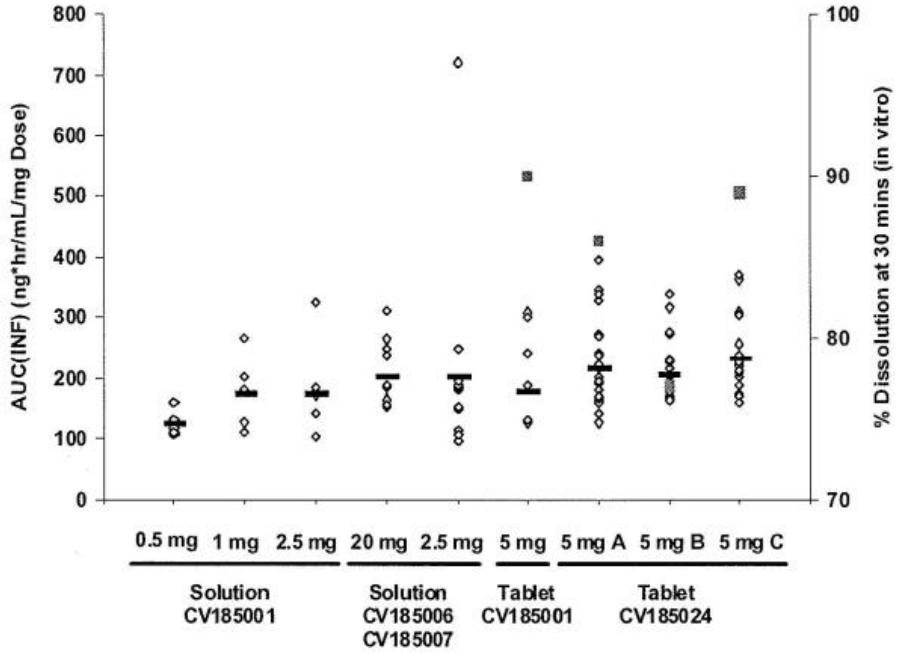
162. Tablets A and B are said to have been made by wet granulation and Tablet C by dry granulation. Other than that, details of their composition are not given, and nor is particle size. It can be seen that Tablet B was the slowest-dissolving. By contrast, the priority document for `021 did give particle sizes. The Claimants made a criticism of this, and BMS responded that one does not need composition or indeed particle size to determine whether dissolution rate affects bioavailability (which is the subject of the experiments that follow, as described below). I agree with BMS on this, although it does not affect my reasoning, and it is rather odd to have removed the particle sizes.

163. Paragraph [0035] gives some further explanation and introduces Figures 1 and 2 which give data for C_{max} and AUC for solutions and for tablets A to C:

> [0035] The results of clinical studies demonstrated that, for tablets with similar dissolution rates (89% and 86% in 30 min at pH 6.8 phosphate buffer containing 0.05% SLS), Cmax and AUC of the coated Phase 3 tablet (C) relative to the uncoated Phase 2 tablet (A), met bioequivalence criteria. Tablets with different dissolution rates (77% and 86% in 30 min) had similar AUCs, but did not meet equivalence criteria for Cmax. The lower boundary of the 90% confidence interval of ratio of geometric mean Cmax was 0.788, indicating that the rate of absorption, as defined by Cmax, was lower for the slower dissolving tablet (77% in 30 min). Since the oral bioavailability from these tablets is shown to be comparable to that from solution (see Figures 1 and 2 below), this dissolution rate (77% in 30min) is defined as the threshold for achieving consistent exposure.

164. Figure 1 is as follows (it is not necessary to reproduce Figure 2 for the purposes of this judgment):

Figure 1: Scatter Plot of Individual Dose-Normalized AUC(INF) Values for Solutions (CV185001, CV185006, and CV185007) and Tablets (CV185001 and CV185024)



Source: CV185001, CV185006, CV185007, and CV185024 Clinical Study Reports

The solid line represents the geometric mean of AUC(INF) and the solid square represents the average %in-vitro dissolved at 30 minutes (using QC method in Table 1.2C). The X-axis represents the dose administered.

For CV185024, 5 mg A = Apixaban Phase 2 tablet (86% dissolution) 2x2.5 mg (reference formulation), 5 mg B = Apixaban Phase 2 tablet (77% dissolution) 2x2.5 mg, 5 mg C = Apixaban Phase 3 tablet (89% dissolution) 2x2.5 mg.

165. From this it can be seen that the slower dissolving tablet (77% in 30 minutes) is not quite bioequivalent to a solution, but it is on the cusp of being so. It is the basis for the dissolution rate limitation in claim 1. Counsel for the Claimants accepted that the fact that the tablet was just outside the limit for bioequivalence was not a separate reason for invalidity. 77% in 30 minutes is very close to the normal target dissolution rates from the CGK; it is very slightly less ambitious.

166. Paragraph [0036] then introduces Figures 3 and 4, which plot the percentage dissolved in 30 minutes against the D_{90} in microns. Figure 3 is for a 2.5mg apixaban tablet whereas Figure 4 is for 5mg. This does not make much difference, but since both were mentioned in evidence I reproduce them both here:

Figure 3: Dissolution Rates of 2.5-mg Apixaban Tablets Using Drug Substance of Different Particle Size

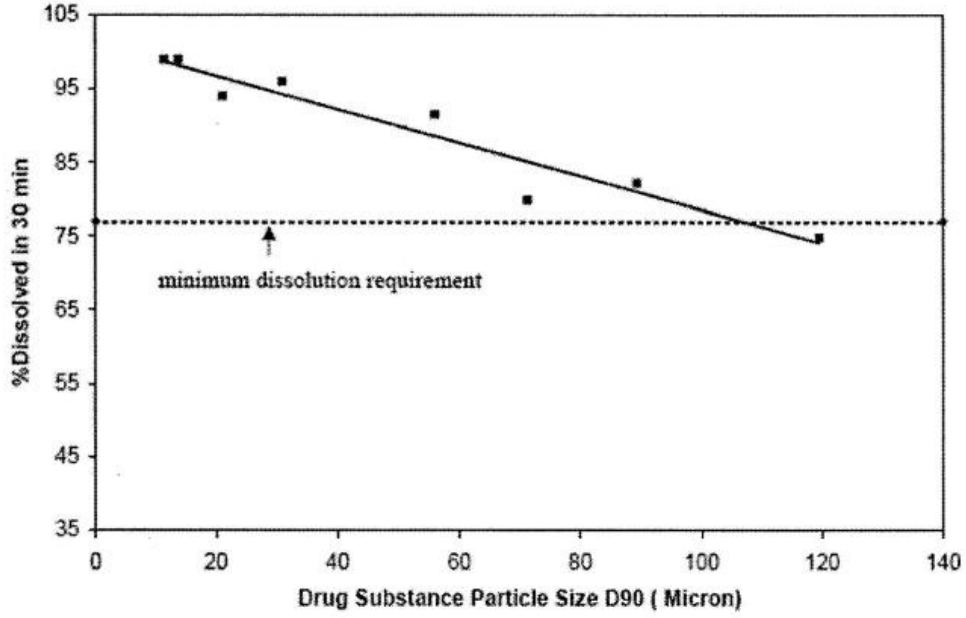
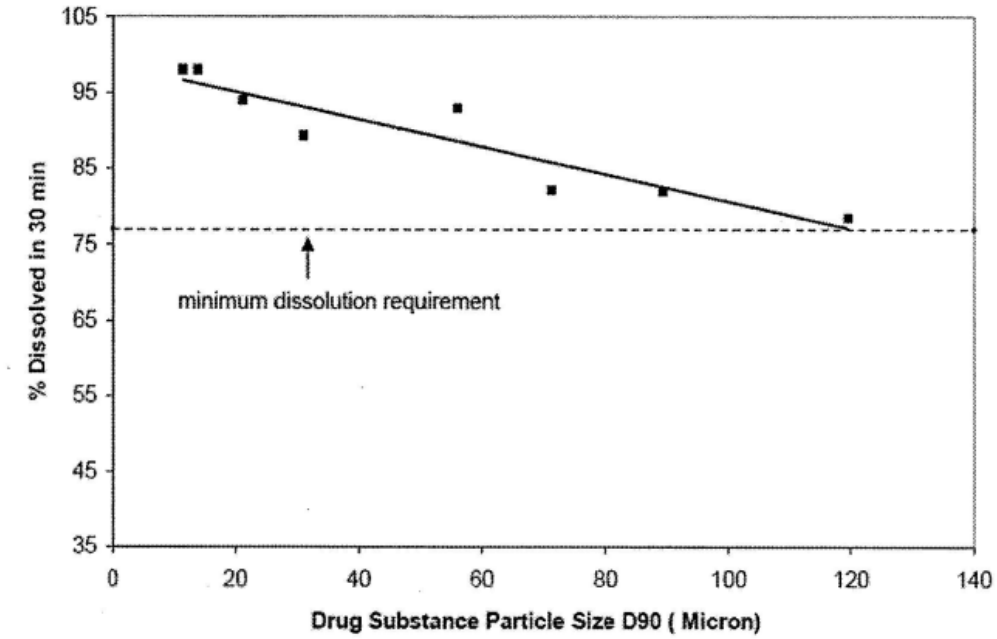


Figure 4: Dissolution Rates of 5-mg Apixaban Tablets Using Drug Substance of Different Particle Size



167. Figures 3 and 4 each show the "minimum dissolution requirement" by means of the horizontal dotted line and which corresponds to the 77% figure in the claims of the Patents (which, as I have said above, comes from [0035]).

168. The Claimants said the specific particle size of 89µm taken into the claims is not important because the dissolution rate threshold of 77% in 30 minutes is reached with particles of around 110µm or 120µm for tablets of 2.5mg and 5mg respectively, as shown by figures 3 and 4. So, the Claimants say, the precise size of 89µm is arbitrary in that any value below 110µm or 120µm could have been chosen. BMS responded by relying on [0036], which explains that for 5mg tablets the particle size at the 77% in 30 minute cut-off is 119µm, but that the claimed size limit is 89µm to allow for variability in dissolution measurements. I agree that a somewhat different number than 89µm could have been chosen, but the approach of leaving a margin of safety over experimentally determined limit is a rational one, so to call the value entirely "arbitrary" is an overstatement. A slightly different number would have done the same job, but the number used represents a safety margin over what was determined experimentally and is meaningful to that extent.

169. The experiments described in the specification are, I find, routine ones done for routine, CGK reasons. It could not have been predicted in advance of doing them that apixaban's dissolution rate could affect bioavailability, but nor would it have been surprising when that result was obtained. The particle size experiments are also routine and done for CGK reasons.

The claims of `021

170. As I have already said, I need only consider claim 1 of `021, which, as proposed to be amended, is as follows:

(a) A tablet comprising up to 5mg crystalline apixaban particles having

(b) a D_{90} less than 89µm as measured by laser light scattering and

(c) a pharmaceutically acceptable diluent or carrier, wherein

(d) the formulation exhibits dissolution properties such that an amount of the drug equivalent to at least 77% dissolves within 30 minutes, wherein

(e) the dissolution test is performed in an aqueous media buffered to a pH range 1 to 7.4 and controlled at 37° C, wherein

(f) the result is established as an average of 6 tablets, and wherein

(g) the dissolution test is performed in 900 mL of dissolution medium containing 0.05 M sodium phosphate at pH 6.8 with 0.05% SDS at 37 °C using USP Apparatus 2 (paddles) at a rotation speed of 75 rpm and the samples are analyzed for apixaban by HPLC at 280 nm.

171. This is a combination of granted claims 1 and 2: features (f) and (g) were originally in claim 2. This had led to an insufficiency attack, as I have already mentioned, which was that the claim was uncertain if the way of doing the dissolution test was not specified. The combining of claims 1 and 2 cured that.

172. However, it was not said by BMS that features (f) and (g) contributed to inventive step in any way (as opposed to clarifying the scope of the claim), and the same applies to feature (e), which was present as granted. Feature (c) is trivial and irrelevant to inventive step.

173. Feature (a) requires *up to* 5mg crystalline apixaban, and Carreiro, as I will come to, discloses tablets of either 2.5mg or 5mg.

174. So what really matters to my decision is whether it was obvious to make an apixaban tablet of 2.5mg or 5mg with the particle size profile of feature (b) and the dissolution rate of feature (d).

OBVIOUSNESS

175. Obviousness is alleged only over Carreiro. As I have mentioned in the Introduction above, there is no dispute that Carreiro would motivate the clinician to recommend the formulator to make immediate release tablets of apixaban in 2.5mg and 5mg doses. Although this is agreed, I will still briefly summarise Carreiro's teaching that justifies the conclusion, before coming to the real meat of the obviousness arguments, which are on the formulation side.

Teaching of Carreiro

176. The authors of Carreiro are two workers at Lenox Hill Hospital in the USA.

177. The abstract of Carreiro is a fairly general introduction to apixaban against a historical backdrop:

> For the last half-century, despite its many limitations warfarin has been the mainstay of treatment for patients with venous and arterial thromboembolic disease. During the past decade, a number of new oral anticoagulant agents have been developed that may offer an alternative to warfarin. Emerging data suggest that Factor Xa may be a target for inhibition. Apixaban is one such agent. It is a potent, selective, reversible, and orally bioavailable FXa inhibitor that demonstrates antithrombotic efficacy, with a favorable pharmacokinetic profile. At present, the safety and efficacy of apixaban for the prophylaxis and treatment of venous thromboembolism is being evaluated in Phase II and Phase III trials involving nearly 25,000 patients. Trials are also underway involving over 20,000 patients for secondary prevention after acute coronary syndromes and the prevention of stroke in patients with non-valvular atrial fibrillation. This review article discusses the discovery, pharmacokinetics, attributes, and current clinical trials of this emerging drug.

178. A longer introduction section covers the same ground, and then there is an explanation that apixaban was designed as a follow-up compound to razaxaban. Section 3 gives some pharmacokinetic and metabolic attributes of apixaban in animal models:

> The preclinical pharmacokinetic and metabolic attributes of apixaban feature a small volume of distribution, a low systemic clearance, good oral bioavailability, multiple elimination pathways and minimal potential for drug-drug interactions. In the rabbit AV shunt thrombosis model, apixaban inhibited thrombus formation in a dose-dependent manner and did not affect bleeding time.

179. Information about pharmacokinetic and pharmacodynamic studies in humans are given in section 4, which begins with the following:

> *In vitro* properties of apixaban show that it is a highly selective and potentially potent antithrombotic agent in human blood from healthy volunteers. Detailed kinetic analysis of apixaban inhibition of human FXa showed that it is a readily reversible competitive inhibitor with a synthetic tripeptide substrate with a K_i of 0.08 nM. K_i is a measure of how potent a drug is to produce half maximum inhibition. The human serum protein binding as measured by equilibrium dialysis was 87%. Weak affinity is observed for thrombin (K_i 3.1 µM), plasma kallikrein (K_i 3.7 µM)), and chymotrypsin (K_i 3.5 µM), trypsin (K_i > 12 µM) and all other serine proteases. The unbound fraction is approximately 13% in humans.
>
> The pharmacokinetic profile of apixaban is consistent with rapid oral absorption and bioavailability. It is well absorbed from the gastrointestinal tract, and peak plasma levels are achieved in about 3 h. The effective half-life is 8 - 11 h when given twice daily and 12 - 15 h for a once-daily regimen.

180. Section 5 moves on to discuss clinical trials. The section is organised according to the various indications under investigation. I will not set out the narration because the overall position is helpfully set out in Table 1:

Table 1. Apixaban clinical trials.

Study	Phase	Indication	Population N, duration	Apixaban dose	Comparator	Status
CV185010 APROPOS	2	VTE prevention	Total knee replacement 1238, 10 days	2.5 mg b.i.d. to 20 mg q.d.	Enoxaparin Warfarin	Completed
CV185017 BOTTICELLI NCT00252005	2	VTE prevention	Acute DVT 520, 3 months	5 mg b.i.d. to 20 mg q.d.	LMWH-VKA	Completed
CV185023 APPRAISE NCT00313300	2	Post-ACS	Post-ACS 1715, 6 months	2.5 mg b.i.d. to 20 mg q.d.	Placebo	Completed
CV185027 NCT00320255	2	VTE prevention	Metastatic cancer 160, 3 months	2.5 mg b.i.d.	Placebo	Recruiting
CV185034 ADVANCE-1 NCT00371683	3	VTE prevention	Total knee replacement 3000, 10 days	2.5 mg b.i.d.	Enoxaparin 30 mg, q12h	Closed
CV185047 ADVANCE-2 NCT00452530	3	VTE prevention	Total knee replacement 3000, 10 days	2.5 mg b.i.d.	Enoxaparin 40 mg q.d.	Recruiting
CV185035 ADVANCE-3 NCT00423319	3	VTE prevention	Total hip replacement 4000, 35 days	2.5 mg b.i.d.	Enoxaparin 40 mg q.d.	Recruiting
CV185036 ADOPT NCT00457002	3	VTE prevention	Acute medical illness 6500, 30 days	2.5 mg b.i.d.	Enoxaparin/placebo	Recruiting
CV185030 ARISTOTLE NCT00412984	3	Stroke prevention	Non-valvular AF 15,000, 18 months	5 mg b.i.d.	Warfarin	Recruiting
CV185048 AVERROES NCT00496769	3	Stroke prevention	Non-valvular AF 5600, 18 months	5 mg b.i.d.	Aspirin	Recruiting
AMPLIFY NCT00643201	3	VTE treatment	Acute DVT/PE, 3625, 6 months	10 mg b.i.d./ 5 mg b.i.d.	Enoxaparin/warfarin	Recruiting
AMPLIFY-EXT NCT00633893	3	Extended VTE treatment	DVT/PE after initial therapy; 2438	5 mg b.i.d./ 2.5 mg b.i.d.	Placebo	Recruiting

ACS: Acute coronary syndrome; AF: Atrial fibrillation; b.i.d.: Twice daily; DVT: Deep vein thrombosis; LMWH-VKA: Low molecular weight heparin- vitamin K antagonist; PE: Pulmonary embolism; q.d.: Once daily; VTE: Venous thromboembolism.

181. Focus during the oral evidence was mainly on the APROPOS trial, the ADOPT trial, the APPRAISE trial, the ARISTOTLE trial and the AVERROES trial. One can see that the doses used varied, but 2.5mg twice daily and 5mg twice daily were used or planned in a number of instances.

182. Section 7 is the conclusion and is as follows:

> Current anticoagulants have many limitations and drawbacks. Warfarin and heparin rank consistently in the 'top 10' lists of drugs associated with serious adverse events, emergency room visits, or hospitalizations. New anticoagulants, especially those available orally, should be welcomed. Apixaban looks promising in Phase II trials, but the results of Phase III trials will be needed to fully assess the potential of this Xa inhibitor. However, there are still unknowns. Will there be any long-term, non-hematologic side effects? Will patient compliance be a problem with an unmonitored anticoagulant? Will new drugs, with their predictable and stable therapeutic effect, have an even greater degree of safety compared to warfarin therapy, where real-world management is poor and adverse events significantly higher than in controlled trials? Will physicians, or patients, adopt these new agents readily? Many of the current trials will conclude in the next 5 years, and the world of anticoagulant therapy may be changed for ever.

> At present, there is great clinical need for an oral anti-coagulant to replace warfarin for long-term prevention and treatment of patients with venous and arterial thromboembolism. The future of anticoagulation will offer non-monitored oral anticoagulants with a wide therapeutic window and a predictable anticoagulant response. Emerging data suggests that Factor Xa is a target for a new anticoagulant. Many clinical trials are underway studying the utility of apixaban in almost 47,000 patients. Initial Phase II studies have been promising, but only the results of Phase III trials will let us know the true value of apixaban compared with existing agents.

183. The upshot is that Carreiro describes tests of apixaban in a variety of clinical trials. It gives the dose sizes and dosing intervals used in the trials and basic pharmacokinetic and pharmacodynamic parameters. It explains why direct Factor Xa inhibitors would be attractive. The only completed trials that it describes are phase 2 trials and its optimistic tone is qualified as a result, with statements that the outcome of the phase 3 trials cannot be taken for granted.

184. I agree with BMS that Carreiro contains no specific teaching about actually formulating apixaban, although the information that I have just summarised would provide necessary and useful inputs to the formulation task.

***Pozzoli* 1 and 2**

185. I have covered the skilled addressee and CGK above.

***Pozzoli* 3**

186. The necessary steps to the claims of `021 are the choice of D_{90} and dissolution rate. These are not changes to anything in Carreiro (it is a "filling in gaps" kind of obviousness case) but have to be supplied from CGK. Hence why I said above that this is in a sense a CGK-alone attack on a formulation patent, albeit based on the clinical information in Carreiro. I have said that I have to take that into account, and I will.

***Pozzoli* 4**

187. It would be the formulator's task to seek to implement the clinician's recommendations. The formulator would come to it with the understanding that the task was a feasible one, since tablets of the relevant doses had been used in the clinical trials listed in Carreiro, although, as was common ground, the formulator would not have any information about how they had been made.

188. To articulate the parties' arguments I will have to set out a number of steps in the argument. I will need to consider in due course whether this means that there is a *Technograph* issue (i.e. injecting hindsight by breaking the invention down into small individual steps).

189. The Claimants' case was that the formulator would first measure the equilibrium solubility of apixaban during routine pre-formulation tests. This

much was common ground, as was the fact that the formulator would find that the aqueous solubility of apixaban was relatively low, at 40µg/mL.

190. Next, the Claimants said that the formulator would regard the low aqueous solubility as a warning sign that apixaban might have a slow dissolution rate so as to cause a problem *in vivo*. I agree with this but it must be noted that the Claimants' case is only that this would be a warning sign, not a trigger in itself for further specific steps at that early stage.

191. The Claimants also argued that the formulator would do kinetic solubility testing and IDR testing. I agreed with the latter but not the former, given my conclusions on the CGK. If done, these could raise further warning signs.

192. The parties agreed that the formulator would make prototype formulations and test them. The Claimants' position is that by this stage and probably a good deal earlier it would have been obvious to settle on a target dissolution rate of 85% in 15 or 30 minutes. BMS's position is that the formulator would have had a lot of confidence that the dissolution rate would be all right, simply from apixaban at the doses under consideration being a Class III drug (or alternatively that a much less ambitious target would be chosen). For reasons given in connection with the CGK above, I agree with the Claimants on this issue.

193. Next, and assuming that there was a problem concerning dissolution rate, it was common ground that the CGK would lead the formulator first to check and if necessary improve the disintegration.

194. The Claimants submitted that if there remained a problem, one CGK way to address it would be by reducing particle size. BMS did not really dispute this, but said that excipient optimisation would be a more preferred route. I find that it would be uninventive to address dissolution rate issues by choosing a more appropriate particle size, and I have found in dealing with CGK that the size specified by the claims of `021 is well within the CGK range. Exactly what size would be chosen would depend on the specific circumstances of any given case including the details of the prototypes.

195. I recognise that this analysis involves multiple sequential steps, as Counsel for BMS emphasised in closing submissions. I also recognise that the attack is a rather conceptual one based on CGK alone. It does not involve putting forward a concrete, complete recipe, for example. These are reasons for caution and I have consciously aimed to take them into account.

196. Nonetheless, I am of the clear view that the obviousness case is made out. On my findings as to the CGK it would be an obvious choice and probably the most obvious choice faced with the complex and costly task of drug development to aim from the outset (and if not then certainly in due course) for the well known goals of either 85% in 15 minutes or 85% in 30 minutes (both are within the claims of `021). I think Prof Davies' confidence arising from apixaban being a Class III drug was much greater than the notional formulator would have, but it is also rather beside the point; it could not be a

reason why it would not be obvious to set a concrete target recognised by the art and by the regulators and then test it.

197. Although the attack involves a number of sequential steps, they are the systematic sequence known to the CGK. For example, trying to remedy disintegration first would be basic and logical.

198. As to particle size, as I have already said, I think the availability of other possible solutions to slow dissolution, particularly excipient optimisation, is a true *Brugger* situation: both routes would be obvious. I am fortified in this view by the fact that the claim covers very typical particle sizes which would not be regarded as unusual or problematic. BMS's case might be improved if there was e.g. such a small size required that handling would become a problem, but that is not the case. The limit in the claims of the Patents is entirely uninventive.

What if there was no problem?

199. It cannot be assumed that the formulator would in fact experience any problem. It could perhaps be the case that by careful and/or lucky choice of excipients the targeted dissolution rate would be achieved without particle size reduction; it might also be the case that small enough particles would be chosen in the first place. BMS did not press this hard and in my view it cannot help to meet the case of obviousness. The claimed dissolution rate and particle size ranges are, for reasons given above, obvious ways to address a potential problem. If and to the extent there were in fact no problem then the Patents do not provide a technical contribution. I should also make clear that BMS cannot argue that this is the kind of case where appreciation of the existence of a problem requires invention. On my findings, the formulator would know that there might be a problem, would look for it by routine means, and would be able to solve it with CGK.

200. In relation to this point, BMS argued that the Claimants should have led evidence about the typical particle size of apixaban as an API at the priority date, to give concrete reality to their case and to show that particle size reduction would, as opposed to could, be used. I reject this. The Claimants are in the business of making apixaban now, but trying to prove the situation at the priority date would be disproportionate and impractical, if not impossible. If anything, it is BMS that could have brought evidence of real particle sizes. But I do not think it is necessary to resolve the issues.

CONCLUSIONS

201. I conclude that:

    i) All the Patents are invalid for obviousness over Carreiro.

    ii) The proposed amendments to the Patents are formally allowable but do not cure the invalidity.

202. I will hear Counsel as to the form of Order if it cannot be agreed. I direct that time for seeking permission to appeal shall not run until after the hearing on the form of Order (or the making of such Order if it is agreed). I draw attention to paragraph 19.1 of the Patents Court Guide, which says that a hearing on the form of Order should take place within 28 days of hand down. Since I am giving this judgment in July that will, understandably, not be met but the argument can, I hope, take place in September and not much outside 28 days. I ask the parties please to liaise straight away to find a suitable time within that period. If there are any difficulties with this they should be communicated via my clerk promptly.