Neutral Citation Number: [2023] EWHC 2571 (Pat)

Case No: HP-2021-000014

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

Rolls Building
Fetter Lane
London, EC4A 1NL

Date: 17th October 2023

Before :

THE HON MR JUSTICE MELLOR

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Between :

ASTELLAS PHARMA INDUSTRIES LIMITED **(a company incorporated under the laws of Japan)**	**Claimant**
- and -	
(1) TEVA PHARMACEUTICAL INDUSTRIES LIMITED **(a company incorporated under the laws of Israel)** **(2) TEVA UK LIMITED** **(3) SANDOZ AG** **(a company incorporated under the laws of Switzerland)** **(4) SANDOZ LIMITED**	**Defendants**

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Thomas Mitcheson KC and **Anna Edwards-Stewart** (instructed by **Hogan Lovells International LLP**) for the **Claimant**
Charlotte May KC and **Katherine Moggridge** (instructed by **Pinsent Masons LLP**) for the **Teva Defendants**
Charlotte May KC and **Joe Delaney** (instructed by **Pinsent Masons LLP**) for the **Sandoz Defendants**

Hearing dates: 21st-22nd, 25th-27th, 29th July 2022

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APPROVED JUDGMENT

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I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.
This judgment was handed down remotely by circulation to the parties' representatives by email. It will also be released for publication on the National Archives and other websites. The date and time for hand-down is deemed to be Tuesday 17th October 2023 at 10.30am.

THE HON MR JUSTICE MELLOR

Mr Justice Mellor:

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Introduction

1. In this action the Claimant (Astellas) alleges that the generic mirabegron tablets proposed to be launched by the two sets of Defendants (Teva and Sandoz) infringe EP(UK) 2,345,410 (EP410 or the Patent). The Patent is entitled 'Pharmaceutical composition for modified release' and concerns a modified release pharmaceutical composition containing mirabegron (or a salt thereof) as an active ingredient. The Priority Date is 30th September 2008.

2. In earlier actions Teva and Sandoz sought revocation of another Astellas patent EP(UK) 1,559,427 B1 (EP427) and Supplementary Protection Certificate SPC/GB13/035 (which relies on EP427 as its basic patent) which protect a remedy for use in the treatment of Overactive Bladder (OAB) syndrome comprising mirabegron or a salt thereof as an active ingredient. Meade J. heard the trial of the EP427 case in March 2022 and found that patent to be valid and infringed: see [2022] EWHC 1316 (Pat). At the date of the trial, Teva and Sandoz had obtained permission to appeal but both Teva and Sandoz were injuncted from launching their generic mirabegron products. Their appeal was later dismissed: see [2023] EWCA Civ 880.

Overview of the issues

3. So far as infringement is concerned, Teva does not contest that its original product ('the Original Teva Product') infringes EP410, but it has brought a

claim for a declaration of non-infringement in respect of its New Teva Product. There was insufficient time to prepare that issue for determination at this trial and the parties agreed it should be determined later, if that is necessary. Sandoz does not admit infringement.

4. Teva and Sandoz each counterclaim for revocation of the Patent on the grounds of obviousness, insufficiency and added matter. By the conclusion of the PTR, Teva and Sandoz had aligned their validity attacks, and added a further added matter attack based on some of the evidence to be led by Astellas (specifically some evidence of Professor Shakesheff). For obviousness the Defendants rely on three prior art citations:

   i) "*Controlled-Release Oral Delivery Systems"*, Joseph A. Fix et al., ACS Symposium Series, American Chemical Society: Washington DC, 2000; 752;14-24 (**Fix**);

   ii) "The Pharmacokinetic Profile of Tamsulosin Oral Controlled Absorption System (OCAS®)", Michel, M., European Urology Supplements Volume 4, Issue 2 (2005) 15–24 (**Michel**);

   iii) "The Oral Controlled Absorption System (OCAS®): The Evolution of Tamsulosin for the Treatment of Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia (LUTS/BPH)", Chapple, C., European Urology Supplements Volume 4, Issue 7 (2005) 20-22 (**Chapple**) when read with Michel.

5. Two insufficiency allegations were pleaded and pursued by the Defendants. The main attack was excessive claim breadth. The subsidiary attack was ambiguity or uncertainty, although this seemed to have died away by the time of written closings, only to be resurrected in the final minutes of the trial if the drug release measure in [0010] was *in vivo*, a point I consider below.

6. On the main attack, the Defendants say it is not plausible that the invention of the Patent works (in the sense of reducing the food effect) with substantially all products falling within the scope of at least claim 1. Accordingly, they say the claim scope exceeds the technical contribution such that the claims of the Patent are invalid. The Defendants also say the Patent is *AgrEvo*-obvious in that it is lacking in any relevant technical contribution.

7. Astellas defends the revocation claim and on 17 June 2022 applied to amend the Patent unconditionally. Astellas also advances 3 conditional amendments to the Patent as fall-back positions. All the amendments are opposed on the grounds that they do not cure the invalidity of the Patent. The Defendants' initial position was that the proposed amendments made the added matter position worse not better.

8. Those are the headline issues, however the issues which took up the most time at trial were first, insufficiency, second, obviousness and third, some disputes as to whether the Skilled Team included a pharmacokineticist and related CGK issues. As I relate in more detail below, the insufficiency arguments continued to develop throughout. Those arguments turn on how the Patent was understood

at the Priority Date by the Skilled Team. For that reason, it is necessary to analyse and understand the Patent in some detail.

The experts

9. The parties called a total of five expert witnesses in the following disciplines:

   i) Formulator: Professor Shakesheff (for Astellas) and Professor Craig (for Teva & Sandoz);

   ii) Clinician: Professor Drake (for Astellas) and Dr Morley (for Teva & Sandoz);

   iii) Pharmacokineticist: Dr Blakey (for Teva & Sandoz). Astellas did not call a separate PK expert but addressed the PK aspects of the case via Professor Shakesheff.

10. The evidence from the clinicians was short and not really controversial at all. Both Professor Drake and Dr Morley gave their evidence clearly and both assisted the Court.

11. Dr Blakey was a guarded witness and sometimes he had to be pressed to provide the answer. Astellas cited two examples. First, where he was initially reluctant to accept that if the skilled team was told that a drug formulation had continuous drug release for four hours or more, they would assume that it was being absorbed in the small intestine. He suggested it was only "a possibility" before conceding that it was the most obvious place for absorption. Second, where he was reluctant to accept the Skilled Team would expect that a formulation with 100% dissolution in two hours would have continuous absorption for well over four hours again insisting it was only "a possibility". These answers were put into context by his admission that he regarded 'a possibility' as synonymous with 'likely'. Once that adjustment is applied to his evidence, his evidence was essentially clear and I accept it.

12. Professors Shakesheff and Craig both gave their evidence confidently and clearly. In certain respects which I identify below, I consider that Professor Shakesheff was trying too hard to support Astellas' case. Astellas levelled the same accusation at Professor Craig. Some of this may be attributable to the way in which they were instructed and/or their interactions with the solicitors. However, what matters is the reasons each put forward for the opinions they expressed, and I will have to examine their reasoning on different issues below. Suffice to say that I did not feel able to accept all of the reasons put forward by one or the other.

13. Having said all that, I am grateful to all the experts for their evidence and for trying to assist the Court to resolve the myriad tricky issues which arose in this case.

The composition of the Skilled Team

Applicable principles

14. The Defendants referred to my review of the authorities in *Alcon v AMO* [2022] EWHC 955 (Pat) from [210] and submitted that the key points from the case law which are relevant to this case are as follows:

    i) The starting point is to identify the problem that the invention aims to solve. That enables the court to identify the established field in which that problem was located. It is the notional person or team in that established field that makes up the skilled person or team for the purpose of assessing obviousness. See Meade J in *Alcon Research LLC v Actavis Group PTC EHF* [2021] EWHC 1026 (Pat) at [30]-[31].

    ii) The Court will have regard to the reality of the position at the time. It is the combined skills of real research teams that matters. See Henry Carr J in *Garmin (Europe) Ltd v Koninklijke Philips N.V.* [2019] EWHC 107 (Pat) at [85]; see too Kitchin LJ in *Medimmune v Novartis* [2013] RPC 27 at [73]-[76].

    iii) The purpose of assembling a team is that each member brings their individual skill and general knowledge. What matters is the combined skill set of the team, not whether that skill set is found in one or two individuals. See Henry Carr J in *Fujifilm v Abbvie* [2017] EWHC 395 (Pat) at [128]-[129].

    iv) It is important to construct the team that fairly reflects the level of common general knowledge that is fair to all the parties. A team that is too narrowly defined to the problem in hand may be attributed with too high a level of CGK that is unfair to the patentee. Similarly a team that is too broadly defined will be equally unfair to the public as it will result in a diluted CGK that then makes things seem less obvious than they really are. See Birss LJ in *Illumina Cambridge Ltd v Latvia MGI Tech SLA & Ors* [2021] EWHC 57 (Pat) at [62]-[63].

15. I accept all those points, which were not disputed.

Analysis

16. In this case, the problem that the Patent aims to solve is a so-called "food effect" that is encountered with a "conventional" formulation of a drug that is now called mirabegron. This is a problem that would have been encountered by a notional team that was interested in developing a formulation of mirabegron.

17. Mirabegron had, by the Priority Date, been disclosed as a potential therapy for both diabetes and overactive bladder ("**OAB**"), but the parties are proceeding on the common assumption that the relevant clinical indication is OAB.

18. The parties agreed that the team would include a clinician (the "**skilled clinician**") and a formulator (the "**skilled formulator**"). The parties also agree that the skilled clinician would provide the input as to the desired characteristics

for a formulation of mirabegron for use as an OAB medication.

19. It was also common ground that there is a pharmacokinetic ('PK') element to this case and that PK expertise is part of the collective skillset of the Skilled Team. The dispute is over the level of that PK expertise and specifically, whether a Skilled Pharmacokineticist ('Skilled PK') would be a member of the Skilled Team.

20. Astellas made two contentions:

    i) First, that the Skilled Formulator (typified by Professor Shakesheff) had sufficient PK knowledge to develop a modified release formulation without input from the Skilled PK.

    ii) Second, to the extent that a Skilled PK might be involved in the Skilled Team, it would only be at a stage well after the decision had been taken as to what type of formulation to take forward, when developing clinical trials and analysing the results.

21. I was unable to square these contentions with the concern (which was common ground) which the Skilled Formulator would have over formulating a long $T_{1/2}$ drug as an extended release formulation because of possible accumulation.

22. Professor Shakesheff explained that the Skilled Formulator would only raise a concern with the Skilled PK if such a point "had reached a threshold of importance". Astellas submitted that it followed from this that it was not the case that whenever a point of detail concerning pharmacokinetics arose, the Skilled Formulator would consult with the Skilled PK. Professor Shakesheff explained (in the context of how a Skilled Formulator might approach the possible risk of accumulation) that the Skilled Formulator's CGK would enable them to assess that risk such that they would be able to work around it without having to consult the Skilled PK, and that such approach went hand-in-hand with their generally risk-averse approach to formulating.

23. This was the foundation for Astellas' case that the Skilled Formulator would reject the idea of an extended-release formulation at the outset because of their concerns about accumulation without even consulting a Skilled PK. On that point, Dr Blakey agreed he would only pass on his expertise if he was asked. Furthermore, if he was not involved until PK data had been generated, he may not be involved at the earlier stage when whether to investigate a modified release formulation was under consideration.

24. However, Dr Blakey gave clear evidence that the Skilled PK would be part of the Skilled Team and involved throughout ('an integral part of that team'). Astellas attempted to sideline that evidence on the basis that it was given based on Dr Blakey's experience as a clinical pharmacologist (as opposed to a pharmacokineticist) in a drug discovery and development team which did not reflect the Skilled Team in this case. It is true that Dr Blakey made reference to his work in clinical pharmacology, but that did not, in my view, detract in any way from the clarity of his answer that the Skilled PK would be an integral member of the team.

25. Dr Blakey's evidence was also supported by two other points. First, consideration of what would be required to implement the Patent. As the Defendants submitted, if the Skilled Formulator had a concern about accumulation regarding mirabegron, the Patent does not discuss this and would not have done anything to assuage that concern. Second, the fact that Professor Shakesheff had made some PK errors in his first report which Dr Blakey corrected in his second.

26. In evidence and submissions, the experts and parties tended to refer to the Skilled Formulator (avoiding the issue over whether the Skilled PK was a member of the team). I have tended to refer to the Skilled Team, but have not changed their references. The Skilled Formulator has the principal role in the Team, but, unless the context otherwise requires, the terms Skilled Formulator and Skilled Team are synonymous.

Common General Knowledge

27. As is now customary, the parties were able to agree large swathes of CGK. I do not underestimate the time which has to be taken up to reach such agreement and I am grateful to the parties for their time and efforts in this regard. What follows is based on the Agreed Statement of CGK with a few edits of my own. It is agreed as the CGK of the Skilled Team i.e. it is not affected by the dispute over whether a pharmacokineticist is a member of the Skilled Team.

1. <u>An overview of the bladder and associated syndromes / conditions</u>

28. The bladder is a muscular organ which stores urine. It fills from the kidneys via the ureters. A smooth muscle tissue known as the detrusor muscle forms the bladder wall. The detrusor muscle is under the control of the autonomic nervous system, which has parasympathetic and sympathetic components. During bladder emptying (known as voiding), the parasympathetic pathway is active and causes bladder contraction. When the bladder is filling (known as the storage phase), the sympathetic pathway is active and causes the bladder to remain relaxed.

29. Issues with the bladder and/or the urethra are grouped together under the term "Lower Urinary Tract Symptoms" or "**LUTS**".

30. Overactive bladder ("**OAB**") and benign prostatic hyperplasia ("**BPH**") are two conditions that may give rise to LUTS.[1]

2. <u>OAB</u>

31. OAB is a symptom complex that is suggestive of lower urinary tract dysfunction. A symptom complex is a group of symptoms that occur together and are characteristic of a certain disease, disorder or condition.

32. In 2002, the International Continence Society ("**ICS**") defined OAB as "Urgency, with or without urge incontinence, usually with frequency and

[1] Urogynaecologists do not treat prostate issues so would not have experience in treating BPH; however, BPH would have been in the remit of urologists.

nocturia, can be described as the overactive bladder syndrome, urge syndrome or urgency-frequency syndrome". This definition did not change before the Priority Date.

33. The symptoms of OAB are not time limited, in that they can affect patients at any time of the day or night, making 24 hours a day efficacy a requirement of any pharmaceutical therapy. OAB is a very common complaint, primarily afflicting older people but occurring in patients of all ages. It is a non-life-threatening, chronic condition, which patients may live with for many years. As such, there was a low tolerance for side-effects in the relevant patient population, particularly for side effects which might be serious in older patients. Patients would, in general, be responsible for administering their own medicine once it had been prescribed, meaning that medicines would preferably be orally administered to help with patient compliance.

3. OAB Treatments at the Priority Date

Antimuscarinics

34. At the Priority Date, the primary pharmacological treatment option was the anticholinergic, and specifically antimuscarinic, class of drugs. Antimuscarinics are often also referred to as "anticholinergics", because muscarinic receptors are one form of "cholinergic receptors" (the other form of cholinergic receptors being the nicotinic receptors).

35. Antimuscarinic drugs have well-known side effects issues such as dry mouth, constipation, dry eyes and blurred vision. There was also the possibility of cardiovascular side effects with antimuscarinics, which would have been a particular concern with patients who have cardiovascular issues. There was also a perceived risk of impaired bladder emptying.

36. Side effects of antimuscarinic drugs can cause issues with patient compliance. Of the antimuscarinics available at the Priority Date:

    i) oxybutynin chloride/hydrochloride, tolterodine, propiverine and trospium chloride were available in multiple times daily and once daily modified release formulations; and

    ii) darifenacin and solifenacin were both launched as once daily products (the former being a modified release formulation).

37. None of oxybutynin, tolterodine, darifenacin or solifenacin were restricted with respect to food (i.e. there was no requirement for the patient to take them either with food or after fasting for a period).

38. Oxybutynin chloride/hydrochloride: Oxybutynin was the mainstay treatment of OAB for many years prior to the Priority Date. Oxybutynin has antimuscarinic activity, as well as local anaesthetic action.

39. Oxybutynin was an oral tablet administered as a twice-daily dose. Despite being the mainstay treatment for OAB, it suffered from a problematic side effect

profile, including dry mouth and blurred vision (which were issues suffered by most antimuscarinics). This, together with the twice-daily administration impacted on patient compliance.

40. An extended release oral tablet formulation of oxybutynin (Ditropan XL) was introduced in 2002. The extended release formulation was shown to retain the efficacy of the immediate release preparation but with fewer side effects and there was an expectation that it would improve patient compliance due to the convenience of a once-daily dose, compared to twice-daily.

41. An oxybutynin transdermal patch (Kentura) was authorised in 2004 and required the patch to be applied every 3 – 4 days. Despite showing a reduced side effect profile and good tolerability, this administration route never gained significant traction as many patients suffered from skin reactions to the patch, which required patients to move it around their body throughout the day, as well as replace it every 3 – 4 days.

42. Propiverine was approved as an oral tablet in 1998 and sold in the EU under the brand name Detrunorm. It was administered 1 – 3 times daily, depending on the patient's symptoms. In addition to antimuscarinic activity, propiverine also has Ca^{2+} antagonist properties, which inhibit contraction of the bladder.

43. In 2006, a modified release formulation of propiverine (Detrunorm XL) was released as an oral capsule administered once-daily. Propiverine was found to have similar efficacy to oxybutynin with a milder, less common incidence of dry mouth. However, it was only prescribed as an alternative second line treatment in the UK as it had different side effects (such as fatigue, tremor and restlessness) to oxybutynin related to its dual mode of action (and was also more expensive).

44. Tolterodine was approved in 1998 and sold in the EU under the brand name Detrusitol. It was administered twice-daily as an oral tablet. It was widely prescribed and was found to be as effective as immediate release oxybutynin but with a significantly lower comparative incidence of dry mouth. However, other antimuscarinic side effects, such as constipation, were still quite high and plasma concentrations of tolterodine varied considerably between patients which impacted on the efficacy of the drug.

45. An extended release oral tablet formulation of tolterodine was developed in 2001. It was administered once-daily, which again improved the convenience of the treatment for patients and in turn patient compliance.

46. Trospium chloride was approved in 2000 and sold in the EU under the brand name Regurin. It was initially authorised as an oral tablet administered twice-daily. It was more popular across mainland Europe than in the UK.

47. Solifenacin succinate was approved in 2004 as an immediate release oral tablet for once-daily administration and sold in the EU under the brand name Vesicare. In comparison to other antimuscarinics authorised at the Priority Date, solifenacin has a degree of selectivity for M3 receptors (the form of muscarinic receptor most implicated in OAB).

48. Darifenacin was approved in 2004 and sold in the EU under the brand name Emselex. As with solifenacin succinate, darifenacin demonstrates some selectivity for M3 receptors. It was formulated as a modified release oral tablet formulation for once-daily administration. It had a similar side effect profile to solifenacin.

49. Fesoterodine was approved in 2007 and sold in the EU under the brand name Toviaz.

50. It was developed as an oral tablet extended release formulation administered once-daily. Fesoterodine was not prescribed as much as the other antimuscarinics listed above.

51. Botulinum toxin: Botox was sometimes used as an unlicensed OAB treatment at the Priority Date.

4. Issues for OAB Treatments

52. The following are relevant for OAB treatments:

i) **Administration frequency** - Patient compliance is a key concern with any therapeutic. Once-daily drug formulations are advantageous for patient compliance (given the reduced opportunities to miss a dose), particularly in older and/or mentally impaired patients, and commercially given the existing drugs were available in once daily dosing formulations. In some cases existing treatments for OAB were available in once daily dosing formulations, including in some cases following reformulation as modified release formulations.

ii) **Administration Route** - Oral administration routes lead to the greatest patient compliance, given their convenience. Patients would, in general, be responsible for administering their own medicine once it had been prescribed, meaning that medicines would preferably be orally administered to help with patient compliance. Patients do not want to take treatments via injection if it can be avoided, particularly for a non-fatal condition such as OAB. Furthermore, transdermal administration through patches was known from experience in previous drugs (such as oxybutynin, as described above at 41) to cause localised side effects such as skin reactions and that to avoid this, patients had to move the patch around the body throughout the day. In addition, other problems can arise with patches, such as peeling off through movement or bathing. All of these issues can decrease patient compliance. Liquid therapies are generally not a popular dosage form for adults as they must generally be kept in a fridge or a safe place and therefore are not convenient. Tablets or capsules, in contrast, are convenient and portable.

iii) **Side effects** - There was a low tolerance for side effects in the relevant patient population, particularly for side effects which might be serious in older patients.

iv) **Efficacy** - Any OAB treatment would ideally be at least as efficacious

as the antimuscarinics that were already on the market.

v) **Food restrictions** - Food independence would be a desirable characteristic of any OAB drug.

5. OAB drugs in development at the Priority Date

53. Alternative targets for OAB treatments were being investigated prior to the Priority Date. The following developments were known:

54. **Antimuscarinics**: As noted, antimuscarinics were the mainstay treatment for OAB at the Priority Date. However, there was a move towards developing more selective antimuscarinics which would improve their side effects profile.

55. **β-adrenoceptors, in particular β3-adrenoceptors**: β-adrenoceptors, in particular β3-adrenoceptors were (and had been for a number of years prior to the Priority Date) being considered as a means to directly relax human detrusor smooth muscle (direct detrusor relaxation is induced by the activation of β-adrenoceptors, which respond to noradrenaline released from sympathetic nerve terminals in the bladder), which would potentially be useful for treating OAB with minimal side effects, due to the selective targeting of the β3-adrenoceptor.

56. β3-adrenoceptors in development included:

i) YM-178 (mirabegron): By the Priority Date, mirabegron had entered phase III clinical trials.

ii) GW427353 (solabegron): Preclinical data on solabegron had showed the drug caused bladder relaxation and increased micturition reflex threshold in dogs. Solabegron had reached phase II studies in 2004.

57. **Other pathways**: Several other pathways were being considered for treatments for OAB, including vitamin D3 analogues, PDE5 inhibitors, NK1 receptor antagonists, centrally acting drugs such as gabapentin, cannabinoids and TRPV1 receptors.

6. Benign prostatic hyperplasia ("BPH")

58. In general terms, prostatic hyperplasia means an enlarged prostate. BPH can cause benign prostatic obstruction, (referring to obstruction of the urinary tract outflow by inwards growth into the urethra), depending on precisely how the prostate is enlarged (as it may enlarge without necessarily pressing on the urethra).

59. The first line drugs for treating the symptoms of BPH were alpha blockers, which work by relaxing the smooth muscle in the prostate. Alpha blockers in use at the Priority Date included doxazosin, tamsulosin, alfuzosin and terazosin.

7. Tamsulosin hydrochloride

60. Tamsulosin hydrochloride is an α_1-adrenergic receptor ('AR') antagonist. α-antagonists were known to reduce blood pressure and were (and are) associated

with side effects linked to this mechanism of action, including postural hypotension. Tamsulosin hydrochloride works by inhibiting contraction of the smooth muscle of the prostate and the urethra (effectively relaxing them) thereby reducing obstruction, increasing maximum urine flow rate, and relieving symptoms. It was originally marketed as 'Flomax' which was a 0.4mg, once daily, modified release formulation. At the Priority Date, a new formulation of tamsulosin was available, marketed as 'Flomaxtra XL', which was again a 0.4mg, once daily, modified release formulation.

61. The only reason why these aspects of tamsulosin form part of the CGK is because that drug features in two of the pieces of prior art: Michel and Chapple.

8. Developing a Formulation

62. The Skilled Clinician provides input on the clinical outcome to be achieved in comparison to existing therapies in the same field, the proposed target population and any restrictions that this would have on the formulation as well as desired product characteristics. A formulation project typically involves the development of a drug product containing an active pharmaceutical ingredient ("**API**"). Such drug products are typically formulated as convenient, stable and reproducible dosage forms, for example as tablets, or injections, by combining the API with various excipients. These dosage forms must release the API in the body in such a way that it reaches the target, and provide the required therapeutic effect.

63. The physicochemical properties of the API will be ascertained as part of standard pre-formulation studies. This information feeds into the subsequent formulation development stage and may highlight any potential difficulties that may be encountered in formulating an effective dosage form.

64. With respect to drugs for a chronic condition such as overactive bladder (requiring long-term treatment), maintaining consistent exposure of a drug within the therapeutic window (i.e. at a blood plasma concentration which demonstrates a clinical effect without causing significant side effects) was important in order to maximise efficacy and reduce risks.

9. The administration of drugs

65. When considering administration of a drug, the aim is for the drug to have its intended effect in the body without causing significant (or ideally any) side effects. A factor that influences the achievement of this aim is the route of administration of the drug. A number of different routes of administration exist, including oral (by ingesting a tablet, capsule, liquid or via enteral feeding tubes), via skin, eyes, ears, nose (nasal), vagina, rectum, lungs (inhaled), intravenous, intramuscular, subcutaneous, and intradermal. The route of administration will usually be stipulated by the clinician (as they are likely to be more aware of the clinical setting that the drug will be taken in e.g. drugs used in intensive care cannot be swallowed).

66. The study of the kinetics of drug absorption, distribution within the body, metabolism and excretion is termed "pharmacokinetics". For the same drug

there can be differing rates of onset and longevity of the pharmacological effect in the body depending on the route of administration. For example, a drug that is injected straight into the bloodstream will generally lead to quicker action than one administered by other routes. Intravenous injection will also result in the drug being 100% bioavailable compared with extravascular administration (i.e. 100% of the drug will reach systemic circulation).

67. Oral administration of drugs requires that the relevant drug has acceptable bioavailability (defined below). Nonetheless, for small molecule drugs the most common route of administration is oral, because orally administered medicines:

    i) are quite convenient as doses can be taken quickly and in most settings;

    ii) are easy to administer (i.e. a patient can self-administer);

    iii) tend to have higher patient acceptability and compliance than some other routes such as rectal or ophthalmic;

    iv) can be easily adjusted in terms of dose by the patient or healthcare assistant by changing the number of dosage forms swallowed; and

    v) are generally low cost to manufacture compared to other types of formulation.

68. A key challenge with orally administered drugs is that it is not always easy to predict where in the gastro-intestinal tract the drug will be absorbed, nor how much will be absorbed in the gastrointestinal tract ("**GI tract**") or how long it will take for a certain proportion of the dose to be absorbed.

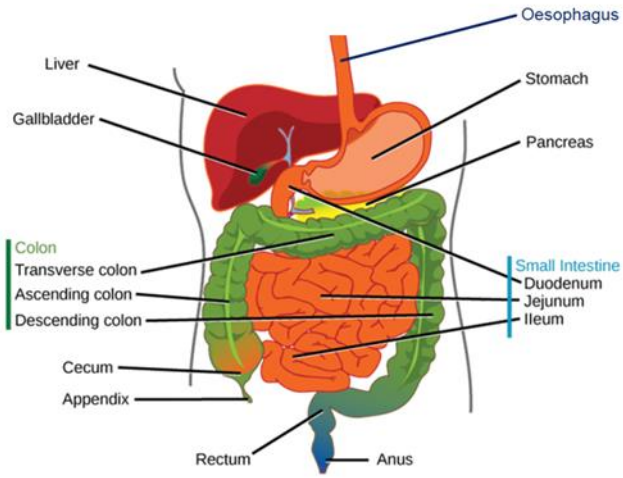
69. Assuming a solid oral dosage form is appropriate, typically the first formulation produced will be a simple immediate release ("**IR**") tablet or capsule formulation containing limited other excipients. IR formulations are usually simple and cost effective to produce. Given that pharmaceutical companies will already have existing manufacturing machinery that can produce IR formulations on a commercial scale at a low cost, a simple formulation that can then be replicated on an industrial scale is typically produced.

70. Unless pre-formulation studies indicate a reason to create a formulation other than an IR formulation, an IR formulation will typically be used for the first in human studies to provide initial human PK data.

10. The gastro-intestinal tract (GI tract)

71. The digestive tract consists of a number of different environments that enable the body to break down and absorb different molecules from different types and sizes of foods. The digestive system also performs an immune function, tackling threats of infection (for example the stomach acts as a line of defence due to its highly acidic pH).

72. The digestive tract comprises the oesophagus, stomach, small intestine, colon (or large intestine), rectum and anus. This is further explained below:



Human Digestive System

73. **The Oesophagus:** The oesophagus links the mouth with the stomach. Dosage forms move into the stomach after swallowing due to contraction waves through the oesophagus.

74. **The Stomach**: The stomach performs a "pre-processing" function to break down food. The stomach does this by producing both acids and enzymes, however, little nutrient absorption takes place in the stomach itself. Average transit time through the stomach can vary but is typically 1 – 3 hours. Activity in the stomach differs depending on what state it is in. For example:

    i) In the 'fed' state (i.e. when a person has recently eaten), a reasonable estimate for residency time in the stomach is around two hours, although residency times can vary depending on (i) the particular person, (ii) the type and amount of food eaten, and (iii) the time of day.

    ii) In the 'fasted' state or during/shortly after sleep (i.e. when a person has not recently consumed any food), the stomach may essentially stop its pre-processing activity. Small dose forms and liquids can move quickly through the stomach in this state but this is unpredictable due to person-to-person variation.

75. **The Small Intestine**: The small intestine is made up of the duodenum, the jejunum, and the ileum (although the boundary between each part is not exact). It is the longest and most convoluted part of the GI tract. A reasonable estimate of transit time through the small intestine is between 2 and 6 hours and typically 3-4 hours. It is the site of most absorption in the GI tract. The walls of the small intestine have a rich network of blood and lymph vessels, as well as lacteals which are important for absorption of fats. Drugs or foods absorbed in the small intestine will enter the hepatic portal vein and will be exposed to the liver before entering the systemic circulation.

76. One of the events in the digestive process is the emptying of the stomach into the small intestine. The stomach has a sphincter at its base through which food is pushed into the small intestine when the stomach contracts. The small

intestine has mechanisms for processing and absorbing molecules, including a network of lymphatics and the secretion of bile, which contains organic solutes that can assist with absorption. The small intestine has a high surface area and a lining that is designed to absorb molecules very effectively. There are also enzymes and bacteria in the small intestine that break down some molecules so that they can be absorbed across the epithelium (the lining) into the bloodstream.

77. **The Colon (or large intestine)**: The main function of the colon is to absorb water, as most absorption of food components has already taken place by the time the molecules travel towards the colon through the small intestine. Therefore it is drier and there is less water available in which a drug can dissolve. In addition, the colon lacks villi, has a small surface area compared to the small intestine and is therefore generally a poor site for drug absorption. The journey through the colon is long and slow – everything slows down to allow the very last parts of food to be absorbed over a period of many hours. Transit time in the colon is highly variable (2 to 48 hours).

11. Orally delivered drugs and their effect on the body

78. The body treats orally delivered medicines in a similar way as it does foods. Therefore, when such a medicine enters the body, the body works to break it down as it travels through the GI tract and possibly absorbs components, including drug molecules, into the blood and/or lymphatic system.

79. What the body does to a drug (pharmacokinetics) can be described by reference to four processes, namely absorption, distribution, metabolism, and excretion (ADME). More specifically:

i) Absorption: This is the process by which a drug enters the bloodstream. For an orally administered drug the process involves dissolution of the drug into the gastro-intestinal fluid before the dissolved drug permeates the intestinal wall into the bloodstream. Some fat-soluble drugs may enter the lymphatic system rather than the bloodstream (before ultimately ending up in the bloodstream). Many factors can affect the absorption of a drug (both with respect to the gastro-intestinal environment and the characteristics of the drug itself).

ii) Distribution: This is the process whereby a drug travels from one location in the body to another, and in particular to its target site.

iii) Metabolism: This is the chemical transformation undergone by a drug in the body and its processing into one or more metabolites that are ultimately excreted from the body.

iv) Excretion: This is the loss of the drug, or its metabolites from the body. Drugs are commonly excreted in urine (via the kidneys), faeces or bile (via the liver), and also in breath, tears and sweat.

80. PK describes what the body does to a drug. PK parameters are used to measure and illustrate the way in which a drug is absorbed, distributed, metabolised and cleared/excreted by the body. PK parameters include the following:

i) C_{max}: This is the peak concentration of the drug in the plasma that is achieved. The concentration of drug in the plasma will be proportional to the concentration of drug in other tissues, including at the target site. C_{max} should not be higher than the minimum toxic concentration (MTC) for that drug. All pharmacokinetic metrics can be measured at different times and often an additional subscript is added to explain the time period within which the metric was obtained. For example, if concentration is measured over a 24 hour period the maximum concentration recorded in that period may be shown as $C_{max.24.}$

ii) T_{max}: This is the time when C_{max} is reached, measured from the time that the medicine is administered.

iii) AUC ("area under the curve"): The curve in question records the concentration of the drug in blood plasma over time. The curve will start at a plasma drug concentration of 0 mg/mL at the time of first medicine administration. The curve will then rise as the drug begins to be absorbed into the blood and will reach a maximum when C_{max} is reached. After the C_{max} point the curve will normally decline as drug elimination predominates. (On that point, Astellas contended it was correct to say that 'distribution and elimination accelerates or dominates', but the Defendants contended that wording was not accurate. This mini-dispute was not explored in evidence and does not seem to me to be material to anything I have to decide). The area under this curve provides an estimate of the total amount of the administered drug that enters the systemic circulation. Subscript notation is used to make the period over which the AUC has been determined clear; for example: AUC_{24} or $AUC_{0\text{-}24}$ is used to denote measurement over 24 hours, AUC_{inf} or $AUC_{0\text{-}inf}$ is used where the AUC has been extrapolated to infinity from the measured data.

iv) C_{min}: This is the lowest concentration of the drug in the blood plasma that is achieved after a dose and within a set period of time. C_{min} is often measured just prior to a repeat dose being administered or at a set time after initial dosing (e.g. after 24 hours for a once-daily drug). For many drugs it is preferable that C_{min} is consistently higher than the minimum effective concentration (MEC) so that the patient consistently obtains the therapeutic benefit.

v) $T_{1/2}$ (Elimination Half-Life): A measure of elimination of a drug within the body. One half-life measures the time for 50% of the mass of drug in the body to be lost.

vi) Steady state: Many drugs will be administered over a long period of time and, therefore, the patient will take multiple doses. If the dosing interval (time between doses) is less than the time to completely eliminate the previous dose there will be an accumulation of the drug in the blood until a steady state is reached. The C_{max} at steady state is termed $C_{max\ ss}$ and will normally be higher than the value of $C_{max.24}$ (i.e. the C_{max} value seen within the first 24 hours). $C_{min\ ss}$ will reflect the accumulation of drug in the blood. It typically takes a period of around five times the drug $T_{1/2}$

(elimination half-life) to reach steady state. The difference between $C_{min\ ss}$ and $C_{min\ 24}$ is called the accumulation ratio and is important in quantifying how much greater the steady state drug concentration in plasma will be compared to the first dose.

vii) Dose Proportionality: if AUC increases with an increasing dose then the response is said to be proportional.

viii) Bioavailability: is commonly used to describe the rate and extent of drug absorption following extravascular administration. It can be measured using AUC and C_{max}. For example, the bioavailability of a drug can be measured by comparing the AUC obtained with an oral administration of the drug compared to the AUC obtained with an intravenous injection. Bioavailability can be expressed as a fraction or percent of the administered dose systemically absorbed intact. A low bioavailability may be problematic because the MEC may not be reached for a sufficient period to achieve an optimal therapeutic effect.

12. **Drug characteristics**

81. As mentioned above in paragraph 63, there are certain chemical and physical properties of drug substances that can affect dissolution and absorption of an orally administered drug, and which may in turn influence how the drug is formulated.

82. These characteristics include:

i) Solubility: is a measure of how much drug substance can be dissolved in a solvent. The solubility of a drug substance will be tested using a solvent subject to pre-set criteria. When formulating a drug, solubility needs to be considered, because the drug needs to dissolve into a solution (e.g. in gastric fluid) in order to be absorbed into the body. A further consideration that affects solubility is whether or not the drug is in a salt form. A molecule in a salt form is likely to have a higher water solubility than the free form of the drug.

ii) Molecular weight: The summed weight of the atoms in a particular molecule. When dealing with small molecule drugs, the molecular weight of the drug substance itself will be low.

iii) Permeability: For orally delivered drugs, this is a measure of the kinetics of the movement of a drug molecule across the semipermeable cell membranes between the GI tract and the bloodstream. Drugs with higher permeability pass through biological membranes with greater velocity.

iv) Charge: A drug molecule may have a positive, negative or neutral charge.

v) Dissolution: For solid oral drugs, the active drug substance needs to be released and dissolved in the gastrointestinal fluids to be available for absorption into the bloodstream. In a tablet formulation, or other solid

> dosage forms, the rate of dissolution of the drug and diffusion to reach the GI tract wall can be influenced by the water solubility of the drug, drug loading and the excipients that make up the rest of the dosage form. Drugs with higher water solubility will tend to dissolve more rapidly than those with lower water solubility in water. Excipients may accelerate or retard the rate at which water penetrates into the dosage form and/or the rate of fragmentation of the dosage form. The dissolution characteristics of formulations can be assessed using established industry and Pharmacopoeia methods.

83. The Biopharmaceutics Classification System ("**BCS**") was being used to classify drugs according to their physiochemical properties, specifically their solubility and permeability. The classifications are Class I (high solubility & high permeability), Class II (poor solubility & high permeability), Class III (high solubility & low permeability) or Class IV (low solubility & low permeability).

84. The physiochemical properties of a drug may influence choice of dosage form. For example, some drugs that have relatively short half-lives (approximately 4-6 hours) are often candidates for MR formulations in order to achieve less frequent dosing.

85. Solubility data is easy to obtain through experiments.

In vitro dissolution testing

86. An *in vitro* dissolution profile demonstrates the release of active substance from a formulation over a period of time and provides an early indication of the likely release behaviour *in vivo*. Dissolution testing can also be used to provide a reflection of how a formulation affects the dissolution of a drug. Understanding the dissolution profile *in vitro* may provide a reflection of how the drug will likely be absorbed *in vivo*. The dissolution profile of a drug will be required for regulatory approval.

87. Standard assays are used to measure drug dissolution *in vitro.* These are set out in the Pharmacopoeias. One common method used to assess the release rate of an oral solid dosage form product *in vitro* is a "paddle test" as described in various Pharmacopoeias (such as the US pharmacopoeia ("**USP**") or Japanese pharmacopoeia ("**JP**"), which is similar. Other pharmacopoeias such as the British or European also exist but were not relied on so it is not necessary to discuss them any further). The tests are similar in all Pharmacopoeias and consist of a defined water-based dissolution medium at a defined volume into which the dosage form is placed. USP method 2 is a method that uses a paddle which is rotated to create sufficient fluid movement to ensure good mixing of any dissolved molecules through the entire fluid volume. The concentration of drug that has dissolved into the medium is measured at regular intervals. The rotation rate of the paddle may be varied. Drug dissolution rate may accelerate with increasing paddle speed.

In vivo testing

88. *In vivo* analysis can be conducted in animal models or humans and enables PK measurements to be taken, such as blood plasma concentration over time. This can be plotted on a plasma concentration – time curve.

In vivo dissolution is slower than *in vitro*

89. In Professor Shakesheff's third report he explained at §4.3(d) that *in vivo* dissolution tends to take place more slowly than *in vitro* dissolution. He confirmed during XX that this would have been CGK to the skilled formulator at the Priority Date.

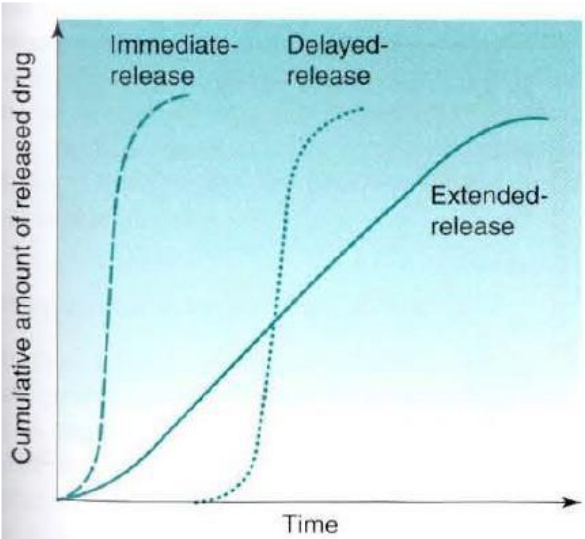
13. Excipient characteristics

90. During storage of a tablet and its journey through the GI tract, the excipients create the environment around the drug molecules or particles. Excipients have many functions and their physical and chemical characteristics can greatly influence the solubility, permeability and diffusion of drug molecules.

91. Some excipients may be included in a formulation to influence the rate of drug dissolution.

92. Other excipients may be included in a dosage form. These include anti-oxidants, film-coating excipients, compression aids, lubricants, solubilizers, pH modifiers, glidants, preservatives and stabilizers.

93. For some drugs, it is desirable to slow the rate of drug dissolution and escape from the dosage form. Excipients can be used to change the period of time it takes for drug molecules to dissolve and/or diffuse away from the dosage form. Various terms are used to describe the change in the period of release. Broadly put, an oral formulation may be characterised as either (i) an IR dosage form, or (ii) a modified release ("**MR**") dosage form. A diagram from Chapter 31 of Aulton (page 455) showing general release characteristics of these dosage forms is included below.



Schematic representation of the cumulative amount of drug released from IR,

delayed-release and extended-release formulations from Aulton.

94. Delayed release formulations such as enteric coated formulations may contain aspects of both IR and MR forms but are typically included in the category of MR. A delayed release dosage form is usually coated to prevent release of drug from occurring in the stomach. Once the coating is dissolved then the formulation may display IR characteristics. Extended-release formulations are a type of modified release, as further set out below.

14. Immediate Release Formulations

95. A range of IR systems were available at the Priority Date. Typical IR formulations are compressed tablets, which may or may not be coated with a protective coat, capsule formulations (a shell filled with powder or liquid form of the API), an oral solution or a suspension. An IR formulation allows the drug to be released without significant restriction from the dosage form. Typically, IR formulations are used with a view to rapid release of drug and rapid absorption by the body.

96. As many oral solid tablets are at least initially formulated as IR (unless there is a clear reason not to do so from pre-clinical or early clinical studies), IR is often referred to as a "conventional formulation". Other IR approaches, such as oral liquid formulations, were less common for medicines (particularly adult medicines) in the UK at the Priority Date.

97. There are a number of situations in which formulating an IR is disadvantageous for a specific drug.

98. Because IR formulations are intended to dissolve rapidly, the rate of absorption of a drug from an IR formulation may often be limited by physical or physiological barriers such as solubility of the drug or permeability through the gut wall, rather than by any release mechanism associated with the formulation. Consequently, IR formulations are typically used when the intended result is for the majority of drug to be dissolved and absorbed by the body in a short period of time. IR is usually characterised by a high C_{max} and low T_{max} compared to a MR formulation of the same drug.

15. Modified Release

99. In general terms, in contrast to an IR, an MR formulation exhibits some form of deliberate control over the release of the drug from the formulation. Typically, MR formulations delay, slow or prolong the release of drug in the body after it has been administered. MR is a widely used umbrella term for a number of different mechanisms, including:

    i) controlled release (which is often used as a similar or synonymous umbrella term),

    ii) delayed release,

    iii) extended release,

iv) prolonged or sustained release,

v) targeted release, and

vi) pulsatile (rarely used in practice).

100. These specific terms were generally understood and each can have situation specific nuances. The terms are not necessarily synonymous or mutually exclusive.

101. As compared with an IR formulation, the blood concentration of an MR formulation typically rises to a lower peak (i.e. lower C_{max}), and then falls away more slowly, as new drug is released and absorbed over an extended period, whilst existing drug already in the blood stream is eliminated. Where a MR formulation reduces the C_{max}, it will also reduce the likelihood of adverse effects associated with higher drug blood plasma concentration.

102. Typically, an MR formulation can also allow a steadier blood plasma level over time, with less variability between peaks and troughs than an IR formulation. This allows for greater coverage and less variability in plasma level over time, meaning the blood concentration will remain in the therapeutic window longer at the appropriate dose. It may also reduce the need for repeated dosing during the same time period.

103. Patient compliance is, in general, likely to be better if the patient is required to take tablets fewer times a day to obtain a therapeutic effect. As noted above, patient compliance in the therapeutic area of OAB was of particular concern with existing treatments.

16. Formulating extended-release drug products – overview

104. There was a substantial range of MR drug delivery systems available at the Priority Date, including:

i) Matrix systems which may release the drug by diffusion and/or erosion;

ii) Reservoir systems (including tablets coated with retaining polymeric film coats);

iii) Osmotic pump systems and related devices; and

iv) Ion-exchange control systems. Very few oral solid drugs have been formulated using ionic exchange, but it remains a classic "teaching example".

105. By 2008, many extended-release formulation types had been used in clinically employed orally administered medicines.

17. Example MR formulations

106. Oral matrix diffusion systems ("**MDS**") were a well-known type of drug delivery system at the Priority Date.

107. Two examples of subtypes of MDS at the Priority Date included: hydrophilic matrices, and lipid or insoluble polymer matrices.

Hydrophilic matrices

108. Polymers appropriate for a hydrogel are by their nature hydrophilic. As such, when the tablet imbibes water or other physiological fluids, the exterior of the tablet initially swells to form a gel or viscous like substance around the remaining solid matrix at the centre of the tablet that water has yet to penetrate into. Initially, drug located on or close to the surface of the matrix diffuses out through the gel layer. A sustained release of the drug then occurs as drug particles embedded deeper in the matrix are dissolved and released by a combination of diffusion (drug diffuses out of the tablet through the gel layer), or by erosion (the gel layer is dispersed into the bulk aqueous phase).

Reservoir systems

109. A reservoir system in the broadest sense involves the encapsulation of an active ingredient within a retaining membrane, through which the drug may be slowly released by controlling diffusion through that membrane.

110. Reservoir systems tended to be used primarily for transdermal applications rather than tablet formulations. This is primarily due to the high risk of "dose dumping" if the system is incorrectly manufactured or damaged (such as by biting or as a result of other mechanical stress). If the membrane is broken in an oral formulation, the entirety of the active ingredient will be available for absorption immediately. This can be very dangerous depending on toxicity of the drug. Although oral reservoir systems were well understood at the Priority Date, for the reasons above they were rarely used commercially.

Osmotic pump / pressure systems

111. Osmotic pumps were well understood at the Priority Date. The first osmotic pump system was patented in the mid-1990s by Alza Corporation and known as the OROS system ("**OROS**"). In general terms the tablet is constructed from a shell formed from a semi or non-permeable membrane on all sides. Laser drilled holes are then made through the shell to permit water to ingress into the centre of the tablet, known as the release unit. The increased volume of fluid inside the release unit will increase the internal pressure forcing the drug solution to be pumped out through the tablet's main orifice. Osmotic pump systems are more costly to design, test and manufacture.

18. Food effects

112. A drug or formulation may fare differently depending on whether the patient is in a fed or fasted state. A change in dissolution or drug absorption resulting in an altered pharmacokinetic profile due to the presence of food is termed a "food effect".

113. Drug-food interactions can cause absorption to be: (i) reduced, (ii) delayed, (iii)

increased, or (iv) accelerated. Alternatively, food can have no effect on absorption. A reduction or increase in amount of drug absorbed when administered with food is sometimes referred to respectively as a negative or positive food effect:

i) For some drugs, a positive food effect is observed in which administration with food increases $C_{max,}$ and/or AUC and the bioavailability of the drug. This may be of no clinical consequence or could result in C_{max} being too high and side effect intensity or incidence increasing.

ii) For some drugs, a negative food effect is observed in which $C_{max,}$ and/or AUC are lower in the fed state than in the fasted state. Again, this could be of no clinical relevance or it could result in reduced efficacy.

114. Therefore, in some cases, even though a food effect exists, it may not be problematic, in that the kinetics of drug absorption in both the fed and fasted state do not lead to any concerning differences in clinical outcome or side effect profiles. In other cases, food effects can lead to changes in C_{max}, C_{min} and AUC that result in the therapeutic benefit for the patient being compromised. For example, a food effect that alters or increases the extent of drug absorption can result in blood plasma levels rising above the minimum toxic concentration and the patient can experience side effects. Conversely, a reduction in C_{min} can result in the patient not experiencing the therapeutic benefit of the drug if the C_{min} falls below the MEC. A reduction of AUC due to an overall reduction in drug absorption can reduce the period of time over which the therapeutic benefit is experienced.

115. Food can have an effect on drug absorption. The presence of food in the GI tract can sometimes influence the rate and extent of absorption of drugs.

19. Causes of Food Effects

116. There are numerous mechanisms that create food effects. Specific mechanisms, and combinations of mechanisms, will be more or less important for different drugs. Broadly, the mechanisms that create food effects are either due to physiological changes or interference with the drug absorption process.

117. It is very difficult to predict the existence, nature or extent of a food effect before detailed investigation of causes in the human.

20. Food effect studies

118. A simple exploratory study intended to identify if a drug displays any food effects may be performed in early-stage clinical trials (phase I or phase IIa) of a drug intended to be orally administered.

119. Food effects studies involve the taking of blood samples at set intervals for analysis to determine if there is any difference in the drug's pharmacokinetic profile as between the fed and fasted groups and any differences in adverse event frequency / severity and toxicity issues (if any occur) are documented and

assessed.

120. It would be difficult (if not impossible) to predict the outcome of any food effects study in advance. In many cases no food effects issue will arise, whilst in others food effects may arise which do not have any clinical relevance; in both instances there may not be any need to alter the formulation (for clinical reasons). Where clinically relevant food effects are encountered it will be necessary to try to reduce them in order to achieve an acceptable balance between efficacy and safety in both the fed and fasted states (this would rely on the formulator undertaking the formulation work needed to try to do so). There was perhaps a minor disagreement between Professor Drake and Dr Morley on the ambit of 'clinically relevant food effects' which it is not necessary to resolve. The outcome of such reformulation attempts might be one of the following:

i) Food effects are essentially removed or remain but are reduced sufficiently that they are no longer clinically relevant. In such cases, if sufficient efficacy remains, it should be possible to proceed with the new formulation.

ii) Clinically relevant food effects remain but the nature of the drug, patient population and possible adverse events mean that it is acceptable for the formulation to be progressed, subject to suitable patient instructions being provided (e.g. 'take with food'). This might be the case if the potential adverse events arising due to patient non-compliance would not be expected to be serious. However, a requirement to take with / without food is obviously not a desirable drug characteristic (given the tendency for patient non-compliance).

iii) Clinically relevant food effects remain and the nature of the drug, patient population and possible adverse events mean that further development is not justified (for example because multiple competitor drugs already exist with similar efficacy and tolerability).

21. Regulatory guidelines for food effects

121. Food effect studies are the subject of guidance from regulatory agencies, including the US Food and Drug Administration and European Medicines Agency.

22. Pharmaceutical Development

122. Clinical trials are conducted in phases. The purposes of each phase (at a high level) are as follows:

i) **Phase I** trials involve small numbers of healthy volunteers.

ii) **Phase II** trials are typically performed in larger patient groups suffering from the relevant condition. Following Phase I, Phase II trials are used to investigate issues which may become apparent in a larger group and/or those suffering from the relevant condition.

iii) **Phase III** trials are typically significantly larger than earlier trials, generally involving hundreds or thousands of participants suffering from the relevant condition.

Disputed CGK

123. Three issues were identified as disputed. I deal with each in turn.

The paddle speed used to test extended release formulations.

124. Paragraph 87 above sets out the relevant background. The dispute seems to boil down to Professors Shakesheff and Craig having different experience in relation the paddle speed used to test extended release formulations.

125. In his written evidence Professor Shakesheff's view was that the paddle speed is typically 50-200 rpm, but he did not cite any references to support that range. Professor Shakesheff also commented that "*in his experience*" extended release formulations may also be tested at faster paddle speeds, but he did not suggest that that was part of the CGK of the skilled formulator, and again he did not give any references to support his view.

126. In her cross-examination of Professor Shakesheff, Counsel for the Defendants put a number of regulatory documents giving examples of lower paddle speeds, consistent with Professor Craig's written evidence. At times he took issue with whether or not the regulatory documents were of relevance to the skilled formulator, for good reason in my view. Ultimately, he agreed that a range of 50-75 rpm is a perfectly reasonable one to use, but equally 200 is used at times.

127. Professor Craig maintained his view in cross-examination that for a controlled-release formulation typically a lower speed of 50 to 75 rpm would be used. He explained that it is a convention in the field – with controlled-release systems the concern has always been if you have a very fast paddle speed, the system may be more sensitive to paddle speed than a normal immediate release dosage form. He fairly accepted that the higher speeds were not wrong, but it is not in line with the FDA guidelines that indicate for a controlled release, typical practice would be to have a relatively slow paddle speed. No documents were put to Professor Craig in XX to challenge this.

128. On this issue, I am inclined to accept Professor Craig's evidence because logic supports the convention he cited. Furthermore, the use of high paddle speed would be liable to increase the difference between *in vitro* and *in vivo* dissolution.

What the Skilled Team would have known about the guidance for conducting food effect studies set out in regulatory guidelines.

129. Astellas addressed this issue in their closing submissions whilst stating they did not understand what the dispute really was, in view of sections 20 and 21 of the Agreed CGK (as set out above). Thus, it was agreed CGK that relevant regulatory guidelines (from the FDA and EMA) were part of the CGK of the Skilled Team. I suspect that the perception that some issue remained stemmed

from some of the regulatory materials which were put in cross-examination, particularly on the paddle speed issue. These included some guidelines which seemed to originate from the Japanese regulatory bodies and various guidance published by the FDA predominantly for obtaining biowaivers. No expert had identified these materials as CGK, and Professor Shakesheff did not accept that they were.

130. Counsel also relied on the 'Japanese guidance' in relation to the Patent. To the extent that this matters, I address it below. So far as this purported CGK dispute is concerned, I was unable to detect any dispute.

Whether accumulation would be a concern for a Skilled Team when considering development of an extended-release formulation.

131. In closing, Astellas submitted it was common ground amongst the experts that the Skilled Formulator in the team would have a concern about formulating a long $T_{1/2}$ drug as an extended-release formulation because of a concern about accumulation. I agree. Professor Craig explained that Professor Shakesheff was entirely correct to have identified this concern and he himself had specifically raised this concern with Pinsent Masons. Dr Blakey accepted that a concern over accumulation was a 'possibility' (note that he regarded 'likely' and 'a possibility' as synonymous).

132. So the short answer is that accumulation would be a concern for the Skilled Formulator, but that led to two further and more substantial issues: first, would the Skilled Formulator raise this concern with a Skilled PK. One answer to this issue is that the Skilled PK is a member of the Skilled Team, so would be there to discuss the concern as soon as it was raised. I have already decided the Skilled PK is a member of the Skilled Team. The second issue is whether the Skilled PK would assuage that concern.

133. This is the related point as to the level of PK knowledge which the Skilled Team would possess. As to this, Astellas contended for a more limited level of PK knowledge. This argument formed one of the bases on which Astellas submitted the Skilled Team would read the prior art and decide not to apply any of that teaching to the task in hand.

134. These arguments revolved around whether the PK knowledge would include an understanding of 'flip-flop kinetics'. Dr Blakey explained that the Skilled PK would be able to model the likely behaviour of MR formulations of mirabegron and conclude that accumulation was unlikely to be a problem.

135. Astellas argued that 'flip-flop kinetics' did not form part of the CGK (even though Professor Shakesheff was aware of the term) and suggested to Dr Blakey that it was 'pretty niche stuff', on the basis they were not able to find the term 'flip-flop' in two textbooks. Dr Blakey accepted the term was not used in one textbook, Goodman & Gilman, because it is not a common occurrence. He also accepted 'It is niche' but that needs to be seen in the context of his whole answer. The relevant passage is as follows:

> 9 Q. You have not been able to reference any textbooks which deal

> with flip-flop kinetics, have you?
> A. No, flip-flop is -- it is discussed in papers that are published around the priority date. It is a term that can be sometimes called absorption rate-limited elimination, but "flip-flop" is a term that I came across when I first started learning about pharmacokinetics, which is quite a long time ago now.
> Q. Yes. We cannot find any reference to "flip-flop" in Goodman and Gillman or Rowland and Tozer, for example. You do not dispute that?
> A. It would not be mentioned in Goodman and Gillman, because it is not a common occurrence. It is a very specific situation where it does occur, so when you are talking about modified-release operations it is, I know there are papers out there discussing flip-flop kinetics of marketed drugs. As you say, it has not made it into the textbooks under that definition, but it does exist as a term and as a concept.
> Q. Can I suggest to you it is pretty niche stuff, doctor?
> A. It is niche. Modified-release preparations are quite a niche area of drug development, so the two, I think, go hand-in-hand.

136. Overall, I found Astellas' attempt to sideline the role of the Skilled PK in the Skilled Team and to downgrade the level of PK knowledge required as artificial. On Astellas' case, the Skilled Team would proceed on a misconception that the long half-life of mirabegron would cause accumulation and related problems if formulated into a modified release formulation, and this would cause them to decide not to implement any of the teaching in the cited prior art.

137. In my view, for the reasons summarised above, the Skilled Team includes the Skilled PK who understands flip-flop kinetics and is able to reassure the Team that accumulation would not be a problem for a modified release formulation of mirabegron.

THE PATENT

138. The insufficiency arguments led to heated debate over what certain parts of the specification mean or, rather, teach the Skilled Team. Accordingly, it is necessary to review the teaching in the Patent n some detail. I will make findings on the disputed paragraphs as I proceed against which I will then be able to determine the insufficiency arguments. As will appear, it is necessary to distinguish clearly between (a) *release* of the drug substance as opposed to its *absorption* and (b) whether the Patent is talking about the situation *in vivo* or *in vitro.*

139. I was told that the priority document, filed in the US, was in Japanese. Translation from Japanese can prove problematic, but the Skilled Team and the Court have to deal with the language as expressed in EP410.

140. The first section of the Patent is headed 'Technical Field' and summarises the invention as follows:

> [0001] The present invention relates to a pharmaceutical

> composition for modified release capable of reducing food effects, which are observed in conventional tablets, by combining an active ingredient with specific ingredients to control a releasing rate of the active ingredient.
>
> [0002] More particularly, the present invention relates to a pharmaceutical composition comprising (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt thereof, an additive which ensures penetration of water into the pharmaceutical composition (hereinafter sometimes referred to as a hydrophilic base), and a polymer which forms a hydrogel, in which the changes in AUC and Cmax caused by the intake of food can be decreased by controlling a releasing rate of the active ingredient.

141. The structural formula of the identified chemical compound is presented in [0027]. It is sometimes referred to in the Patent as Compound A. Although the Patent does not identify it as mirabegron, it is common ground that it is. For simplicity I will refer to it simply as mirabegron however it is referred to in the specification itself.

142. Under the next heading 'Background Art', mirabegron is identified as being useful to treat diabetes and for OAB. Then in [0005] the specification relates that an unpublished clinical trial of mirabegron in conventional formulations revealed a food effect. Some data are provided:

> 'For example, the rate of decrease of Cmax in a fed state was 67% and the rate of decrease of AUC in the fed state was 47%, in comparison with those in a fasted state. In this case, Cmax in the fasted state was three times higher than that in the fed state.'

143. It was common ground that the Skilled Team reading the Patent would understand the reference to 'rate of decrease' to be erroneous but would be able to work out what was meant from a later paragraph [0024]. It is convenient to clear away this point now. This point is just one example where the drafting of the specification is infelicitous. [0024] provides:

> 'The rates of decrease of Cmax and AUC are calculated by the following equations:
>
> Rd(Cmax) = [Cmax FS − Cmax FI] × 100 / Cmax FS
>
> Rd(AUC) = [AUC FS − AUC FI] × 100 / AUC FS
>
> Rd(Cmax): Rate of decrease of Cmax (%)
>
> Cmax(FS): Cmax in administration in the fasted state
>
> Cmax(FI): Cmax in administration after food intake
>
> Rd(AUC): Rate of decrease of AUC (%)

AUC(FS): AUC in administration in the fasted state

AUC(FI): AUC in administration after food intake

144. Dr Blakey said the Skilled PK would consider the use of the term 'rate' in this context was technically inappropriate since rate is a time-dependent measure and the equations relate only to magnitude. He also said the Skilled PK would put aside that linguistic point and would appreciate these equations provide a percentage difference in Cmax and AUC following administration in the fed and fasted states. His evidence was not challenged, and I accept it.

145. [0006] and [0007] acknowledge a prior document which is said to disclose a MR formulation comprising a hydrogel sustained release tablet containing an additive which ensures penetration of water into the tablet, but it is distinguished on the basis that the document does not refer to mirabegron. Further improvements are said to be needed.

The central teaching

146. Under the heading Summary of Invention, [0008] describes the technical problem addressed: to provide a pharmaceutical composition for MR for [mirabegron] in which the efficacy is the same or higher than those of conventional formulations and which 'has no limitations on food intake'.

147. [0009]-[0013] contain the description of the 'Solution to the Problem'. It was common ground that [0010] contained the central teaching in the Patent namely, the inventors' theory as to how the invention reduces the food effect for mirabegron. [0010]-[0012] in particular were the subject of intense debate. To explain the arguments and my findings, I will set out [0009]-[0013] here, with my emphasis added:

> [0009] The elimination half-life ($T_{1/2}$) of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide is long (approximately 18 to 24 hours), and thus, a formulation thereof for modified release is not necessarily needed to maintain its blood level. Taking into consideration the results of the clinical trial described above, the present inventors conducted intensive studies to design the formulation by paying attention to the control of a release rate of the drug from a formulation to the extent that the release is not affected by food intake or the like, rather than the addition of release control.
>
> [0010] On the basis of blood concentration profiles (in a fasted state/after the intake of food) after administration of a conventional formulation (rapid release formulation), the absorption rate of the drug in a fed state was calculated by a deconvolution method to predict continuous absorption for about 4 hours. The present inventors considered from this result that a formulation capable of continuous drug release for 4 hours or more would be able to reduce the effects by food, because the drug release from the formulation would become the rate-

> limiting step for absorption.
>
> [0011] The present inventors carried out a clinical trial in human using three types of formulations in which the release rate of the drug was controlled (Time when the release percentage of the drug from the unit formulation was 80% (T80%) = 4 hr, 6 hr, and 10 hr), and found that all formulations could reduce the effects by food, to complete the present invention.
>
> [0012] It is generally known that the retention time in the stomach and the release rate of formulations for modified release vary according to the presence or absence of food intake, and as a result, there is a possibility that blood concentration profiles is changed. However, surprisingly, when using this formulation, the change of the blood concentration profiles was small in the presence or absence of food intake.
>
> [0013] The present invention is characterized by providing a pharmaceutical composition for modified release which is not affected by the effects of food intake and exhibits a decreased change in AUC or Cmax.

148. The point being made in the first sentence of [0009] is that, because the elimination half-life of mirabegron is long (18-24 hours, approx.), one does not necessarily need a MR formulation to sustain an effective level of the drug in the blood. Then in the second sentence (and as a prelude to [0010]), the inventors explain that their focus was not on release control but on paying attention to the control of a release rate of the drug from a formulation so that the release is not affected by food intake. The significance of the difference between release control and control of release rate is not immediately obvious. Of the experts, only Professor Shakesheff sought to explain this sentence. The prelude to it is the Skilled Formulator's own expectation for drugs with long half-lives, which he said was in line with the first sentence, that an MR formulation is not necessarily needed. Professor Shakesheff then explained the second sentence in these terms:

> 'Accordingly, in light of the clinical data, the focus for the inventors was to provide a formulation whereby release is less affected by food but without unduly extending the release beyond a point where food effects will no longer be problematic.'

149. The Professor was not challenged on this explanation and scant, if any, attention was paid to this second sentence in [0009]. However, as I explain further below, the point made by Professor Shakesheff is of some significance. It is a foundation for his 'mid-range' theory which he said underpinned the Patent.

150. The first sentence of [0010] refers to another unpublished *in vivo* study (which may or may not be the same as the clinical trial in [0005] – it does not matter which) in which blood concentration profiles were measured after administration of a conventional formulation in both the fed and fasted states.

From those data, '*the absorption rate of the drug in a fed state was calculated by a deconvolution method to predict continuous absorption for about 4 hours'*. As Professor Blakey said, convolution is a process where two functions produce a third. His evidence was that:

> 'From a PK perspective this could be the convolution of the intravenous ('iv') plasma concentration time curve with absorption rate to get the extravascular ('ev') concentration time curve. Deconvolution can be used to obtain the absorption rate when only iv and ev concentration time profiles are known.'

151. The message so far is that continuous absorption for about 4 hours from a conventional formulation in the fed state gave rise to a food effect. The second sentence of [0010] contains the central theory of the Patent. In other words, to reduce the food effect, you need a formulation capable of continuous drug *release* for 4 hours or more because then the drug release from the formulation is the rate-limiting step for *absorption i.e.* it is necessary to slow the drug release from the formulation so that absorption continues beyond 4 hours. The focus on drug release is understandable since that forms part of the design of the modified release formulation, but, in terms of reducing the food effect, the important measure seems to be absorption. After all, the ways to measure a reduction in food effect explained in [0023] and [0024] are by reference to concentrations of the drug in the blood (i.e. after absorption). The concentrations in the GI tract caused by release are not material in that regard.

152. In closing submissions, there was a lively debate over whether this drug release measure was *in vivo* or *in vitro*. In his reply speech, Mr Mitcheson submitted that the Defendants had completely misunderstood the disclosure of [0010]. He submitted that in the second sentence of [0010] the inventors are saying that they have identified that if the drug release from the formulation in the body is four hours or more, that is going to reduce the effect by food because the drug release in the body would become the rate-limiting step for absorption. After Mr Mitcheson had finished his reply, Miss May complained that this was a new (and a third) case from Astellas in response to the Defendants' insufficiency attack. She complained it was not in any written evidence and was not foreshadowed in his oral or written opening. It may not matter overmuch, but I consider it was foreshadowed in Mr Mitcheson's oral opening. Having read out the second sentence of [0010], he said 'The experts, or at least one of the experts, has addressed this and explained that in these *in vivo* release studies you would expect the drug to be released more slowly *in vivo* than you necessarily find with an *in vitro* dissolution experiment. That, no doubt, will be explored a bit further in the evidence.' (T1, page 4).

153. Turning to the substance of the point, Miss May submitted it was clear that the drug release measure was an *in vitro* measure. Her argument started with the reference in the first sentence of [0010] to the conventional formulation. This is defined in [0021] by reference to an *in vitro* dissolution measure, so, the argument goes, the reader is put in mind of an *in vitro* dissolution profile. Next, reference is made to [0011] where it was common ground that the $T_{80\%}$ release percentage would be measured *in vitro*. Accordingly, so the argument goes, the key second sentence in [0010] is sandwiched between *in vitro* dissolution

measures and it is natural to read that second sentence as referring to *in vitro* release.

154. I do not find this argument at all persuasive. There is no need at all, when reading the first sentence of [0010], to have in mind how the Patent defines the conventional formulation dissolution limit. Furthermore, [0011] is talking about how the inventors sought to obtain support for their central theory, but [0011] is clearly not presented as direct proof of an *in vitro* four hour + release.

155. I consider it is clear that the second sentence is talking about drug release for 4 hours or more *in vivo*. The first sentence is plainly talking about blood concentration profiles obtained from *in vivo* testing. I consider it is equally clear that it is also talking about the absorption rate of the drug *in vivo*. So the prediction was that the conventional formulation displayed continuous absorption (in the body) for about 4 hours.

156. The inventors plainly seek to slow the absorption of the drug (in the body). They postulate that a formulation capable of drug release (in the body) for 4 hours or more would be able to reduce the effects by food, because the drug release (in the body) from the formulation would become the rate-limiting step for absorption (in the body).

157. This is, in my view, not only the natural reading of [0010], it is also a reading which is more consistent with the *in vitro* dissolution limits set out in [0025] and in Claim 1 than the suggested alternative. Furthermore, the inventors make clear when they are referring to *in vitro* dissolution because they specify the test conditions from a Pharmacopoeia (see e.g. [0021], [0025], [0105] and in the final integer of claim 1).

158. Returning to the specification, [0011] refers to a clinical trial in humans (again it does not matter whether this was done as part of the trial referred to in [0005] or not) where three formulations were administered. In each, the release rate of the drug was controlled by reference to $T_{80\%}$ (the time when the percentage of the drug released from the formulation was 80%) of 4 hours, 6 hours and 10 hours. It is said it was found that all three formulations could reduce the food effect. As I have already indicated, it was common ground that $T_{80\%}$ would have been measured *in vitro*.

159. As an aside, I record that in his oral opening, Counsel for Astellas submitted that the 10-hour formulation was not within claim 1. Counsel for the Defendants did not agree that necessarily followed. For a considerable time I was even more sceptical. This small group of paragraphs comprises the key teaching in the Patent. All three formulations are said to reduce the food effect. There is no teaching in the Patent which indicates that the Patentee wished to exclude the 10-hour formulation from the scope of claim 1, and I received no expert evidence to that effect. Furthermore, the 10-hour formulation seems to me to fit within the way that the limits in the claim were explained (see paragraph 243 below). The fact this submission was made perhaps indicates a concern on Astellas' part (at least at that stage of the case) about the release of the drug extending significantly into the colon, a point I return to later.

160. [0012] refers to some CGK that food can have an effect followed by what can be a fairly routine expression of surprise from a Patentee that his invention works.

161. [0013] characterises the invention as providing an MR formulation of mirabegron 'which is not affected by the effect of food intake and exhibits a decreased change in AUC or Cmax'.

162. [0014] contains a series of consistory clauses of the unamended claims. [0015] contains an acknowledgement of some further prior art relating to a sustained release formulation for tamsulosin hydrochloride, which is distinguished by reference to that drug and a low dose (0.4mg per unit formulation), in contrast to the high dose required of mirabegron.

163. The 'Advantageous Effects of Invention' are specified in [0016]-[0018]. To summarise, the formulation of the invention has no limitations on food intake, is stable, the AUC may not be reduced plus, in comparison with the rate of decrease of Cmax in the fed state of 67% in comparison with that in the fasted state for the conventional formulation (as also reported in [0005]), for the MR formulation of the invention, the rate of decrease of Cmax was 42% in the fed state compared with the fasted state. The specification claims that this result showed that 'reduction of Cmax caused by food intake could be significantly alleviated' by the MR formulation of the invention.

164. The single figure, Fig 1, is described in [0019] as a graph showing dissolution profiles of the MR formulation in Example 11. I will discuss it in that context.

165. The next heading is 'Description of Embodiments'. [0021]-[0027] contain a series of definitions, some of which appear to be nested. Notwithstanding the way in which these definitions are expressed, the applicability of some of these definitions was disputed by Astellas. I need to summarise these definitions in order to then address the arguments. In my quotes I have underlined the defined terms for clarity.

166. [0021] starts:

> 'The term '<u>rapid release formulation (conventional formulation)</u>' as used herein means a formulation in which the dissolution rate of the drug from the formulation is 85% or more after 30 minutes from the beginning [of] a dissolution test…'

167. Two dissolution tests are mentioned, both using paddle methods. The first is from the US Pharmacopoeia using 900mL of test fluid (such as a USP buffer, pH 6.8) at a paddle rotation speed of 100 rpm. The second is from the Japanese Pharmacopoeia, again in a suitable buffer at pH 6.8 and at 50 rpm.

168. Although the terms are reversed in [0010], I consider the Skilled Team would take this definition to apply to [0010], as well as elsewhere in the specification.

169. In [0022], I have put certain words in bold, the significance of which will emerge after I have covered [0025]:

> [0022] The term "pharmaceutical composition for modified release" as used herein means a **formulation in which** the dissolution rate of the drug from the formulation is less than 85% after 30 minutes from the beginning a dissolution test carried out under the above conditions, and the drug release is controlled to the extent that **the effects by food are reduced**. More particularly, it is a formulation in which an additive (hydrophilic base) which ensures penetration of water into the formulation is combined with a polymer which forms a hydrogel.
>
> [0023] The wording "the effects by food are reduced" as used herein means, for example, a 10% reduction, a 20% reduction in another embodiment, and a 30% reduction in still another embodiment, in comparison with Cmax of a conventional formulation. Alternatively, the term means, for example, a 10% reduction with respect to the rates of decrease of Cmax and AUC in administration after food intake, in comparison with Cmax and AUC in administration in the fasted state, a 20% reduction in another embodiment, and a 30% reduction in still another embodiment.
>
> [0024] *quoted and discussed above.*
>
> [0025] The term "formulation in which the effects by food are reduced" as used herein means a formulation in which the dissolution rate of the drug from the formulation is 75% or less after 1.5 hours and 75% or more to 100% or less after 7 hours from the beginning a dissolution test, which is carried out in accordance with a dissolution test (paddle method) described in the United States Pharmacopoeia under the conditions that 900 mL of USP buffer, pH 6.8 is used and the paddle rotation speed is 50 to 200 rpm.

170. It is not necessary to set out [0026] – which defines '"stable" as used herein' or [0027] which sets out the structural formula of mirabegron and says 'hereinafter sometimes referred to as compound A'. However, it is necessary to tackle a dispute which arose over the alternatives set out in [0023]. Astellas also raise a separate point that [0023] does not provide any definitions at all, but I will deal with that below.

171. The experts were agreed that [0023] sets out two alternative meanings – which Dr Blakey referred to as Meaning 1 in the first sentence and Meaning 2 in the second.

172. Read literally, the first sentence seems to require simply a reduction in Cmax for the MR formulation when compared with Cmax for the conventional formulation. Dr Blakey explained this would not be a technically meaningful way to describe any reduction in food effect because an MR formulation which simply reduces Cmax may show the same or an even worse food effect. This latter point was demonstrated in the cross-examination of Professor Shakesheff who had adopted a literal interpretation of the first sentence but accepted that it

was possible the skilled formulator would not interpret it in the same way. In the context of the first sentence, I accept that the only way to assess whether a food effect has been reduced is to carry out a fed/fasted study to assess the size of the food effect gap (when Cmax and/or AUC are measured) for a conventional formulation and the MR formulation and then to compare whether the 'gap' has reduced. This is reinforced by consideration of the second sentence.

173. As the Defendants pointed out, the second sentence contains another nested definition – of the term 'the rates of decrease' which is explained in [0024]. I have already explained how this term would be understood by the Skilled Team, by reference to [0024]. Thus the second sentence requires there to be a reduction in Cmax and AUC when the drug is administered after food intake when compared with Cmax and AUC when the drug is administered in the fasted state, but this only makes any sense if the reductions in Cmax and AUC are compared as between the conventional formulation and the MR formulation, as Dr Blakey and Professor Shakesheff agreed.

174. Hence Dr Blakey said that Meaning 1 would be understood to require the same comparison as was agreed for Meaning 2. I agree. With those disputes out of the way, the difference between the two alternatives is simple. Meaning 1 requires a reduction in just the Cmax gap whereas Meaning 2 requires a reduction in both Cmax and AUC gaps. These alternatives are consistent with [0013] 'a decreased change in AUC or Cmax' and [0017] 'a pharmaceutical composition for modified release in which AUC is not reduced can be provided.'

175. Two final points arise on these percentage reductions. The first is an ambiguity pointed out by the Defendants. Examples of the size of the reduction are stated to be 10%, 20% or 30% but the gaps themselves are already expressed as percentage figures. Hence it is ambiguous whether the stated percentage reductions are absolute or relative. The Defendants gave an example based on the Rd figures from [0018]. The absolute percentage reduction between the conventional Cmax gap of 67% and the MR Cmax gap of 42% is 25% (42-67= -25%), whereas the relative percentage reduction is 37% ((42-67)/67 * 100 = -37%). As the Defendants also accepted, this ambiguity does not seem to matter because both sides were agreed that the claims do not require any particular level of reduction. The percentage reductions in both Meanings are just examples.

176. This leads to the second point. Astellas contended that [0023] does not contain definitions at all because the two alternatives are presented merely as examples. This is at the heart of the dispute on construction – see further below.

177. Taking a step back from the detail of these definitions, in my view the Skilled Team would understand the inventors were setting out in these paragraphs their own lexicon of terms **'as used herein'**. Leaving aside the terms in dispute:

    i) The term 'rapid release formulation (conventional formulation)' is used reversed in [0010]. Several other paragraphs refer simply to conventional formulation ([0005], [0008], [0018], [0023], [0111] and

[0112]);

ii) The term 'pharmaceutical composition for modified release' is used in many paragraphs in the specification and in all the claims;

iii) The term 'stable' is used in [0016], [0107], [0108] and [0109].

178. Accordingly, the expectation is that the terms defined in [0023] and [0025] are to be understood as performing the same function.

179. The term 'the effects by food are reduced' is used only in [0022], in the definition paragraph itself [0023] and in [0025]. The term 'formulation in which the effects by food are reduced' is not used in that exact form other than in the definition paragraph [0025]. However, it can be seen that the expression is contained within [0022] – see the emboldened words above.

180. The final dispute between the parties on these paragraphs is whether [0025] is part of the definition in [0022]. I will address this when considering construction.

The Remaining Disclosure in the Patent

181. Paragraphs [0027]-[0084] provide various details about how the compositions of the invention can be formulated and used. The Defendants drew attention to the following points:

i) The suggestion that the compositions can be administered once daily or in 2-4 doses per day (paragraph [0029]).

ii) The wide range of doses of mirabegron that can be used (1mg-500mg) (paragraph [0030]).

iii) The requirement that the hydrogel forming polymer "can control the release rate of the drug to the extent that the blood concentration profile of the drug is not affected by the presence or absence of food intake" ([0031], and [0034] to similar effect).

iv) Examples of the *"hydrogel forming polymer*" are PEO, HPMC, and HPC ([0034]), and these can be used in combination ([0038]).

v) That "the content of the hydrogel forming polymer is not particularly limited so long as it is an amount to the extent that the blood concentration profile of the drug is not affected by the presence or absence of food intake" ([0039]). Professor Shakesheff agreed that the skilled formulator would understand this disclosure to be teaching that the amount of polymer used did not matter, so long as there is a reduction in the food.

vi) The "*additive*" of the composition is also referred to as a "*hydrophilic base*", which ensures water penetration into the formulation, examples of which are PEG, PVP, D-mannitol, lactose, sucrose and others ([0041]).

vii) As is the case with hydrogel polymer, "the content of the hydrophilic base is not particularly limited so long as it is an amount capable of controlling the release of the drug to the extent that the release of the drug is not affected by food" ([0044]). Again, Professor Shakesheff agreed that the Skilled Formulator would understand this disclosure to be teaching that the amount of additive used did not matter, so long as there is a reduction in the food effect.

viii) Standard manufacturing methods are discussed at [0060]-[0080], which are all said to be known. It is not suggested that the process of manufacture has any relevance to the invention.

The Examples

182. The Examples are set out in [0085]-[0112].

183. There are 17 examples of modified release compositions that use different combinations of mirabegron, hydrogel-forming polymer and additives. There is also a 'Comparative Example 1' ([0104]) which is a conventional formulation of mirabegron.

184. Three of the modified release examples (Examples 2, 8 and 9) and the Comparative Example are subjected to an *in vitro* dissolution test – see [0105]. The results are set out in Table 4, and it is stated ([0106]) "*The dissolution rate after 1.5 hours of the pharmaceutical composition for modified release prepared in each Example was less than 40%. By contrast, the composition prepared in Comparative Example showed a high dissolution rate of 85% or more after 0.5 hour.*

185. The dissolution profiles are not shown plotted, but the Skilled Team would be able to plot the three points provided for each one. From that, he or she would see almost linear profiles, starting from the origin, with little variation between the three. All would fit within the dissolution limits of the claim. Miss May accepted the dissolution rates of all the modified compositions appear broadly the same, with each appearing to achieve release over a period of more than 4.5 hours (93%, 95% and 92%). She pointed out there are no data showing the amount of dissolution at 7 hours and also submitted that without further data it is not possible to determine when release concluded, or if it plateaued before 4.5 hours.

186. However, these data would be considered in the light of the stability data which are described in [0107]-[0109] and which are said to show that some of the example modified release compositions are stable in a variety of storage conditions. [0107] is concerned with the composition prepared according to Example 11. The dissolution profile of Example 11 composition before preservation and after it has been stored under different conditions is illustrated in Figure 1. It is not possible to extract precise data points from this Figure, but it appears that less than 40% had dissolved after 1.5 hours (consistent with Examples 2, 8 and 9) but that the release at 4.5 hours was lower (at about 85%). Professor Shakesheff agreed that Figure 1 appeared to show 75% dissolution at about 4hrs with a plateau around 6hrs.

187. In my view, the Skilled Team would not share the Defendants' scepticism and would expect the dissolution profiles of Examples 2, 8 and 9 to be similar. Thus the Skilled Team would expect that those profiles had not plateaued before 4.5 hours but would have plateaued between 5-6 hours.

188. The Defendants were keen to point out that these are all the data there are in the Patent regarding the *in vitro* dissolution rates of any modified release compositions or conventional formulations of mirabegron. That is true and, as is often the case, additional data would have been desirable, but it does not detract from the significance of the data which are presented.

189. There is then a single *in vivo* "PK test" described at [0110]-[0112]. Healthy individuals were given a single modified release composition (Example 8). For comparison, healthy individuals were given two pharmaceutical compositions prepared according to a conventional composition (Comparative Example 1). The compositions were given in a fasted state or after 30 minutes from intake of food, and the respective plasma levels of mirabegron were then measured.

190. It is stated:

    i) That in the conventional formulation "the rate of decrease in Cmax in the fed state was 67% compared to the fasted state, and the rate of decrease in AUC was 47% (Cmax in the fasted state was approximately three times higher than the fed state)". The Defendants pointed out that these are the same data as those set out in [0005] of the Patent.

    ii) That in the modified release formulation "the rate of decrease of Cmax in free-feeding was 42%, in comparison with that in a fasted state, and the rate of decrease of AUC was 25%".

    iii) And that "These results indicated that the reductions of Cmax and AUC caused by food intake could be significantly alleviated by the pharmaceutical composition for modified release of the present invention."

191. The Defendants were keen to point out that:

    i) These are the only *in vivo* data in the Patent.

    ii) No data are given for the measured values of Cmax or AUC in any of the subjects. The only data are the % Rd values, which (as they pointed out) reflect the magnitude of the <u>difference</u> between the fed and fasted values, but shed no light on what the actual measured values were.

    iii) Different doses of mirabegron were administered using the particular conventional composition (Comparative Example 1) and the modified composition (Example 8). Example 8 was administered as one tablet containing 200mg of the active, and Comparative Example 1 was administered as two capsules containing 160mg of the active. For this reason the Defendants submitted that, irrespective of any effect caused by the change in formulation, the change in dose would have been

expected to affect Cmax and/or AUC in any event.

iv) Although the Rd values are lower for both Cmax and AUC for the modified composition, the Patent does not say what % reduction this is. Hence this does not help to resolve the ambiguity which the Defendants raised regarding [0023].

v) The Patent does not include any detail of the human studies, such as the food ingested (as Dr Blakey said, a high fat meal can generate different results from a low-fat meal), the sample size or whether the studies were designed to detect a particular change in AUC or exposure. Geometric mean values and the associated confidence intervals along with statistical interpretation are not provided.

192. There was some debate between the experts as to whether the skilled team would assume that the Patentee had administered a high fat meal, based on regulatory guidance. Professor Drake agreed in XX that the Patent is completely lacking in any information about the protocol of the food effect study that was undertaken, and that as a result, the Skilled Clinician is not going to make any assumption about what the protocol was. Dr Blakey said that if you looked at the guidance you might assume that a high fat meal had been used in the absence of other information, but noted that there are no data to confirm that a high fat meal was used. This evidence is consistent with the fact that the claim is not limited to assessing the food effect by reference to any particular meal type, and so covers both a high fat and a low fat meal.

193. Under the final heading of Industrial Applicability, [0113] says:

> 'According to the present invention, a pharmaceutical composition for modified release in which the changes in AUC and Cmax caused by food intake can be decreased by controlling a releasing rate of the active ingredient can be provided.'

194. This, in my view, offers some further support for my view that [0010] is talking about release in the body.

The Claims

195. Neither side drew attention to any claim other than claim 1. It is convenient to set it out here with the proposed amendments added (in underline and strike-through):

> **A:** A pharmaceutical composition for modified release, comprising: (1) 10 mg to 200 mg of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof,
>
> **B:** (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and

> **C:** (3) a hydrogel-forming polymer having an average molecular weight of 100,000 to 5,000,000 or a viscosity of ~~12 mPa·s or more in a 5% aqueous solution at 25°C,~~ 400 mPa·s or more in a 2% aqueous solution at 25˚C and 7,500 mPa·s or less in a 1% aqueous solution at 25°C;
>
> **D:** wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrose, sodium chloride, and polyoxyethylene polyoxypropylene glycol and wherein the amount of the additive which ensures penetration of water into the pharmaceutical composition is 20% by weight to 60% by weight to the total weight of the pharmaceutical composition;
>
> **E:** wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose and wherein the amount of the hydrogel-forming polymer is 10% by weight to 40% by weight with respect to the total weight of the pharmaceutical composition; and
>
> **F:** wherein the drug dissolution rate from the pharmaceutical composition is 75% or less after 1.5 hours and at least 75% after 7 hours from the beginning of the dissolution test and wherein the dissolution test is carried out in accordance with the paddle method described in the United States Pharmacopoeia under the conditions that 900 mL of USP buffer, pH 6.8, is used and the paddle rotation speed is 50 to 200 rpm.

196. The amendment to Integer A is unconditional. The amendment to integer C is Conditional Amendment 1, the amendments to integers D and E is Conditional Amendment 2. Conditional Amendment 3 combines 1 and 2.

CONSTRUCTION

197. My task is to undertake a 'normal' interpretation of the claims: see *Eli Lilly v Actavis UK Ltd* [2017] UKSC 48. This is a very familiar test, but I am reminded that it remains an exercise in purposive construction (*Icescape Ltd v Ice-World International BV* [2018] EWCA 2219 at [60] per Kitchin LJ (as he then was). It is an objective exercise and the question is always what a skilled person would have understood the patentee to be using the words of the claim to mean.

198. In this case there is an accusation of 'meticulous verbal analysis' so I have also reminded myself of the useful dictum of Pumfrey J. in *Halliburton v Smith* [2005] EWHC 1623 (Pat), [2006] RPC 2 at [69]. In [68], he set out the principles to be applied from *Kirin-Amgen* and then added three observations of his own. I refer to the third which I consider continues to be applicable:

> 'Finally, and most importantly, over-meticulousness is not to be equated to carefulness. Care in working out what the patentee was aiming at when he chose the words he used is absolutely necessary.'

199. The only point in dispute is the construction of 'a pharmaceutical composition for modified release' in integer A. Both sides appeared to accept that the issue turned on the approach one took to the definitions in paragraphs [0022], [0023] and [0025].

200. Mr Mitcheson for Astellas argued that the definition in [0022] applied. In that definition, the expression 'formulation in which ….the effects by food are reduced' is found which thereby incorporates the definition in [0025]. The Skilled Team would see these dissolution limits included in the claim. Mr Mitcheson argued that this construction has the benefit of clarity and simplicity – whether a formulation falls within claim 1 can be ascertained simply by reference to its composition and a routine dissolution test and avoids the necessity for costly and time-consuming clinical trials.

201. On this last point, Astellas elicited evidence from Professor Craig in cross-examination that in 2008 ethical approval would have been required to conduct *in vivo* studies in animal or human models to enable PK measurements to be taken. The next question and answer was as follows:

> 16 Q. It is unlikely you would have approval granted if the only
> 17 reason for doing those studies was a patent case?
> 18 A. I could not comment on that. I am afraid I do not know enough
> 19 about regulatory law or patent law to comment on that.

202. Accordingly, Miss May was correct in pointing out in closing that there was no evidence that the Skilled Team would know that *in vivo* studies would not be allowed to prove infringement, as Mr Mitcheson had submitted. Although he did not state this explicitly, his retort appeared to be an invitation to me to take judicial notice of the point. I do not feel able to do so.

203. If this fact had been notorious, one would have expected, at the very least, that the Patentee and its advisers would (a) have been well aware of it and (b) taken steps so to draft the Patent and its claims specifically to avoid the need for any *in vivo* studies. However, it is clear they did not do so. At best, they ran the risk that the Patent would be construed so as to require *in vivo* studies in order to prove infringement. It is fruitless to speculate why these definitions were included and drafted as they were because the Court does not know what influences were operating on the Patentee at the time.

204. These arguments in Astellas' opening skeleton argument were framed by reference to Sandoz's infringement argument. Sometimes infringement arguments help to pinpoint the construction issue but in this case I prefer to leave those matters entirely out of account. As has been said, the Patent must be construed as if the defendant had never been born.

205. Furthermore, despite the fact that the expression defined in [0025] contains the

expression 'the effects by food are reduced', Mr Mitcheson argued that this did not incorporate [0023] for three reasons, as I understood his argument. First, because [0025] contains a complete definition of the phrase which is found in [0022], thus [0023] is not needed. Second, because [0023] is not a definition at all because it merely presents examples. Third, Mr Mitcheson relied on some evidence from Dr Blakey's first report where he discussed [0105] and [0106], as follows:

> 'Paragraphs [0105] and [0106] set out a dissolution test using formulations prepared according to Examples 2, 8 and 9 and Comparative Example 1. The dissolution profiles of Examples 2, 8 and 9 meet the definitions of "pharmaceutical composition for modified release" and "formulation in which the effects by food are reduced" and the profile for Comparative Example 1 meets the "conventional release" definition.'

206. In cross-examination, Dr Blakey agreed that the terms in inverted commas were references to the definitions found in [0022] and [0025]. However, it was clear from his answers that he was focussing on dissolution profiles and whether they were within the limits of the claim. Further the unspoken assumption on which this cross-examination proceeded was the PK results from humans in [0110]-[0112] which demonstrated a reduction in food effect.

207. Although Mr Mitcheson submitted this evidence from Dr Blakey settled the question of construction in Astellas' favour, I do not agree. With no disrespect at all to Dr Blakey, to defer to this bit of his evidence would be a mistake for several reasons. First, the question of construction is not for the experts. Second, there is nothing to indicate that Dr Blakey had the correct principles in mind. Third, and relatedly, my impression that he was simply focussing on the dissolution limits is a positive demonstration that he did not.

208. Miss May for the Defendants made three main points:

i) Her first point was that only a lawyer would find the expression 'formulation in which the effects by food are reduced' in [0022]. This, she submitted, was over-meticulousness.

ii) Second, in any event, there is no need to incorporate the dissolution limits contained in [0025] into the definition of 'pharmaceutical composition for modified release' because those dissolution limits are in integer F of claim 1.

iii) Third, and most importantly of all, the debate over whether [0025] is incorporated into [0022] is a sideshow and does not matter. What matters is that [0022] contains the expression 'the effects by food are reduced' which thereby incorporates the definition in [0023].

Discussion

209. The arguments seemed to focus on the fact that certain terms are defined rather than the content of the 'definitions'. I consider it is helpful to focus on what is

going on in each definition.

210. First, in [0021] the key characteristic of the 'rapid release (conventional formulation' is that the dissolution rate of the drug is 85% or more after 30 minutes, applying the stated dissolution test.

211. Second, in [0022], the first characteristic of the 'pharmaceutical composition for modified release' is that the dissolution rate of the drug is 85% or less after 30 minutes, drawing a distinction between the two. I realise that the claim includes a more stringent distinction – a dissolution rate of 75% or less after 1.5 hours – but in these two paragraphs, the Patentee clearly wanted to delineate a boundary between conventional and modified release formulations.

212. The second characteristic of the 'pharmaceutical composition for modified release' is that the drug release is controlled to the extent that the effects by food are reduced'. At this point, this is a promise as opposed to teaching the Skilled Team how to achieve that end.

213. [0023] does not specify any particular reduction in food effect but presents examples of % reductions in different embodiments, by reference to two alternative measures as I have discussed.

214. I recognise that, ordinarily and subject to insufficiency arguments, a claim need not specify what the medicament is for (see Birss LJ in *Idenix v Gilead* at [57], quoted at paragraph 235 below) and these claims do not do so in their express wording. The whole promise of the invention is that the effects by food are reduced and yet, on Astellas' construction, the claims do not require any reduction at all in food effect. The contrary argument is that the promise of the Patent is that if the Skilled Team applies the requirements in claim 1, he or she will achieve a reduction in food effect. This leads to the insufficiency argument, which I consider below.

215. In circumstances where I have found the Patent to be sufficient, a question arises as to whether that should influence the approach to construction. After all, the effect of my rejection of the Defendants' insufficiency attack(s) is that it is plausible that all formulations within claim 1 produce a reduction in food effect, so the Skilled Person/Team would be justified in assuming that.

216. It seems to me however that this is not an 'ordinary' case (and the finding of sufficiency cannot influence or determine the issue of construction) because the inventors and Patentee went to the trouble of setting out a definition in [0023] and [0024] of 'the effects by food are reduced' and furthermore, they used that defined term in [0022] (and elsewhere), yet, of all the defined terms in the Patent, this one is said not to apply at all. Miss May submitted that, on Astellas' case, [0023] may as well not be in the Patent at all, because it adds nothing.

217. An argument in favour of Astellas' approach (not one made by Mr Mitcheson) would be that in [0023] and [0024] the Patentee was just trying to be helpful to the Skilled Team, giving them (a) two possible measures of reduction in food effect (in [0023]) and (b) how to calculate them, in [0024]. This argument is not at all persuasive. The Patentee could have provided all the information in

those two paragraphs without defining the term 'the effects of food are reduced'.

218. There is no escaping this point. The Patentee was not forced to set out the definition in [0023] nor to use the defined term in [0022]. All these paragraphs were of the Patentee's own choosing. One has to pose this rhetorical question: why does the Patentee carefully set out a defined term and then not use or apply it? In my view the only logical conclusion is that the term was defined and used. After all, each of the defined terms is expressly said to be 'as used herein'. Accordingly, my conclusion is that the correct interpretation of the term 'a pharmaceutical composition for modified release' is as that term is defined in [0022] which itself incorporates the definition in [0023].

219. I entirely accept that [0023] only presents examples of the size of the reduction required and allows for a reduction in Cmax or Cmax and AUC, so that the claims do not require any particular reduction to be demonstrated. However, in my view, the claims do require some (more than minimal) reduction in either Cmax or Cmax and AUC to be demonstrated.

220. For what it is worth, I also find that the definition in [0025] is used in [0022]. In this regard, there is a distinction between [0023] and [0025]. The former focusses on how to demonstrate a reduction in food effect – the result. The latter focusses on something different – the dissolution characteristic of the formulation itself, which is said (along with the other elements of the claim) to produce that result. The Skilled Team would notice the definition in [0025]. Care would be required to fit all these definitions together. Thus, a careful approach by the Skilled Team would find the expression in [0022]. This is not over-meticulousness. The fact that certain expressions are defined is cause enough for the Skilled Team to go and find where they are used in the specification. The Skilled Team would notice there was a degree of redundancy in claim 1 because the dissolution characteristic would be both explicitly stated in integer F and incorporated via the expression 'pharmaceutical composition for modified release'.

221. As a separate and additional point to what I have set out above (so not relied upon as part of my conclusion) I also note the emphasis which is now placed by Astellas on the dissolution characteristic in [0025] which also features in integer F of claim 1. In the context of the other ingredients required in claim 1, this dissolution characteristic is the defining feature which is said to provide the promised reduction in food effect. However, in the Application as filed, this dissolution characteristic did not feature explicitly in any of the claims. Yet, on the construction I have set out above, it would have been implicit in all the claims through [0025] forming part of the definition in [0022].

222. Although I have reached a clear conclusion on the proper construction of integer A, I will consider the other points which arise on each of the rival constructions i.e. whether at least some reduction in either Cmax or Cmax and AUC is required in claim 1 or not.

INSUFFICIENCY – EXCESSIVE CLAIM BREADTH

223. As pleaded, there were two aspects to the Defendants' case. The first aspect

was that none of the claims contain any limitation on the amount of mirabegron in the claimed compositions. This is addressed by the unconditional amendment to integer A. I need say no more about it.

224. The second aspect was pleaded on the basis that Experimental Example 3 (which presented the only PK data in humans in [0110]-[0112], using the composition of Example 8) could not sustain the scope of the claims. To the same effect, at trial, the Defendants' case was that it is not possible to make a reasonable prediction (i.e. it is not plausible) that the invention works with substantially all the products falling within the scope of claim 1. They submitted that this is the case for all of the proposed amended forms of claim 1, and on either party's construction of Integer A and that therefore, the claim scope exceeds the technical contribution of the Patent such that all the claims are invalid.

Applicable principles

225. The Defendants drew my attention to the following principles from the caselaw which were not in dispute. Their starting point was Kitchin LJ's judgment in *Regeneron v Genentech* [2013] EWCA Civ 93, at [95]-[103], where he set out the four central legal principles - see in particular the fourth principle as follows (emphasis added):

> "98 Fourth, it is permissible to define an invention using general terms provided the patent discloses a principle of general application in the sense that it can reasonably be expected the invention will work with anything falling within the scope of these terms. As Lord Hoffmann said in *Biogen Inc. v Medeva* plc [1977] R.P.C. 1 at pp.48–49:
>
> 'If the invention discloses a principle capable of general application, the claims may be in correspondingly general terms. The patentee need not show that he has proved its application in every individual instance. On the other hand, if the claims include a number of discrete methods or products, the patentee must enable the invention to be performed in respect of each of them.
>
> Thus if the patent has hit upon a new product which has a beneficial effect but cannot demonstrate that there is a common principle by which that effect will be shared by other products of the same class, he will be entitled to a patent for that product but not for the class, even though some may subsequently turn out to have the same beneficial effect: see *May & Baker Ltd v Boots Pure Drug Co. Ltd.* (1950) 67 R.P.C. 23, 50. On the other hand, if he has disclosed a beneficial property which is common to the class, he will be entitled to a patent for all products of that class (assuming them to be new) even though he has not himself made more than one or two of them.'
>
> 99 In *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2004]

> UKHL 46, [2005] RPC 9 Lord Hoffmann further explained the concept of a principle of general application in this way:
>
> "112. In my opinion there is nothing difficult or mysterious about [a principle of general application]. It simply means an element of the claim which is stated in general terms. Such a claim is sufficiently enabled if one can reasonably expect the invention to work with anything which falls within the general term. For example, in *Genentech I/Polypeptide expression* (T 292/85) [1989] O.J. EPO 275, the patentee claimed in general terms a plasmid suitable for transforming a bacterial host which included an expression control sequence to enable the expression of exogenous DNA as a recoverable polypeptide. The patentee had obviously not tried the invention on every plasmid, every bacterial host or every sequence of exogenous DNA. But the Technical Board of Appeal found that the invention was fully enabled because it could reasonably be expected to work with any of them.
>
> 113. This is an example of an invention of striking breadth and originality. But the notion of a 'principle of general application' applies to any element of the claim, however humble, which is stated in general terms. A reference to a requirement of 'connecting means' is enabled if the invention can reasonably be expected to work with any means of connection. The patentee does not have to have experimented with all of them."
>
> 100. **It must therefore be possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim or, put another way, the assertion that the invention will work across the scope of the claim must be plausible or credible**. **The products and methods within the claim are then tied together by a unifying characteristic or a common principle.** If it is possible to make such a prediction then it cannot be said the claim is insufficient simply because the patentee has not demonstrated the invention works in every case.
>
> 101. **On the other hand, if it is not possible to make such a prediction or if it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within the scope of the claim then the scope of the monopoly will exceed the technical contribution the patentee has made to the art and the claim will be insufficient**. It may also be invalid for obviousness, there being no invention in simply providing a class of products or methods which have no technically useful properties or purpose.

226. The criterion for plausibility is that stated by Lord Sumption in *Warner-Lambert Co LLC v Generics (UK) Ltd* [2018] UKSC 56, [2019] Bus LR 360 at [36]: "the specification must disclose some reason for supposing that the implied assertion

of efficacy in the claim is true".

227. On the Defendants' construction of Integer A, the assertion of efficacy is express rather than implied (because integer A is to "a pharmaceutical composition for modified release" and that is expressly defined in [0022]-[0023] to "reduce the effect of food"), but the threshold for plausibility is the same. On Astellas' construction of integer A, the assertion of efficacy is implied.

228. It is important to note Lord Sumption's explanation as to what the threshold was designed to guard against, and his warning that the threshold that the Court of Appeal had applied in that case was too low.

229. At [20], Lord Sumption quoted from the judgment of Floyd LJ in the Court of Appeal:

> …the requirement of plausibility is a low, threshold test. It is designed to prohibit speculative claiming, which would otherwise allow the armchair inventor a monopoly over a field of endeavour to which he has made no contribution. It is not designed to prohibit patents for good faith predictions which have some, albeit manifestly incomplete, basis. Such claims may turn out to be insufficient nonetheless if the prediction turns out to be untrue. A patent which accurately predicts that an invention will work is, however, not likely to be revoked on the ground that the prediction was based on the slimmest of evidence. Thus, the claims will easily be seen not to be speculative where the inventor provides a reasonably credible theory as to why the invention will or might work. The same is true where the data in the specification is such that the reader is encouraged to try the invention."

230. Lord Sumption continued at [36] (with the Defendants' emphasis added) to explain why this approach set the bar too low:

> 36…Plausibility is not a distinct condition of validity with a life of its own, but a standard against which that must be demonstrated. Its adoption is a mitigation of the principle in favour of patentability. **It reflects the practical difficulty of demonstrating therapeutic efficacy to any higher standard at the stage when the patent application must in practice be made. The test is relatively undemanding. But it cannot be deprived of all meaning or reduced, as Floyd LJ's statement does, to little more than a test of good faith.** Indeed, if the threshold were as low as he suggests, it would be unlikely to serve even the limited purpose that he assigns to it of barring speculative or armchair claims.

231. "*Some reason for supposing*" as explained by Lord Sumption is therefore the relevant threshold for plausibility and this has to be disclosed by the specification.

232. Both sides referred in their opening skeletons to the fact that *Regeneron v Genentech* was considered further in *FibroGen v Akebia* [2021] EWCA Civ 1279, where Birss LJ suggested that the fourth principle set out above was better described as being one of "*reasonable prediction rather than simply plausibility*" ([52]), and explained how the principle was to be applied:

> 53 To apply the reasonable prediction principle one has to take three steps. First one must identify what it is which falls within the scope of the claimed class. Second one must determine what it means to say that the invention works. In other words what is it for? Once you know those two things, the third step can be taken: to answer the question whether it is possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim.

233. The Defendants submitted it is helpful to distinguish between structural and functional claim limitations. Structural claim limitations are nearly always relevant at 'step 1', because it is usually clear that they serve to limit the scope of the claim (structural limitations in product-by-process claims may raise different issues, but this does not arise in this case). As explained in *FibroGen*, functional claim limitations can feature at both 'step 1' (identifying the scope of the claimed class) and 'step 2' (determining what it means to say the invention 'works'), and there are many examples of claims that have both types of functional feature.

234. As Birss LJ said at [56] "It will be a matter of construction to work out what sort of functional features one is dealing with".

235. Reviewing the authorities, Birss LJ gave as examples of 'step 1' functional features '*a cGMP PDE enzyme inhibitor*' (per *Lilly ICOS v Pfizer*) and '*VEGF antagonists*' (per *Regeneron v Genentech*). The 'step 2' functional features in those cases were, respectively, '*treatment of male erectile dysfunction*', and '*treatment of certain non-cancerous diseases characterised by excessive blood vessel growth*'.

236. Birss LJ also explained that in some cases the 'step 2' functional features were implied rather than express – the example he gave was '*anti-flavivridae activity*' in *Indenix v Gilead*. As he explained at [57]:

> '57 In some cases the second step is the aspect which is a bit more involved. So in *Idenix v Gilead*, claim 1 was to a Markush class of molecules (see Kitchin LJ para [61]). The claim language did not include any reference to what they were for and so one could not answer the question at the second step by looking at the words of the claim. This is also not unusual. If the compounds are new, then a claim to those compounds will be novel without including a claim feature which refers to what they are actually for. However that does not prevent the reasonable prediction principle being applied. In fact the answer in *Idenix* was clear from the patent specification. That showed that the point of the invention was to treat infections caused by

> viruses in the Flaviviridae family. So one can assess the validity of the claim on the basis that it is a claim to compounds with anti-*Flaviviridae* activity, which is what Kitchin LJ said at paragraphs [113] and [124]. So, in the language coined above, anti-Flaviviridae activity was a step two functional feature. The issue in *Idenix* arose in the context of inventive step but the same approach applies to reasonable prediction/plausibility. Note that this does not mean that claims to compounds *per se* are actually limited to using the compounds for treating Flaviviridae infections, but for the purposes of assessing questions like inventive step and reasonable prediction/plausibility, one needs to know what the compounds are supposed to be useful for. In fact in *Idenix* the outcome of the third step was against the patentee. The court held that it was not plausible that substantially all the claimed molecules would be effective against Flaviviridae infections, and hence it was *Agrevo* obvious and also insufficient for lack of plausibility for the same reason (see paragraphs [129] and [140]).'

237. Miss May submitted this is relevant on Astellas' construction of integer A. Even if it is correct on construction, all that means is that Astellas wins on infringement as against Sandoz; it does not mean it escapes having to address the issue of what the compounds are useful for and whether it is plausible that substantially all compounds that satisfy the other structural and functional requirements of the claim will reduce the effects of food.

238. In *FibroGen* itself, the claims (EPC 2000 and Swiss-style claims which were treated alike) had various structural limitations and three functional limitations – see [14]-[24]. The structural limitations related to the features of the molecules in question (certain heterocyclic carboxamides). The three functional limitations that the compounds needed to satisfy were that they (1) inhibited an enzyme called HIF-PH, (2) increased endogenous EPO, and (3) were suitable to treat anaemia associated with chronic kidney disease. Birss LJ held that the first two functional limitations of '*HIF-PH inhibition and increasing endogenous epo*' (referred to as features C and E) were both 'step 1' functional features ([99]-[101]), and the third function limitation, '*treatment of CKD anaemia*' (referred to as feature F and G), was a 'step 2' functional feature.

239. He explained his reasoning at [99]-[102]:

> 99. Considering claim 8A as the best example, it is manifest that the answer at the first step, to identify what is it which falls within the scope of the claimed class, is as follows. What falls within the scope of the claim are compounds satisfying both the structural features A and B (and in claim 19A feature H) and also functional features C and E - HIF-PH inhibition and increasing endogenous epo. Those are the claimed compounds. If someone took a compound within Formula I which was not a HIF-PH inhibitor and did not increase epo, but used it successfully to treat CKD anaemia, they would not infringe the claim.

> 100. It is also clear (see judgment paragraph [260]) that functional feature C (HIF-PH inhibition) can be tested for in an appropriate biochemical *in vitro* assay and functional feature E (increase in endogenous epo) can be tested *in vivo* in a suitable animal model (mouse or rat). Whether these tests are difficult to perform is a matter for undue burden, below.
>
> 101. Thus the conclusion at step one ought to have been that the claimed compounds are compounds within the relevant structures which satisfy the *in vitro* tests for feature C and the *in vivo* animal model tests for feature E. The judgment contains no finding to this effect. That is an error of principle and approach.
>
> 102. The answer to the second step, determine what it means to say that the invention works, is also clear. Working, in this case, means treating the CKD form of anaemia. In terms of the problem to be solved, it is to treat CKD anaemia (or to find compounds which will treat anaemia, the difference does not matter). In other words it is the achievement of the therapeutic effect, features F and G. The fact that it is not necessary to demonstrate success in a clinical trial (paragraph [260]), does not mean that the claims do not require the therapeutic effect to be achieved.

Application to this case

The Defendants' case

240. Applying the three-step approach to claim 1 of the Patent, the Defendants submitted the answer to the first two steps is as follows:

i) Step 1: On both sides' constructions, compositions that fall within the scope of the claim are compositions that satisfy the structural requirements of integers B, C, D and E (and the latter part of integer A, i.e. 10-200mg of mirabegron), and the functional requirement of integer F (the *in vitro* dissolution profile). (The Defendants drew an analogy with *Fibrogen* to the effect that if someone took a composition of mirabegron that satisfied integers B, C, D and E but which did not satisfy the *in vitro* dissolution profiles of integer A and integer F but nonetheless used it successfully to reduce a food effect, they would not infringe the claim.) It is not necessary to include the dissolution profile of integer A as a separate functional requirement since a formulation that satisfies the requirement of integer F of a dissolution rate of 75% or less after 1.5 hours will necessarily satisfy the requirement of integer A of a dissolution rate of 85% or less after 30 minutes.

ii) Step 2: The answer to the second step, determine what it means to say that the invention works, is again clear. "Working", in this case, means the formulation reduces a food effect. In terms of the problem to be solved, it is to provide a composition that is capable of reducing the food effect that is seen in conventional tablets (see e.g. the first sentence in

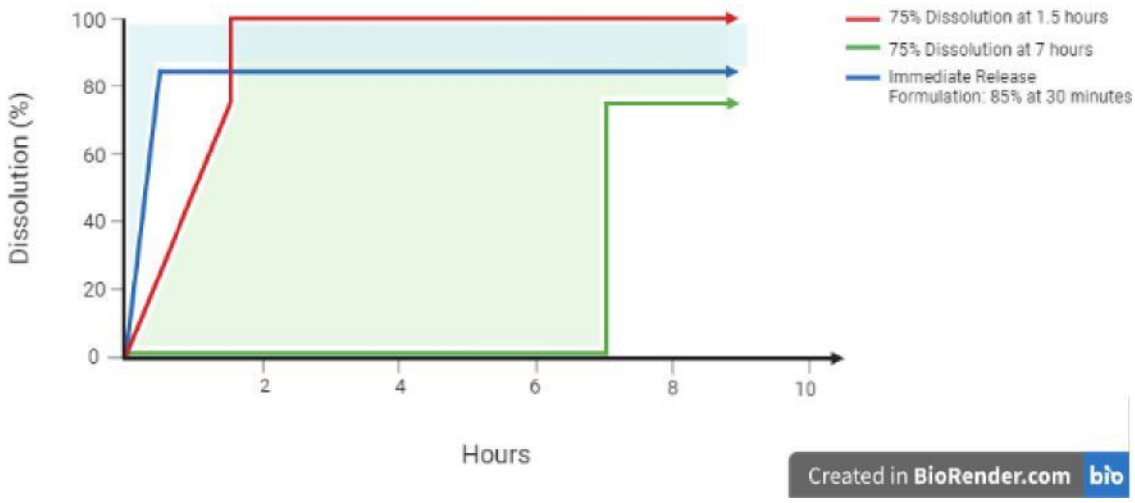
the Patent). In other words, it is the achievement of the effect in [0023]. On the Defendants' construction, this requirement of reducing the effects by food is expressly incorporated in integer A. On Astellas' construction, it is not an express feature of the claim (and therefore not relevant to infringement) but for the reasons Birss LJ explained in *Fibrogen* at [57] (by reference to *Idenix*) it is nonetheless a 'step 2 functional feature' for the purposes of inventive step and reasonable prediction/plausibility (because one needs to know what the compounds are supposed to be useful for).

241. On that basis, the Defendants submitted that the question to ask as Step 3 is therefore the same on either sides' construction: is it possible to make a reasonable prediction (i.e. is it plausible) that compositions which satisfy the structural features of claim 1 and which also satisfy the functional feature of integer F (the *in vitro* dissolution profile), will be capable of reducing the food effect that is seen in conventional tablets of mirabegron?

242. I did not understand Astellas to dispute that this was the appropriate question to address, notwithstanding that in their opening skeleton they submitted that an analysis along *FibroGen* lines ('step 1, step 2') was an "over complication" in this case.

243. During the trial much of the debate took place against the backdrop (either explicitly or implicitly) of Dr Blakey's Figure G from his second report which shows in graphical form the various dissolution limits referred to in claim 1 and which is best viewed in colour (Blue = Immediate Release, Red = the lower dissolution limit in claim 1, Green = the upper dissolution limit):

Figure G



244. Some care is required with this diagram. In his second report, Dr Blakey identified some profiles by reference to the red and green lines in Figure G, representing the lower and upper limits respectively. However, in cross-examination, it turned out that Dr Blakey had not considered whether his mooted profiles were the type of profiles the Skilled Team would expect using the excipients claimed in Integers B-E because this was outside his expertise.

245. In their written closing, the Defendants put forward the following reasons in support of their submission that the answer to the Step 3 question is 'no' on either of the possible meanings in [0023]:

i) The only explanation in the Patent for why the modified formulations reduce the food effect is at paragraph [0010], which states that the inventors considered that "*a formulation capable of continuous drug release for 4 hours or more would be able to reduce the effects by food, because the drug release from the formulation would become the rate-limiting step for absorption."* This could not be clearer: the hypothesis in the specification is that if drug release is extended to last longer than 4 hours, then drug release will become the rate limiting step, and because of this the effects by food will be reduced. There is no further attempt to explain how or why the modified formulations reduce a food effect.

ii) The only data relating to the reduction in the food effect are (1) the data described in paragraph [0011], and (2) the data arising out of the Human PK Study in which a single modified release formulation (Example 8) was said to reduce the food effect when compared with a single comparator (Comparative Example 1).

iii) All the example compositions in paragraph [0011] and the single example in the Human PK Study have dissolution profiles that are consistent with the requirement from paragraph [0010] of having a release profile "of 4 hours or more" ($T2/266_{10\text{-}15}$). In other words, there are no examples at all of any modified release compositions that have a release profile of less than 4 hours, far less are there any examples or data suggesting that a modified release composition having a release profile of less than 4 hours would reduce the food effect.

iv) Professor Shakesheff's written evidence was consistent with this being the teaching of the specification – see Shakesheff 1 §17.23, where he explained that the key to reducing the food effect was to ensure dissolution continues beyond 4 hours (emphasis added):

> 17.23 …**the skilled formulator would understand the Patent to teach that, provided these dissolution requirements are met, the effects of food will be reduced**. This would make sense to the skilled formulator given that the dissolution requirements ensure dissolution (and consequently absorption) continues beyond the window in which food effects were observed for the rapid release formulation of mirabegron (but with most to all dissolution taking place in the upper GI tract). The skilled formulator would also understand that these dissolution requirements would produce a range of outcomes with respect to the reduction of the food effects. For example, a formulation with a dissolution profile at one end of the permitted dissolution range would have a different impact on food effects to a formulation with a dissolution profile at the other end of the range (although both would result in reduction of the food

effects).

v) This theme was continued in Shakesheff 2 – see §§6.7, 6.14-6.15. An additional point made by Professor Shakesheff in Shakesheff 2 was that the nature of the excipients specified in the claim meant that the compositions would release drug "*slowly and continuously over time, and would not display a rapid acceleration or deceleration in dissolution*" (§6.15). This was in answer to Blakey 1 §§6.39-6.40 where Dr Blakey pointed out that the dissolution limits of claim 1 permitted dissolution profiles that displayed rapid accelerations (e.g. 75% dissolved at 1.5 hours and 76% dissolved at 7 hours).

vi) However, as was also pointed out in Blakey 1 §6.42, the dissolution limits in claim 1 cover formulations with dissolution rates notably different to those in respect of which the Patent provides data. In particular, the claim is not defined by reference to the Patentee's rationale that "*a formulation capable of continuous drug release for 4 hours or more would be able to reduce the effects by food*", because the claimed range includes formulations in which dissolution is 100% in less than 4 hours (e.g. 2 hours).

vii) The example was put to Professor Shakesheff of a modified formulation that released continuously over 2hrs (25% dissolved at 30mins, 50% dissolved at 1hr, 75% dissolved at 1.5hrs and 100% at 2hrs). He agreed that this was the kind of continuous and steady dissolution profile that could result from the hydrogel formulations of the claim, and that it was within the limits of integer F ($T2/262_{12}$-263_6). However, such a composition would not be capable of continuous drug release for 4hrs or more, and therefore is not one that - on the Patentee's own hypothesis - would be thought "to be able to reduce the effects by food", on any construction of that term. The only reason Professor Shakesheff had for disagreeing with this was based on the new argument that emerged for the first time in his XX about absorption rather than release being the key to reducing the food effect.

viii) Professor Shakesheff never suggested that any dissolution profile within integer F would reduce the effects of food on the basis of <u>his</u> understanding of 'Meaning 1'– see $T2/258_{15}$-259_9[2]. That was unsurprising given (1) the only data in the Patent provided by way of demonstrating a reduction in food effect are data showing the "rate of decrease" of Cmax and AUC, i.e. data that show a reduction in food effect in accordance with Dr Blakey's interpretation of Meaning 1 and Meaning 2, and (2) there are no data at all in the Patent relating to measured values of Cmax (in fed or fasted states, with any compositions), and therefore no data demonstrating a reduction in Cmax in the fasted state as between a modified and conventional composition, i.e. there are no data that shows a reduction in food effect in accordance with Professor Shakesheff's interpretation of Meaning 1.

[2] "Meaning to" at line 9 should obviously be "Meaning 2"

ix) Dr Blakey's evidence was that at the lower (faster) end of the dissolution range claimed it is unlikely that the modified release formulation would demonstrate a significantly different Cmax compared to an immediate release formulation or a reduction in the rate of decrease of Cmax and AUC (Blakey 2 §5.6, not challenged).

246. For those reasons, the Defendants submitted that:

i) It is therefore not credible that substantially every formulation within the dissolution range will necessarily show the required reduction in food effect compared to a conventional composition of mirabegron.

ii) Both the lower and upper limits in integer F were arbitrary.

iii) Therefore, all the claims are overly broad and are invalid.

The Claimant's Response

247. Astellas' response was that the evidence went all one way and established that products with the dissolution profile required by the claim and made with the excipients disclosed in the claim would all be expected to alleviate the food effect to some degree, as required.

248. This response was based on their argument that all the profiles on which the Defendants relied were hypothetical:

i) First, the profiles mentioned in Dr Blakey's evidence. Specifically, the 2-hour example referred to in the Defendants' submissions (see paragraph 245.vi) above. This, as I understand it, is the same as the second example put to Professor Shakesheff (see below).

ii) Second, the first profile put to Professor Shakesheff in cross examination involved a dissolution profile in which 100% of the drug was undissolved at 4 hours, thus satisfying the lower limit of the claim. However, his response was that a formulation of 0% dissolution at 4 hours was unlikely to meet the higher limit of the claim. He said *'these matrix systems have smooth release curves. They do not jump up or they are not – it is not a delayed system or a system that is programmed to accelerate'.* I note that the Defendants did not rely on this example in Closing.

iii) Third, the second example put to Professor Shakesheff, on which the Defendants did rely in Closing (see paragraph 245.vii) above. However, it is important to note that this was explicitly put as *in vitro*, consistent with the Defendants' argument on the key sentence in [0010], which I rejected at paragraphs 152-157 above.

Analysis

249. It seems to me that the Defendants' argument suffers from two principal flaws. The first was their misunderstanding of the teaching in [0010]. The second was their argument ignored what Professor Shakesheff indicated was the normal

shape of release curves of matrix systems i.e. smooth release curves, with no rapid acceleration or deceleration (cf the shape of the dissolution curves in Figure 1 of the Patent, which fit neatly into the area defined by the claim limitations in Dr Blakey's Figure G). Although this point was acknowledged in the Defendants' closing submissions (paragraph 245.v) above), I do not believe that it was taken account of in the questions put to Professor Shakesheff in cross-examination.

250. However, the Defendants attacked both the lower and the upper limit in integer F and I must examine how these flaws impacted their arguments.

The attack relating to the lower limit

251. Reverting to the first point, on the Defendants' understanding of [0010] the central theory of the Patent was that the modified formulation should exhibit drug release *in vitro* for 4 hours or more. This led to the Defendants' Counsel putting the example formulation in cross-examination which exhibited continuous dissolution (*in vitro*) over 2 hours where 25% of the mirabegron had dissolved after 30 mins, 50% after 1 hour, 75% after 1½ hours and 100% after 2 hours. Although Professor Shakesheff agreed that this was the kind of continuous and steady state release profile that he was envisaging as typical, I am not sure he agreed that such a linear release profile was typical, but it may not matter. The point was that such a formulation would fall within the dissolution limits in integer F of claim 1 but was inconsistent with the Defendants' understanding of the central theory of the Patent in [0010].

252. Professor Shakesheff responded to this example by drawing a comparison with the conventional formulation (rapid release) which is predicted, in [0010], to exhibit continuous *absorption* for about 4 hours. In [0021] the *release* characteristic of the conventional formation is 85% or more after 30 minutes (which is consistent with the data in Table 4 which shows the conventional formulation used in Comparative Example 1 was 95% dissolved after 30 minutes). The Professor's point was that the example formulation which was fully dissolved only after 2 hours *in vitro* would be expected to exhibit continuous absorption for '*considerably longer than that four-hour period*'. This, however, did not meet the further point put to him that the example did not meet the teaching in [0010] of having continuous drug release for 4 hours or more (and it must be kept in mind that the point was put *in vitro*). In response, Professor Shakesheff said he did not think it excluded 'releasing for a shorter period'. The cross-examination went as follows:

> Q. Do you at least agree that the two-hour example that I have given which, obviously, falls within the integer (f) dissolution range ----
> A. Yes.
> Q. ---- is one whereby it does not meet the teaching of the patent of having continuous drug release for four hours or more?
> A. That is in the claim, yes, you are looking?
> Q. No, it is the teaching in paragraph 0010.
> A. Paragraph 0010 tells me that an approach to the food effect was to "release for four hours or more". I do not think it

> excludes releasing for a shorter period.
> Q. Do you agree that the only examples in the patent that are said to reduce the food effects all have dissolution profiles consistent with the requirement in paragraph 0010, namely that the release of the drug from the formulation should be four hours or more?
> A. Yes, I agree.
> Q. As a result, the patent does not give the skilled formulator any reason to suppose that a formulation with the example of the two-hour dissolution profile we have just discussed will reduce the food effects relative to the conventional formulation of mirabegron; correct?
> A. If I use the example of the rapid release and the fact that the deconvolution of continued absorption for four hours, then potentially any formulation that is longer than that could reduce the food effect.

253. Those answers indicate to me that Professor Shakesheff had seen the conundrum coming, hence the counter-intuitive answer that the teaching in the Patent did not exclude releasing for a shorter period. I consider his answer is counter-intuitive because it goes against the express teaching in [0010]. In closing, Mr Mitcheson sought to justify that answer on the basis that the Professor was talking about the situation *in vitro*, to which my response was to indicate that was a bit of a stretch. If the Professor had in mind the *in vivo/in vitro* distinction, it is far more likely that he would have mentioned that expressly. Although the Skilled Team would not think that there were any sharp boundaries between food effect and no food effect, I do not think their thought process would lead them to think they should complete drug release for a shorter period than 4 hours. Professor Shakesheff's answer was a product of this litigation process and does not represent what a Skilled Team would think outside this process.

254. Having said that, I still need to adjust (as far as I can) for the *in vivo/in vitro* distinction. As I mentioned, the whole of the questioning was put on the Defendants' understanding of [0010]. If, as I have held, [0010] is talking about 4 hours or more of drug release *in vivo*, and one takes into account that dissolution/release takes place more slowly *in vivo* than *in vitro*, the question is: how much more slowly?

255. As the Defendants submitted, the Patent contains no *in vivo/in vitro* correlation data. In the absence of data, any answer to that question is essentially guesswork. As far as I could see, only one question was put on this and it seems speculative. The passage of cross-examination (which was directed at the upper limit of the claim) started with a question based on a statement made by the Professor in his third report:

> Q. … It is just over halfway down paragraph (d). It says:
> "In vitro tests represent dissolution in ideal conditions, and generally represent the fastest rate of dissolution; in vivo dissolution will tend to take place more slowly."
> Do you see where I am?
> A. Yes.
> Q. That would have been common general knowledge to the skilled

> formulator at the priority date; yes?
> A. Yes.
> Q. For example, if a drug takes seven hours to be 75% dissolved in vitro, it is likely to take significantly longer than that to be 75% dissolved in vivo?
> A. Yes.
> Q. Something that is 75% dissolved after seven hours in vitro might only be, say, 50% or 60% dissolved after seven hours in vivo?
> A. It is one of a lot of possibilities. It is a possibility.

256. Even though I have no concrete data, it seems to me to be unlikely that the dissolution *in vivo* took twice as long as *in vitro*, with the consequence that the Defendants' point retains some force, because the 2-hour *in vitro* example still indicates continuous drug release *in vivo* of less than 4 hours, contrary to the teaching in [0010].

257. However, Professor Shakesheff's reversion in his final answer to the comparison with the conventional formulation requires further consideration. I should also keep in mind that Professor Shakesheff had in his mind the 'normal' shape of the smooth dissolution curves for this type of matrix system.

258. In this regard, I should mention briefly the data provided in Table 1, which provide, for each of Examples 2, 8 and 9, four data points, albeit no data at 7 hours. The four data points provided indicate more or less linear dissolution, but it remains unclear whether in fact the rate of dissolution would remain constant or tail off as 100% dissolution was approached. These data lend some support to the idea that the Defendants' 2-hour *in vitro* dissolution example was realistic.

259. Before reaching a conclusion on the lower limit, I propose to examine the arguments on the upper limit.

The attack on the upper limit

260. After the passage quoted in paragraph 252 above, the cross-examination of Professor Shakesheff then focussed on the upper limit of the claim, after a more general question:

> Q. … There is no reason why the skilled formulator, at the priority date, would suppose that the data in the patent make it credible or plausible that a formulation that falls within the dissolution range of integer (f) will reduce the food effect?
> A. The four examples where there is in vivo data do fall within integer (f).
> Q. What is the technical rationale that takes the dissolution data of Example 8 where there is 95% dissolved in four and a half hours to the upper limit of the claim, which is 75% or more in seven hours?
> A. I cannot think of how that data relates to the upper.
> Q. Similarly, what is the technical rationale that takes the dissolution data of the formulations in paragraph 0011 to the

> 21 upper limit of the claim of 75% or more in seven hours?
> 22 A. I do not think there is an example there that takes it is to
> 23 the seven hours.

261. On the basis of the last two answers, the Defendants submitted that the upper limit in claim 1 was arbitrary. However, from an insufficiency perspective, there is nothing wrong with what appears to be an arbitrary limit, provided that the promise of the Patent is delivered up to that limit.

262. In any event, Astellas argued that the upper limit is not arbitrary, based on Professor Shakesheff's mid-range theory, which I must now discuss. I should also mention that, in their submissions, Astellas chose to characterise this as the inventors having hit upon the 'sweet spot' so far as reducing or ameliorating food effects. I see the 'sweet spot' argument as different, for reasons I will explain below.

Professor Shakesheff's 'mid-range' theory

263. Professor Shakesheff explained this in both his first and second reports. It suffices to note his explanation in his second report, where he was responding to Professor Craig's evidence that the limits in integer F appeared to be arbitrary (other than excluding immediate release formulations) and to Dr Blakey's evidence that there was no explanation for the limits. I summarise his 5 points as follows:

i) First, based on [0021] and [0022], the Skilled Formulator would understand the lower limit to reflect the requirement that the formulation should not be one for rapid release (as he said Dr Blakey recognised).

ii) His second point concerned [0009] (which I addressed above at paragraphs 148-149 above). On that basis, Professor Shakesheff explained:

> 'The skilled formulator would be aware that very extended release (i.e. beyond the upper GI tract and into the colon, approx. 4-7 hours after administration (which is CGK, as Dr Blakey agrees at his paragraph 5.22), is undesirable for a drug with a long elimination half-life, particularly one like mirabegron with low water solubility. The data in Figure 1 show that 7 hours is the first point at which complete drug dissolution has occurred.'

iii) For his third point, he referred to the results of the clinical trials reported in [0011]. He said that whilst the Skilled Formulator would understand that the $T_{80\%}$ 10-hour release had been shown to reduce food effects, this long a release period (i.e. with extensive colonic release) would be unnecessary and undesirable for mirabegron.

iv) His fourth point was Example 8, where 39% of the dose was dissolved at 1.5 hours and 95% at 4.5 hours.

v) His fifth point was that the formulation was one of continuous release so

> that the Skilled Formulator would understand that the use of the hydrogel-forming polymer would result in a formulation which released the drug gradually and continuously over time.

264. Based on those five points, his evidence was:

> 'Taking this teaching together, the skilled formulator would understand that the time points in claim 1 (understood in the context of the rest of the formulation claimed) were provided to ensure, firstly that the formulation was not an immediate release formulation (by reference to the dissolution requirement at 1.5 hours), secondly, that there was continuous release including some release beyond the stomach (by reference to both dissolution requirements and in light of the gradual and continuous nature of release that would be provided by the claimed excipients), but thirdly, that release wasn't too extended beyond the upper GI tract - i.e. into the colon (by reference to the dissolution requirement at 7 hours).'

265. It is fair to say that the Defendants were extremely dismissive of this theory and, for some considerable time, I too was sceptical. Indeed, in closing, the Defendants submitted forcefully that the 'mid-range' theory had not survived cross-examination, and, because of that, the theory was never put to the Defendants' experts.

266. My scepticism stemmed from the dismissal in the claimant's oral opening that the $T_{80\%}$ 10-hour example fell outside the claim. This struck me as a rather transparent attempt to distance the claim from the teaching in the prior art. However, on reflection, Professor Shakesheff's third point (paragraph 263iii) above seems valid, in particular in the light of his explanation that the reduction in food effect was probably caused by what occurred before the entry of the formulation into the colon.

267. In passing, his second point depends in part on mirabegron having low solubility. I discuss the solubility issue further in the context of the obviousness arguments below. However, bearing in mind the likely pH in the colon (7 or 8), in that environment, it seems mirabegron does have low solubility so his point seems to me to remain valid.

268. Perhaps the most important point, so far as the mid-range theory is concerned, is its foundation in [0009], as explained by Professor Shakesheff. He was never challenged on that explanation. Furthermore, it is consistent with and supported by the others of his five points and the evidence generally. Once the significance of that teaching is understood, it can be seen that the central theory and teaching of the Patent lies in two propositions:

    i) First, to reduce or ameliorate food effects, it is necessary to ensure that continuous drug absorption is for 4 hours or more.

    ii) Second, it is important to limit the period of drug release so it was not extended too far beyond the upper GI tract. Some release in the colon

(after 7 hours) was acceptable, but not too much (less than 25%).

269. It is true that the mid-range theory was not put in terms to the Defendants' experts, but I am satisfied that Counsel did put questions relating to each of the limits in integer F and obtained answers which were consistent with it. Although Dr Blakey was a somewhat guarded witness, he bridled at the lack of supporting data, and, rather strangely, he regarded the words 'possible' and 'likely' as synonymous, his evidence established, in my view, the following propositions concerning the Skilled Team's understanding from his or her reading of the Patent:

    i) That [0010] taught that the invention was all about extending the period of four hours continuous absorption.

    ii) That anything with a dissolution profile of less than 85% at 30 minutes is likely to give more than 4 hours continuous absorption.

    iii) That complete dissolution for the immediate release formulation would be likely to occur in about 45 minutes.

    iv) A MR formulation with complete dissolution after 90 minutes is likely to give more than about 4 hours continuous absorption.

    v) That if one notionally creates the dissolution curves from Table 4 (for Examples 2, 8 and 9) they are in the same ballpark as the curve(s) shown in Figure 1.

    vi) That, on the basis of [0010], the 2-hour example put to Professor Shakesheff would be likely to have continuous absorption for over 4 hours.

270. Those points relate principally to the lower limit in the claim. So far as the upper limit is concerned, again, his cross-examination established the following propositions concerning the Skilled Team's understanding from his or her reading of the Patent:

    i) If told that a drug formulation had continuous drug release for 4 hours or more, that the most obvious and likely part of the GI tract where the drug would be absorbed was in the small intestine.

    ii) In the majority of individuals, one would expect the drug to be at the interface between small intestine and colon at 7 hours after oral administration.

    iii) It was CGK that the colon was generally regarded as a poor site for drug absorption.

271. In his written evidence, Dr Blakey had expressed the opinion that he did not believe it was credible that every formulation made according to Claim 1 would reduce the food effect. His opinion was based on his extreme examples of profiles in his second report by reference to the red and green profiles in his Figure G, but it turned out that he had not considered whether those profiles

were the types of profiles which the Skilled Team would expect using the excipients claimed in integers B-E because that was outside his expertise. More importantly so far as the upper limit is concerned, Dr Blakey accepted in cross-examination that he had not taken the teaching in [0011] into account when he expressed that opinion in either his first ([6.42]) or his second ([5.10]) reports. For these (and other reasons), I conclude his opinion in his written evidence carries no weight.

272. The final point in the Defendants' argument is that both lower and upper limits are arbitrary. In one sense, they are arbitrary, because there are no sharp boundaries between food effect and no food effect. However, the Patentee had to place some boundary on the scope of his claim. As I have said, from an insufficiency perspective, there is nothing wrong with what appears to be an arbitrary limit, provided that the promise of the Patent is delivered, in this case, between those limits.

Astellas' 'sweet-spot' argument.

273. On one point, the evidence from Professor Shakesheff and Dr Blakey coincided. I refer to Professor Shakesheff's explanation that the reduction in food effect was probably caused by what occurred before the entry of the formulation into the colon. As recorded in paragraph 270 i) above, Dr Blakey seemed to agree.

274. On the basis of this evidence (and I am fully aware that this was based on theories, which themselves have rather slender foundations in the Patent), the upper dissolution limit in the claim do not delimit a 'sweet spot' in terms of amelioration of food effects. The amelioration stems from controlled release of the majority (i.e. around 75% or more) of the drug before it reaches the colon, principally in the small intestine. No evidence or theory was put forward to suggest that what thereafter occurred in the colon had any influence on food effects, and the $T_{80\%}$ example at 10 hours in [0011] supports this. In other words, amelioration of food effects may well be observed beyond the upper dissolution limit of the claim, provided controlled release of a good proportion of mirabegron occurs in the small intestine.

275. This points to the upper dissolution limit as being arbitrary, but that does not support the Defendants' insufficiency argument. The reasons why the Patentee imposed this upper limit are speculation, but one reason may have been because it was aware of the OCAS prior art.

Conclusions

276. In order to finally resolve the attacks on both the lower and upper limits in integer F, I have found it helpful to compare all the various measures of release and absorption in tabular form. I indicate the outstanding points which matter by way of numbered questions. I take release and dissolution as synonymous. It is also helpful to have in mind the following points:

    i) First, the CGK as to the time taken to pass through the various parts of the digestive system: stomach 1-3 hours (but can vary); small intestine 2-6 hours but typically 3-4 hours, so that a modified release formulation

can be expected to reach the colon after about 7 hours, a point confirmed by Dr Blakey;

ii) Second, the CGK point that *in vivo* dissolution is slower than *in vitro*; and

iii) Third, that the real measure of significance that the Skilled Formulator takes away from [0010] is absorption (see paragraph 151 above) and the teaching is to ensure continuous drug absorption over 4 hours or more.

Formulation	Dissolution/Release			Absorption	Food Effect?
Conventional	85% or more after 30 minutes, *in vitro*			About 4 hours *in vivo*	Yes
Comparative Example 1	95% after 30 minutes				Yes (inferred)
MR 2 hour example	100% dissolution in 2 hours *in vitro*			Qn1?	Qn2?
[0010] teaching re modified release	4 hours or more *in vivo* (i.e. 100% dissolution/release)			release is rate limiting step for absorption, therefore > 4 hours *in vivo*	Reduced
[0011]	80% dissolution after 4, 6 and 10 hours *in vitro*			Qn3?	Reduced for all formulations
	1.5 hours	2.5 hours	4.5 hours		
Example 2	35%	57%	93%		
Example 8	39%	61%	95%		Reduced, data in [0112]
Example 9	32%	54%	92%		
Claim 1	75% or less after 1.5 hours 75% or more after 7 hours *in vitro*			Qn4?	Qn5?

277. Addressing the five questions in the table in turn:

Qn1. Professor Shakesheff indicated that the absorption would be greater than 4 hours *in vivo* and this appears entirely logical. The teaching in [0010] also tends to confirm that the period of absorption would be likely to be above 4 hours *in vivo.* [0011] also lends some indirect support to that conclusion.

Qn2. The answer to question 1 indicates that the answer to question 2 is 'Reduced'.

Qn3. [0011] is principally concerned with the higher limit in the claim, but, as I have just indicated, it has some influence on the 2-hour example. Comparing [0010] and [0011] indicates that absorption for each of the three formulations will be greater than 4 hours *in vivo*, consistent with the express teaching that the food effect was reduced for all three.

Qn4. In these circumstances, the teaching indicates that within the limits of claim 1, absorption will continue for more than 4 hours. There are no data to indicate that, towards the upper limit of integer F, the reduction in food effect runs out or disappears. In fact, the $T_{80\%}$ example at 10 hours in [0011], is a positive indication it has not.

All those answers are supported by the evidence extracted from Dr Blakey in cross-examination, which I have summarised above.

Qn5. All these considerations point to the answer to Qn 5 as being 'Reduced'. In other words, the Defendants' insufficiency attack fails.

278. This conclusion also disposes of the Defendants' argument based on lack of technical contribution and *AgrEvo* obviousness.

Uncertainty?

279. In the introduction I mentioned the Defendants' case of insufficiency on the ground of ambiguity or uncertainty. In the Defendants' opening skeleton, the point was explained as only live on Astellas' interpretation of Meaning 1, which I have rejected above. It was put as a paradigm case of the Skilled Person not knowing what test to apply to determine whether something fell within the claim or not. The Defendants did not address this case in their written closing, which is why I said the point seemed to have died away by the time of written closings. It was however, resurrected in the final minutes of the trial if the drug release measure in [0010] was *in vivo*, but only, it seems, on a conditional basis – only if I was unable to form a view as to the correct construction in relation to [0023]. Not only have I been able to reach a concluded view on construction, but in addition I am unable to detect any ambiguity or uncertainty in the claim.

INVENTIVE STEP

Applicable principles

280. Both parties referred to the analysis of the law of obviousness by Lord Hodge in *Actavis v ICOS* [2019] UKSC 15 at [52]-[73], and in the main both identified the same salient points, which I have gathered here, supplemented with some other principles from well-known authorities.

281. First, the statutory question is whether the invention is obvious, having regard to the state of the art at the Priority Date. In some cases, it is helpful to answer this question by adopting the structured approach set out in *Pozzoli*. In other cases, it is helpful to adopt the problem/solution approach (PSA) favoured by the EPO. But neither approach can replace the statutory question itself. It must be assessed by reference to the facts and circumstances of the case.

282. Second, Lord Hodge at [63] endorsed the statement of Kitchin J (as he then was) in *Generics (UK) Ltd v H Lundbeck A/S* [2007] EWHC 1040 (Pat) at [72]:

"The question of obviousness must be considered on the facts of

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

283. Third, he went on to identify a non-exhaustive list of factors which may be relevant in the assessment from [64]. As Astellas pointed out, the factor that the Defendants seem to rely upon in this case is "obvious to try". This was considered by Lord Hodge at [65] where he said:

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

284. In the *MedImmune v Novartis* decision referred to by Lord Hodge above, Kitchin LJ (as he then was) said (at [90]-[91]):

> "One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of technology such as pharmaceuticals and biotechnology which are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them worthwhile. But denial of patent protection in all such cases would act as a significant deterrent to research.

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

285. In *Omnipharm Ltd v. Merial* [2011] EWHC 3393, Floyd J (as he then was) summarised the position as follows:

> "i) There is but one statutory question: was the invention obvious? It is to be answered by reference to the non-exhaustive list of factors identified by Kitchin J in *Generics v Lundbeck*, including whether it was obvious to try the invention as a solution to a technical problem, as well as the nature of the invention itself.
>
> ii) "Obvious to try" is not an independent ground of invalidating a patent under the statute, but one of a variety of factors considered in an overall assessment of inventive step. It must be coupled with a fair expectation of success, the degree of success necessary depending on the other factors present in the individual case.
>
> iii) Where an invention is claimed plausibly in terms that it would achieve a technical effect, it is correct to ask whether it was obvious that the invention would achieve that effect, and wrong to ask whether the invention might achieve that effect."

286. The Court of Appeal in *Teva v Leo* [2015] EWCA Civ 779 at [29] emphasised the importance of assessing the question of obviousness by reference to what real-life skilled people would think and do.

287. The Defendants also reminded me of the following additional principles. There can be multiple obvious avenues or routes and an obvious route is not rendered less obvious for this reason. At [69] in *Actavis v ICOS* the Supreme Court approved the well-known passage from *Brugger v Medic-Aid* at 661:

> "[I]f a particular route is an obvious one to take or try, it is not rendered any less obvious from a technical point of view merely because there are a number, and perhaps a large number, of other obvious routes as well.

288. Lord Hodge noted his agreement and added that "[a]s a result, the need to make value judgments on how to proceed in the course of a research programme is

not necessarily a pointer against obviousness."

289. Further, the Supreme Court in *Actavis v ICOS* was clear that if a skilled team engages in familiar and routine testing and it is obvious to undertake that testing as part of routine development, that is sufficient for obviousness. The end result of those routine tests does not need to be known or to be anticipated or expected. It is obtained by the application of routine work (see for instance [85] and [88]).

290. The law concerning arbitrary parameters was explained by Jacob LJ in *Actavis v Novartis* [2010] EWCA Civ 82; [2010] F.S.R. 18 (emphasis added by the Defendants):

> 36. Another aspect of obviousness which is not readily answered by the PSA is illustrated by the 5¼ inch plate paradox. This runs like this. Suppose the patent claim is for a plate of diameter 5¼ inches. And suppose no-one can find a plate of that particular diameter in the prior art. Then (a) it is novel and (b) it is non-obvious for there is no particular reason to choose that diameter. The conclusion, that the plate is patentable, is so absurd that it cannot be so.
>
> 37. What then is the answer to the paradox? It is this: the 5¼ inch limitation is purely arbitrary and non-technical. It solves no problem and advances the art not at all. It is not inventive. And although "inventive step" is defined as being one which is not obvious, one must always remember the purpose of that definition – to define what is inventive. **That which is not inventive by any criteria is not made so by the definition.** Trivial limitations, such as specifying the plate diameter, or painting a known machine blue for no technical reason are treated as obvious because they are not inventive.

291. A patentee cannot rely upon a perceived problem in taking a particular course of action in support of inventive step, unless the patent itself overcomes that problem (see *Philips v Asustek* [2019] EWCA Civ 2230 at [73] – see also Jacob LJ in *Pozzoli v BDMO* [2007] EWCA Civ 588 at [28]).

292. In *Philip Morris v Nicoventures* [2021] EWHC 537, Meade J referred to Birss J (as he then was) in *Optis v Apple* [2020] EWHC 2746 where Birss J explained that although having an arbitrary feature in a claim is not a ground of invalidity, if a claim is found to contain an arbitrary limitation in it, then that limitation cannot assist the patentee in defending an obviousness case (see at [212]).

293. All these principles are pertinent in this case and I have kept them well in mind. Furthermore, although neither side conducted a formal *Pozzoli* analysis, it is useful to adopt that staged approach to ensure one keeps on the straight and narrow. I apply it below.

THE PRIOR ART

294. All three pieces of prior art relied upon disclose aspects of an Oral Controlled

Absorption System called OCAS, developed by Yamanouchi Pharma, which the Defendants were keen to identify as now part of Astellas. Fix was taken first, followed by Michel. The Defendants only rely on Chapple when read with Michel, on the basis that Chapple provides further detail regarding the background and development of OCAS in addition to that disclosed in Michel. In the end, very little time was spent on either Michel or Chapple, an indication that the case really rested on Fix. I will consider Fix first, and then whether either Michel and/or Chapple make any difference.

FIX

295. To explain what follows, the major issues relating to Fix were as follows, which I address in turn:

i) Perhaps the most significant issue was over what Fix disclosed to the Skilled Team. In essence, Astellas' contention was that Fix was all about drug release in the colon. The Defendants submitted that was wrong and that Fix taught two things. I expand on this below.

ii) Second, as to what the Skilled Team would do, having considered Fix. Professor Shakesheff took the view that Fix would be put to one side as of no real interest. By contrast, Professor Craig's view was that the Skilled Team would be motivated to seek to apply the teaching in Fix to try to develop an MR formulation of mirabegron which reduced the food effect encountered in the IR formulation. This issue depended in part on the outcome of the first issue.

iii) Third and relatedly, the nature of the project which the Skilled Team would have to undertake to apply that teaching.

iv) Fourth, whether the project could lead to a formulation which fell within claim 1.

v) Fifth, whether it was obvious for the Skilled Team to pursue the project to the point where they had a formulation which reduced the food effect and fell within claim 1.

296. Astellas put a lot of effort into the first two issues, so my analysis of them will take some time.

First, what Fix discloses to the Skilled Team

297. When determining what Fix discloses to the Skilled Team, naturally I have read and considered what Professors Shakesheff and Craig said about the disclosure and also the submissions made by each side. I consider I have been sufficiently educated to read Fix through the eyes of the Skilled Team. Accordingly, I have attempted to put the rival contentions out of my mind and to approach my reading and interpretation of Fix as the notional Skilled Team would consider the document, insulated from the litigation process. It is convenient nonetheless to record where I agree with a view expressed by one of the experts.

298. Fix is Chapter 2 in 'Controlled Drug Delivery', published in 2000 in the ACS Symposium Series of the American Chemical Society. It is entitled 'Controlled-Release Oral Delivery Systems' but promotes OCAS. It is a short but compact chapter of some 11 pages.

299. The debate over what Fix teaches the Skilled Team at the Priority Date was reflected in the debate over the content of the abstract, which, in my view, is a reasonably accurate summary of Fix. The abstract reads as follows, in which I have numbered the sentences:

> '[1] The advantages of controlled-release oral delivery systems, particularly those achieving once-a-day efficacy, have long been recognized. [2] Outcomes can include better therapeutic efficacy via improved control of blood plasma levels and reduced peak-associated side effects. [3] Oral controlled-release dosage forms can also afford advantages in drug stability, patient compliance, and reduced total drug exposure. [4] Applications for once-a-day administration must balance release kinetics, dosage form and *in vivo* drug stability, absorption kinetics and variable physiologic parameters such as g.i. transit, enzymes, pH, motility and fluid level. [5] In spite of major efforts to develop once-a-day oral dosage forms, relatively few products have been introduced. [6] In many cases, once daily therapeutic efficacy cannot be easily achieved due to poor control of drug release or poor drug absorption in the colon. [7] Food effects can also introduce significant variability. [8] OCAS is an oral controlled absorption gel matrix system that exhibits pH-independent, pseudo-zero order drug release with minimal food effects. [9] The rapid hydration and formation of a rigid gel leads to effective drug release in the colon. [10] Future advances in once-a-day oral delivery systems must address improving drug absorption in the colon and may extend applications of controlled-release technology to biomolecules.'

300. Sentences [1]-[5] were agreed as representing CGK, sentence [5] accurately reflecting the difficulty of the task. The sources of variability are summarised in sentence [4], with food effects mentioned in sentence [7] as another source of variability. Whether sentence [6] reflected the CGK was in dispute.

301. Astellas relied in particular on sentences [8]-[10], contending that sentence [9] was what Fix was all about. The Defendants and Professor Craig disagreed, pointing to sentence [8] and its reference to 'minimal food effects'. The debate was over whether Fix teaches that the way to reduce food effects was through effective drug release in the colon, or whether the reduction in food effect was attributable to the effects of the OCAS system before the drug reaches the colon.

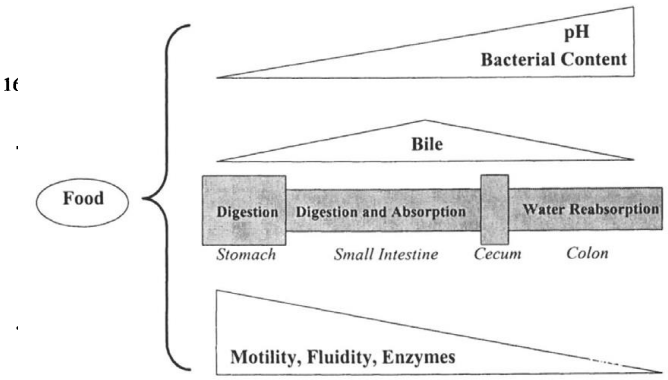
302. In the body of the Chapter, by way of introduction, Fix gives an overview of controlled release technology. After showing representative plasma profiles for immediate, continuous, pulsatile and delayed oral delivery systems in Fig 1, Fix then directs attention on once-a-day dosing regimes. Fix says that despite the availability of numerous technologies to achieve up to 24 hour controlled drug

release, relatively few products that are efficacious for once-a-day dosing have reached the market. Table I lists some such products. Then Fix postulates two reasons for this (which I have labelled A and B):

> '[A] In some cases, controlled-release dosage forms that provided up to 24 hour in vitro drug release do not achieve the same release profile in vivo due to influences from the milieu of the gastrointestinal tract. [B] Also, poor colonic drug absorption can effectively limit the once daily efficacy of dosage forms that otherwise afford 24 hour drug release.'

303. The first section is entitled Physiologic Influences, the Skilled Team would note this concerns reason A:

> 'Once-a-day controlled release dosage forms are subject to numerous physiologic influences in the gastrointestinal tract, including pH, bile salts, fluidity, motility, enzyme activity, and absorption windows. Ideally, a once-a-day dosage form should function independent of variations in the parameters shown in Fig 2.'



Physiologic Influences

304. In view of the issue over what Fix discloses, the Skilled Team would note from Fig 2 both (a) the rise in pH through the GI tract and (b) the stated function of the small intestine: digestion and absorption, both points being CGK in any case. The text continues:

> 'During transit from stomach to lower colon, the pH exposure can range from pH 1.0 to pH 7.5 or greater. Bile salts and degradative enzymes are present in relatively high concentrations in the small intestine. Fluid content and gastrointestinal motility are high in the upper intestine and diminish in a distal direction. In order to reliably control drug release in an extended release product, the formulation would ideally function independent of these changing variables.'

305. In the next sentence, it is clear that the authors turn to consider reason B:

> 'Additionally, the decrease in fluid content in the colon, which is a water re-absorption site, can lead to altered drug release profiles (normally a decrease in the release rate if the release mechanism is dependent on the continued presence of high water content).'

306. There is then a reference to an osmotically driven delivery system developed by Alza which is said to be 'quite effective in performing in a uniform fashion even in the presence of limited water'. Fix then gives two examples of other prospective dosage forms which did not perform as well, illustrated in Figure 3.

307. Figure 3A shows plasma nicardipine levels after oral dosing of nicardipine hydrochloride to dogs and humans. The text explains that '*In Figure 3A, the absorptive phase for nicardipine terminates upon arrival of the dosage form in the colon .... of both dogs and humans*.' The second example in Figure 3B showed *in vitro* and *in vivo* acetaminophen (i.e. paracetamol) release from HPMC (hydroxypropylmethylcellulose) matrix sustained release tablets, and the text explains '*Acetaminophen release dramatically decreased when the dosage form reached the colon*.'

308. Fix then says:

> 'Several reasons may account for the discrepancies between *in vitro* and *in vivo* drug release, including effects of the gastrointestinal milieu on the controlled-release dosage form. In the colon, very little free water exists since the colon is a water absorptive region of the gastrointestinal tract.'

309. After further reference to the Alza osmotic system, the text then makes a point reflected in the abstract:

> 'The future development of once-a-day dosage forms depends on the ability to design and develop sustained-release dosage forms that will function independent of influences from the gastrointestinal milieu. Since sustained-release dosage forms spend the majority of their residence time in the colon, future once-a-day dosage forms must be designed to release drug in a predictable fashion in the relatively low water content of the colon.'

310. The bulk of the chapter is contained under the next heading: 'Oral Controlled Absorption System (OCAS^{TM})', which starts as follows:

> 'In an effort to design a sustained-release formulation suitable for once-a-day dosing that will perform reproducibly whether in the small intestine or colon, modifications to gel-forming matrix tablets were investigated. The OCAS system described here contains, as its major components, the active drug, a gel-forming polymer (polyethylene oxide, PEO) and a gel-enhancing agent (polyethylene glycol, PEG). The design concept is to achieve rapid gelation, pseudo first-order drug release, consistent colonic

drug release, and ease of manufacturing.'

311. The experts were agreed that this reference to 'pseudo first-order drug release' was probably a mistake and the authors intended to refer to 'zero-order' i.e. a linear drug release profile, which the Skilled Team would regard as a desirable profile for a MR formulation.

312. Figure 4 of Fix is a schematic that describes the basic performance characteristics of OCAS. It demonstrates the operation of the gel-forming matrix tablet in the small intestine and colon.

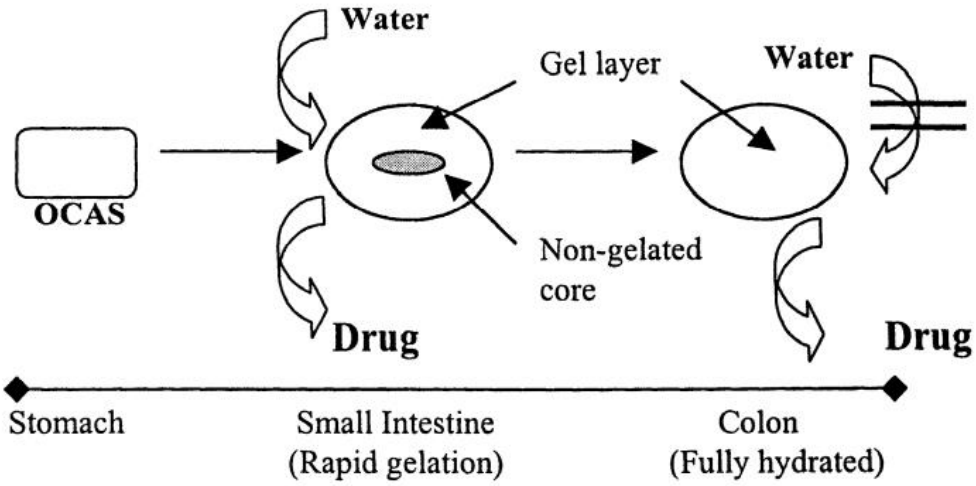


Figure 4: Schematic of OCAS hydration and drug release in small intestine and colon.

313. As Professor Craig said, the Skilled Formulator would understand from Figure 4 of Fix that the tablet is introduced to the stomach by the oral route and then enters the small intestine. Water would have begun permeating into the matrix of the tablet, beginning in the stomach, and continuing into the small intestine. The initial penetration of the water causes rapid gelation of the outer surface of the matrix that surrounds the dry, non-gelated tablet core. The non-gelated core diminishes in size as water penetrates the tablet and the drug is released by diffusion and/or erosion. By the time the tablet reaches the colon, it is fully hydrated and hence there will be no non-gelated core present. Further, even though little or no further water penetrates the tablet once it is in the colon (as indicated by the water arrow on the right-hand side of the Figure being crossed out by the double lines running through it), nevertheless the drug continues to be released (as indicated by the lower curved arrow in the colon).

314. Fix teaches that:

i) The design concept of OCAS is to achieve nearly complete hydration in the small intestine.

ii) The key to sustaining consistent drug release, as designed in the OCAS dosage form, is very rapid hydration of the gel matrix such that nearly

> complete hydration occurs prior to arrival of the dosage form at the colon. In most cases, the transit time for dosage forms from the stomach to the colon is approximately 3-4 hours, perhaps longer in the fed state depending on the extent of gastric retention.

315. Fix then moves on to discuss combining fillers with the gel-forming polymer (PEO) in order to ensure nearly complete pre-colonic hydration. The results from various fillers are presented. PEG6000 is identified as the desired filler because of its high gelation index and pharmaceutical acceptability. Then four different gel-forming polymers were tested for their ability to achieve pseudo zero-order drug release for 12 hours. Matrix tablets were prepared from acetaminophen:PEG:polymer (1:1:2) and their *in vitro* profiles determined by the paddle method. The Skilled Team would note the use of acetaminophen (paracetamol), which they would know was routinely used to model formulation systems.

316. PEO was identified as the preferred polymer for two reasons: first, because it was the only polymer tablet which exhibited diffusion dominated drug release (as opposed to erosion dominated release) and second, because it was the only tablet which achieved a pseudo-zero order release profile.

317. A comparison between the release profiles of PEO and HPMC matrix tablets is shown in Fig 5, including the change wrought by the addition of (relatively extreme) mechanical stress after 1 hour. The PEO formulation showed only a minimal increase in drug release whereas the HPMC tablet showed an abrupt and dramatic increase. Fix says this shows the gel formed with PEO possesses significant structural rigidity which is important in maintaining both physical integrity and consistent drug release during contractile activity in the gastrointestinal tract. The Skilled Team would note that Fig 5 PEO showed about 60% dissolution at 7 hours, albeit this was *in vitro* dissolution.

318. Fix then turns its attention to the *in vivo* performance as the critical test of functionality. Conventional PEO matrix tablets (gelation index 21%) were compared with OCAS PEO/PEG tablets (gelation index 76%, the gelation index being the % of the portion of the tablet which has undergone hydration). Both are reported as demonstrating reasonably pH-independent *in vitro* drug release between pH 1.2 and 6.8 over a 12-hour dissolution time, both achieving > 85% drug release within 10 hours, the OCAS release being somewhat more linear.

319. Then two different *in vivo* experiments were conducted in dog models. The results from the first *in vivo* study are presented in Table IV and in Figure 6. Fix reports they:

> ‘clearly indicate that this conventional gel matrix tablet exhibits decreased *in vivo* drug release in the colon. In contrast, drug release from OCAS appears to remain consistent even when the dosage form enters the colonic region. It is proposed that the reason for the consistent OCAS performance is the fully hydrated state of the dosage form prior to its arrival in the "water-deficient" colon region’.

320. Fix does not state the paddle speed that was used to generate the dissolution data of Fig 6. As I discussed above, Professors Craig and Shakesheff disagreed over the paddle speed normally used for MR formulations. One thing is clear, however, the greater the paddle speed, the greater the degree of *in vitro* dissolution.

321. The next three paragraphs in particular focus on the food effect. They start with this:

> 'As mentioned in the introduction, the gastrointestinal variables that can impact the performance [of] sustained-release once-a-day dosage forms are generally influenced by the presence of food. Enzyme activity, motility, pH, fluid content, and bile salts are all modified in the fed state versus the fasted state.'

322. Fix then discusses the second *in vivo* study which compared absorption of a different drug, nicardipine hydrochloride, from OCAS and conventional gel tablets in fed and fasted dogs (although no formulation details are provided). The results are shown in Table V:

Table V: Pharmacokinetic Parameters of OCAS and Conventional Gel Nicardipine Hydrochloride Tablets in Fed and Fasted Dogs

Formulation	*Food*	*AUC 0-24hr (ng.hr./ml)*	*Cmax (ng/ml)*	*Tmax (hr)*
OCAS	Fasted	547 ± 180	82 ± 14.8	3.9 ± 1.1
	Fed	681 ± 108	87 ± 17.8	4.7 ± 1.5
Conventional	Fasted	125 ± 32	54 ± 12.5	1.3 ± 0.2
	Fed	239 ± 62	47 ± 12.6	4.3 ± 1.2

N = 6, mean ± S.E.

323. The data in Table V indicate that significantly greater absorption (AUC) is achieved with the OCAS formulation than with the conventional one. As the Defendants submitted, this would be of interest to the Skilled Formulator as it indicates improved bioavailability over the conventional formulation. Higher bioavailability indicates improved absorption and also means that the same plasma concentration can be achieved with a lower drug loading dose (reducing cost).

324. These data also indicate (a) that the OCAS system is relatively free of food effects because the difference between AUC, Cmax and Tmax in the fed and fasted states is relatively smaller than that of the conventional tablets, and (b) a positive food effect (AUC is higher in fed than fasted state) and a higher AUC and Cmax for OCAS compared to the conventional formulation.

325. Thus, in the second paragraph, the authors suggest:

> 'The data presented in Table V indicate that significantly greater absorption (AUC) is achieved with OCAS compared to the

> conventional gel and that the OCAS system is relatively free of food effects (547 vs 681 ng.hr./m1 AUC for fasted vs fed, respectively). By contrast, an approximate 2-fold food effect was observed with the conventional gel formulation. Again, it is likely that the very rapid hydration of the OCAS formulation is an underlying cause for the relative food effect independence.'

326. Fix concludes (this being the third paragraph of the three):

> "In summary, OCAS is a rapidly hydrating gel matrix tablet that performs relatively independent of the effects of pH, mechanical stress, and location in the gastrointestinal tract. In addition, at least with the model compound employed, food effects appear minimal. As such, the technology represents an advance in sustained release formulations that might have applications in once-a-day drug therapy."

327. The final section of Fix is entitled 'Future Challenges and Opportunities'. Fix states that although significant advances have been made in developing and commercialising once daily dosage forms there is still room for improvements. Improving colonic absorption and applications of once-a-day technologies for biomolecules are identified as probably the two most critical fields for investigation. In terms of colonic absorption, Fix states that:

> 'Technologies such as OCAS can achieve effective drug release in the colon. However, until pharmaceutical approaches are available to improve colonic absorption, once-a-day products will be limited to those few drugs that exhibit high colonic permeability. In normal gastrointestinal transit, it can be expected that dosage forms will have approximately 4-6 hours available for drug release prior to arrival at the colon. This time window will continue to limit development of once-a-day dosage forms unless colonic absorption improvement is adequately addressed.'

328. Fix concludes with Table VI which lists future challenges and opportunities for once daily oral delivery systems, with particular emphasis on biotechnology products.

The rival contentions as to what Fix discloses

329. I refer to paragraph 301 above, where I summarised the key difference between the parties on the disclosure of Fix. In his first report, having just set out figure 4 of Fix, Professor Shakesheff said this (emphasis added):

> 'The skilled formulator would understand that the OCAS formulation operates <u>by delaying drug release until the preparation has travelled through the stomach and small intestine</u> where many physiological factors influence drug absorption. The skilled formulator would be aware, however, that there are equally physiological factors that influence drug absorption in

> the colon (which has its own pH, bacterial content and is water deprived). Therefore, in order for the OCAS formulation to achieve its stated aim of colonic release, it would need to ensure that the drug was able to dissolve in an efficient and predictable way in such an environment. Indeed, Fix notes in its conclusion that, while technologies such as OCAS can be effective to achieve drug release in the colon, until pharmaceutical approaches are available to improve colonic absorption, once-a-day products will be limited to those few drugs that exhibit high colonic permeability.

330. In my judgment, Professor Shakesheff was plainly wrong in saying that the OCAS formulation operates by delaying drug release until the preparation has travelled through the stomach and small intestine i.e. reached the colon. There are numerous and clear indications that a significant amount of drug release occurs from the OCAS formulation in the small intestine and before the preparation reaches the colon. Fig 4 clearly shows drug release in the small intestine and its title refers to 'drug release in small intestine and colon'. See also Fig 5 regarding PEO. All these indications are entirely consistent with the stated aim to design a sustained-release formulation that will perform reproducibly whether in the small intestine or colon.

331. This erroneous view seems to me to have permeated Professor Shakesheff's evidence on Fix. Later in his first report, he said of the OCAS tablet:

> 'It is essential for the tablet to go through the stomach and small intestine without being damaged by the contractions as ideally it reaches the colon and starts dissolving in a linear way.' (emphasis added).

332. By way of further example, in his second report, Professor Shakesheff rebutted in forceful terms what Professor Craig had said about the disclosure and it is apparent he maintained the views set out above. For example, he said '*I do not accept that the skilled formulator would take a 'try it and see' approach, given that Fix seeks to obtain extended colon release over 12 or more hours…'.*

333. As another example, Fix states in terms (see paragraph 321 above for context) that '*Again, it is likely that the very rapid hydration of the OCAS formulation is an underlying cause for the relative food effect independence.'* Yet, in cross examination, Professor Shakesheff said he disagreed with that statement and slightly later expressed the view that '*I do not understand mechanistically how rapid gelation leads to any decrease in food effect....'* His opinions are understandable on his view that drug release does not start until the preparation reaches the colon and that in the small intestine all that happens is gelation, but the reason he disbelieves the opinion expressed in Fix, in my view, is because he has dismissed the notion that drug release takes place in the small intestine.

334. It is of course true that Fix speaks of 'consistent colonic drug release', but it is inaccurate to say, as Astellas effectively submitted (based on Professor Shakesheff's evidence) that Fix is all about drug release in the colon. Indeed, this very point was put to Professor Craig in cross-examination. His answer was

clear and one which I accept:

> Q. Just look at the abstract of Fix again, if you have Fix there. It explains in the abstract, the penultimate sentence: "The rapid hydration and formation of a rigid gel leads to effective drug release in the colon."
> A. Yes.
> Q. That is what Fix is all about.
> A. No, it is not "what Fix is all about". It is one of aspects that Fix teaches. If you look at the previous sentence, it then mentions the "minimal food effects". Again, Fix is not saying in order to get the mitigation of the food effects you have to have the colonic effect. The rapid hydration can have more than one consequence and I think I have already explored this before the break, but they are not necessarily equivalent.

335. In their closing the Defendants submitted that in his written reports, Professor Shakesheff had only focussed on colonic release and absorption. This was not quite true, because one can find references in his many paragraphs discussing Fix to the teaching about overcoming food effects (particular in relation to the dog studies). It is noticeable that Professor Shakesheff was very critical about the lack of detail provided for these dog studies, saying it is '*highly problematic in interpreting the data generated'*. This attitude was in marked contrast to his attitude to the amount of data supporting the teaching in the Patent.

336. In cross-examination, Professor Shakesheff was constrained to agree that a focus of Fix was a formulation that is aimed at achieving food independence, but he was dismissive of this. When asked whether food independence was a focus of Fix but also one that the Skilled Formulator would have appreciated, he said '*I think at a superficial level, I agree.'*

337. I agree with Professor Craig's view that Fix taught two key things, as encapsulated in the Abstract: '[8] OCAS is an oral controlled absorption gel matrix system that exhibits pH-independent, pseudo-zero order drug release with minimal food effects. [9] The rapid hydration and formation of a rigid gel leads to effective drug release in the colon.'

338. Astellas submitted that:

i) on the basis of sentence [9]: *'..it follows that the food independence is being taught to be the result of effective drug release in the colon.*' Astellas also submitted that: '*Professor Craig's refusal to accept this was unreasonable and did him no credit. It was classic ex post facto reasoning, driven by the target being aimed at*.'

ii) In conclusion on the disclosure of Fix that: '*Properly understood the teaching of Fix was that the food effect was avoided by extending drug release and absorption into the colon.'*

339. Professor Craig was pressed numerous times in his cross-examination with this point in various guises. He was consistent in his view that Fix presents two issues '*which may or may not be inter-related'* because '*We simply do not know*

enough about the nature of the food effect, nor do we understand why getting the drug down to the colon would necessarily mitigate the food effect in and of itself anyway. None of this is known.'

340. In my view, neither in the abstract, nor in the body of Fix is it suggested that these two aspects of the teaching of Fix are necessarily related, and I do not consider that the Skilled Formulator, reading Fix with interest, would so conclude. Plainly, an important part of Fix is drug release in the small intestine.

341. Furthermore, the accusation of *ex post facto* reasoning can work both ways. In this instance, the accusation is properly levelled at Professor Shakesheff and Astellas, interpreting Fix so as to increase unfairly the distance between it and the patent.

342. To reinforce their contention that a key objective of Fix was to achieve independence of food, in their written closing, the Defendants drew together all the parts of Fix which they contended supported that view, as follows:

i) **The Abstract**: [7] 'Food effects can also introduce significant variability.' [8] 'OCAS is an oral controlled absorption gel matrix system that exhibits pH-independent, pseudo-zero order drug release with minimal food effects.'

ii) Under the heading "Physiologic Influences" it says "*Ideally, a once-a-day dosage form should function independent* (sic) *of variations in the parameters shown in Figure 2*". Those parameters include food.

iii) **Internal p.21:** The penultimate paragraph states "As mentioned in the introduction, the gastrointestinal variables that can impact the performance sustained-release once-a-day dosage forms are generally influenced by the presence of food. Enzyme activity, motility, pH, fluid content, and bile salts are all modified in the fed state versus the fasted state."

iv) Pausing there, this reinforces the teaching at p.16 that dosage forms should function independently of food. The same teaching is also repeated at **internal p.17, first line** "*In order to reliably control drug release in an extended release product, the formulation would ideally function independently of these changing variables*." See too **internal p.18 first line** "*The future development of once-a-day dosage forms depends on the ability to design and develop sustained-release dosage forms that will function independent* (sic) *of influences from the gastrointestinal milieu*." Professor Shakesheff agreed that this was the teaching: see $T2/285_{20}$-287_{20}.

v) **Internal p.21:** The penultimate paragraph goes on to state "In order to determine whether OCAS would perform independent (sic) of the effects of food, a dog study was conducted comparing nicardipine hydrochloride absorption from OCAS and conventional gel tablets."

vi) **Internal p.21:** The final paragraph states: The data presented … indicate

> that significantly greater absorption (AUC) is achieved with OCAS compared to the conventional gel and that the OCAS system is relatively free of food effects… Again, it is likely that the very rapid hydration of the OCAS formulation is an underlying cause for the relative food effect independence."

vii) **Internal p.23**: The first paragraph states "In summary, OCAS is a rapidly hydrating gel matrix table that performs relatively independent (sic) of the effects of pH, mechanical stress, and location in the gastrointestinal tract. In addition, at least with the model compound employed, food effects appear minimal. As such, the technology represents an advance in sustained release formulations that might have applications in once-a-day drug therapy."

343. I agree that all these passages support sentence [8] in the abstract, as a separate disclosure from sentence [9]. It is certainly true that there is a lot in Fix about extending drug release into the colon and extended colonic absorption. However, in my view, the Skilled Team would be likely to conclude that Fix set out to produce a formulation for effective drug release in the colon but discovered it produced the added benefit of significantly reducing a food effect, at least for nicardipine hydrochloride.

344. In summary, I concluded that Astellas and Professor Shakesheff did not treat the disclosure of Fix fairly. Furthermore, their approach appeared to me to be highly defensive.

Second, what would the Skilled Team do, having considered Fix

345. In view of my findings as to the disclosure of Fix, it is relatively easy to deal with Professor Shakesheff's evidence to the effect that the Skilled Team would have no interest in Fix and would set it on one side. That evidence (and the related contentions made by Astellas) was founded on Professor Shakesheff's erroneous understanding of the disclosure, which is reason enough to reject it.

346. That, however, does not mean that I must necessarily accept the alternative analysis put forward by Professor Craig, which was the subject of extensive and sustained criticism by Astellas. However, it is necessary to take into account the fact that much of Astellas' criticism was based the erroneous understanding of the disclosure of Fix.

347. A major part of the battle at trial on this point was concerned with the Skilled Team's motivation having read each piece of prior art. This resolved into three main areas of dispute: the first concerned the context in which each piece of prior art was read; the second concerned whether the drugs the subject of study in each piece of prior art had sufficiently similar characteristics to mirabegron, and the third concerned the alternatives to developing a once-a-day controlled release formulation. It is convenient to discuss the first and third points here because, in Astellas' argument, they are the setting for much of their allegation that the Defendants' approach is irremediably tainted by hindsight.

Context and alternatives

348. The starting point is, as the Defendants submitted, that the Skilled Team would as a matter of routine, look for and identify the food effect with the conventional immediate release formulation of mirabegron. It was common ground that (a) the Skilled Team would assume the food effect was clinically significant and (b) the Skilled Team, in particular the Skilled Formulator, would have input from the Skilled Clinician regarding the desirable attributes that a formulation of mirabegron should have. The Skilled Team are motivated to seek to address the food effect encountered with an IR mirabegron formulation because it is undesirable for a drug to have to be marketed with a requirement to take it with or without food. Therefore, the Skilled Team would seek to address the food effect.

349. In his first report, Professor Craig stated that the Skilled Formulator at the Priority Date would have known that using different formulation approaches such as a MR formulation had been shown with some drugs to mitigate the effects of food experienced when they are formulated as an IR formulation.

350. This did not seem to be disputed. However, Astellas were highly critical that Professor Craig had not mentioned any of these alternatives (to the OCAS system, as disclosed in each piece of prior art) in his reports, as having been successfully used to mitigate food effects. In cross-examination, Professor Craig readily acknowledged that the Skilled Formulator would know of some of these other alternatives, including the OROS system and lipid delivery systems, in this passage:

> 4 Q. You say there that different formulation approaches such as
> 5 modified-release formulations had been shown with some drugs
> 6 to mitigate food effects; yes?
> 7 A. Yes, that is correct.
> 8 Q. You do not actually give any examples there. Which common
> 9 general knowledge drugs are you thinking of there which had
> 10 food effects?
> 11 A. I cannot remember the specific references off the top of my
> 12 head, but there would be, certainly there would be knowledge,
> 13 the OROS system, for example, lipid delivery systems were also
> 14 known to help with some food effects. I have also seen some
> 15 literature of just conventional controlled-release systems
> 16 having been used. However, as I say, the information is very
> 17 scanty and it is, as a whole, within the field, I do not think
> 18 that if you spoke to a skilled formulator in industry at 2008
> 19 they would necessarily point to a specific system, but what
> 20 they would be aware of is that there are formulation
> 21 approaches possible.
> 22 Q. Yes, but you have not been able to give any common general
> 23 knowledge references to support your assertion in 7.55, have
> 24 you?
> 25 A. It is not a question of not being capable of doing so. It
> 2 would have been a simple matter to have included some
> 3 references. I have already mentioned to you that OROS and
> 4 lipid delivery systems were two areas where I think it would
> 5 be within the common general knowledge that these had been
> 6 looked at.

351. Astellas submitted that the fact that Professor Craig had not considered these other CGK systems affected the mindset he attributed to the Skilled Formulator and that the effect was that his Skilled Formulator did **not** consider the prior art against a CGK backdrop comprising a range of other approaches, to fairly assess whether, compared to those other options, the prior art represented a reasonable and/or attractive way to proceed.

352. He had already set out various MR forms, and these are included in section 16 and 17 of the Agreed CGK above. He explained that controlling the rate of release by diffusion and erosion from hydrophilic matrices had been part of the formulator's toolkit for many years. He mentioned the other main subtype of matrix diffusion systems: lipid or insoluble polymer matrices, where the drug particles are dispersed in a wax or insoluble matrix and the drug becomes available as solvent enters the matrix and dissolves the drug. In relation to these, he said by 2008 lipid and insoluble matrices '*were not commonly used and are not relevant to the Patent, so I have not discussed these further.'* This sentence was fastened on by Astellas as indicating his hindsight approach, because the Skilled Formulator in 2008 would not know that those matrices were not relevant, as Professor Craig agreed. I consider that Astellas have better points. The experts have to draw the line somewhere otherwise reports become unwieldy.

353. Counsel suggested to Professor Craig that ion exchange control systems would also have been 'on the radar' of the Skilled Formulator without the benefit of hindsight. Professor Craig had already stated in his first report that very few solid drugs had been formulated using ion exchange, but that it remained a classic 'teaching example' even today. His answer was that there are many other dosage form approaches which he could have listed in his report, but his instruction was to focus on those dosage forms which are most likely to be relevant to this case, which is why he did not discuss nano crystal and other systems.

354. Professor Shakesheff said in his report that there were no universally accepted approaches to mitigate food effects using formulation changes – a point which was common ground. He mentioned possibilities such as reducing drug particle size to accelerate dissolution and multi-particulate formulations that release small particles in the stomach which may result in transit of the drug into the small intestine in advance of any food transport plus, more generally, seeking to reduce drug molecule interactions with food or luminal contents.

355. A further aspect of Astellas' hindsight attack was their contention that Professor Craig's Skilled Formulator saw the prior art as the 'only' option (a 'lifeline', in effect) which meant that his formulator was more willing to overlook any complications or difficulties when it came to applying the teachings to mirabegron. Astellas relied on two examples from his cross-examination, but I need only mention the passages which relate to Fix. Professor Craig had suggested that the question the formulator would ask themselves is, is this technology something that would be worth exploring? Counsel suggested that the Skilled Formulator could not make any reasonable prediction that this OCAS system would work for another drug, because there is so much that is not understood and so many differences with the other drug you are trying:

24 A. That is one view, but can I also put -- I think a lot of this
25 is to do with motivations and drivers. Let us say there is a
2 fictitious pharmaceutical company and there is a Managing
3 Director and a new drug is being developed and they find at
4 Phase I there is a problem with the food effect. The
5 formulator and the rest of the skilled team, the
6 pharmacokineticist and the clinician are called in and
7 basically they are told this is a very valuable drug to the
8 company and to the patient and, therefore, we need to find a
9 solution. However, we are not able to abandon it and we are
10 not able to simply put on a label. We need you, therefore, to
11 explore what formulation approaches might be useful for this
12 drug.
13 If that was your motivation, you would look at
14 approaches that had been described in the literature and you
15 would ask yourself the question, is it worth pursuing this?
16 If you did not have that motivation and the Managing Director
17 was saying put on the label before or after food, I completely
18 and utterly agree with you, you would not take any risks
19 associated with developing these formulations, but if we are
20 in the territory whereby it is necessary to develop a
21 formulation to mitigate the food effects, then you would
22 consider what options you had, and this is one of the options.
5 Q. You admitted that there is no understanding at all as to why
6 the nicardipine food effect is being achieved.
7 A. Your question is why would the skilled formulator take this
8 forward when we do not understand how it is working with
9 nicardipine?
10 Q. Yes?
11 A. Yes, a perfectly reasonable question and the simple answer is
12 because the skilled formulator would have very limited range
13 of choices. If the skilled formulator was charged with
14 developing a formulation approach to a food effect, then there
15 is no way the skilled formulator can turn around to that
16 fictitious Managing Director and say, "Do you know what, I am
17 not going to try anything because I do not know, I cannot
18 guarantee right here, right now, (a) how it is going to work
19 and (b) whether it will work." That is not the duty of the
20 skilled formulator. The skilled formulator would be there to
21 say to the Managing Director, "I cannot guarantee but what I
22 will do is I will look at the options and I will make a
23 professional judgment about which ones can be taken forward."
24 That is point No. 1.
25 Q. Can I just interject there?
2 A. Please.
3 Q. If you have no understanding as to the reason it is working,
4 all you can be doing is hoping that it might work for
5 something else; correct?
6 A. Essentially, yes. Yes, I would agree with that.

356. Astellas also relied on this later exchange:

8 Q. It is still a substantial research project?
9 A. Yes, it is still a substantial research project but again, I
10 go back to my earlier point, you are doing this because you
11 need to find a solution. You need to find a formulation
12 solution to your problem. You are not doing this because you

> 13 have an easy alternative of changing the label of your system.
> 14 Otherwise you would be doing that.
> 15 Q. Why do you say that, professor? Why could you not just leave
> 16 mirabegron, be taken with food?
> 17 A. One could do. I am talking about, in the broader sense. My
> 18 understanding is that what the skilled formulator has been
> 19 asked to do is to find a formulation solution to a food
> 20 effect.
> 21 Q. You are assuming that one of the options is not to do nothing
> 22 and just put on the label that it has to be taken ----
> 23 A. Absolutely, because if that was the option, that is what you
> 24 would do.

357. Prior to the first exchange I quoted, Professor Craig had said the Skilled Formulator would be interested in the OCAS system described in Fix because it was quite simple and inexpensive, and in that context the Skilled Formulator would pose the question: is this technology something that would be worth exploring?

358. Although Astellas sought to characterise Professor Craig's approach that the prior art represented the only option, so that it would be pursued almost to the death, I consider that is an unfair characterisation of his approach. He was envisaging a real-life team given the task of investigating whether a reformulation approach could mitigate the food effect observed with the IR formulation of mirabegron. The alternative approach presented by Professor Shakesheff was that the Skilled Team would not take any of the prior art forward – dismissing each piece as of any interest to the Skilled Team. In essence, what Professor Craig was saying was that the Skilled Team would not give up on the prior art so easily but I did not understand him to say the investigation would be pursued relentlessly.

359. So far as the alternatives were concerned, other than the fact that some of them were known approaches which had worked to mitigate food effects, whether any of them might have been perceived as promising avenues for investigation with mirabegron was not really explored at all. Certainly, there was nothing nearly as concrete as the proposals in each piece of prior art. Let me assume, however, that there were several alternative obvious avenues to pursue. The existence of those alternatives does not render Fix any less obvious, if that is the conclusion.

360. Professor Craig identified that the Skilled Team in these circumstances would generally have four options:

i) Provide the patient with label instructions that told them to take the drug either before or after food.

ii) Direct the Skilled Formulator to find a formulation whereby the food effect was reduced so it was no longer clinically significant to the patient.

iii) Conduct a series of mechanistic studies to seek to determine how and why the presence of food impacts the absorption of the drug, with a view to developing a formulation which is less affected by these mechanisms.

iv) Terminate the drug development project.

361. Professor Craig described the fourth option as the nuclear option – the worst-case scenario. The third would not commonly be conducted because it was expensive and time-consuming and there was no guarantee the studies would determine the mechanism(s) by which food affects the drug or formulation. The disadvantages of the first option were clearly explained by Dr Morley. He explained that patient compliance in the therapeutic area of OAB was of particular concern with existing treatments, particularly for the available antimuscarinics, where he said patient compliance was poor. He mentioned that new formulations of some of the antimuscarinics became available in the years leading up to the Priority Date, many of which were extended release and therefore administered once-daily, which assisted with improving patient compliance.

362. Professor Craig considered that the first or second options will generally always be preferred, given the usual pressures to bring a new drug to market as quickly as possible.

363. Professor Craig was cross-examined about these options. Where his evidence ended up was that his Skilled Formulator would say to his team: I cannot guarantee that we will find a formulation solution to this problem, but there is a precedent that formulation solutions may be applicable. He agreed the Skilled Team would not pursue Option 2 regardless but was plainly of the view that it would be well worth investigating.

Similarity to mirabegron

364. On the second issue, the experts were agreed that the Skilled Team would need to assess key drug characteristics before beginning any formulation development. Professor Shakesheff drew attention to the following characteristics of mirabegron. He said it (a) has a long elimination half-life (thought by the inventors to be 18-24 hours); (b) was classed as 'practically insoluble' (with a measured solubility of 0.0082 mg/mL); (c) has an assumed dosage of 100mg (based on an earlier patent with an oral formulation example).

365. Professor Shakesheff's evidence in his reports was that the Skilled Team would be interested in formulations for drug molecules with similar physicochemical and PK properties (such as BCS Class, if known), water solubility, half-life and dosage) to mirabegron that had produced the same type of food effects. On this basis, Professor Shakesheff considered that each prior art citation would be read but then set aside because each would be considered as not particularly applicable to the problem faced by the Skilled Team with mirabegron. In contrast, Professor Craig's evidence in chief was that the Skilled Team would be motivated to develop a MR mirabegron formulation using the OCAS system described in the prior art and based on 'routine development' in the course of doing so, the Skilled Team would be likely to develop a formulation falling within the scope of claim 1 of the Patent.

366. In their reply evidence, both experts maintained their positions. Professor Shakesheff disagreed with Professor Craig's 'try it and see' approach, but also

considered that such an approach would not result in a formulation within claim 1. For his part, Professor Craig considered Professor Shakesheff's approach as 'far too pessimistic'.

367. Astellas developed a sustained attack on the Defendants' approach to the prior art, alleging that hindsight permeated the whole approach, both at a structural level (i.e. on the way Professor Craig had been instructed) and at an evidential level. I have addressed certain aspects of this attack already. However, the force of the hindsight allegations can really only be assessed once I have decided the circumstances in which the Skilled Team read each piece of prior art and what each teaches.

368. In his first report, Professor Shakesheff set out a list of key drug characteristics which he said the Skilled Team would need to know for the purposes of trying to develop an improved formulation for mirabegron, namely:

i) the elimination half-life, for which he referenced the 18-24 hours mentioned in the Patent.

ii) the water solubility, for which he took information from the FDA's prescribing information for Myrbetriq, where it is classed as 'practically insoluble', and a solubility value of 0.082 mg/mL in water.

iii) BCS classification, on which he said that no information was available on mirabegron's BCS class as of 2008. He noted that permeability information had not been provided. Based on the water solubility figure he had quoted, he considered it was safe to declare that mirabegron 'is not in BCS Class I (or III) given its low water solubility'.

iv) Dose: he was asked to assume from information supplied by Astellas' solicitors (from an earlier patent application) that the active ingredient was 100mg.

v) Side effects profile: he was asked to assume no significant side effects were experienced.

369. Professor Craig agreed that the Skilled Formulator would want to assess key drug characteristics before beginning any formulation development. He said that if the Skilled Team had not been provided with the details mentioned by Professor Shakesheff, they would have ascertained water solubility through routine experiments and, so far as dose was concerned, he said that a dose of 100mg may have been determined as an appropriate dose, but further studies would have been conducted to confirm the appropriate doses and in particular the lowest therapeutically effective dose.

370. It is notable however, that when responding to Professor Shakesheff's list, Professor Craig did not mention permeability or elimination half-life. It emerged at trial that Professor Craig had asked the solicitors for the physicochemical data relating to mirabegron, but he was not given it. Professor Craig ought, as Astellas submitted, to have pointed out he did not have access to any permeability data.

371. Astellas submitted that the position regarding the elimination half-life $T_{1/2}$ was even worse. Professor Craig had specifically raised a concern that mirabegron was a drug with a long half-life, adding that it is unusual to put a long half-life drug into a controlled release formulation. This issue was taken by the solicitors to Dr Blakey who concluded that half-life was not an issue that would put off the Skilled Formulator. Professor Craig was told that Dr Blakey was dealing with it and for that reason, he did not mention it in his report.

372. I agree with Astellas that this was not handled well, but the fault lies largely with the solicitors. They should have ensured that the interaction on these issues was properly set out in the expert reports. However, I remain unconvinced that this has had any detrimental impact on the evidential position that was reached.

373. The Skilled Formulator's concern over $T_{1/2}$ would have led to the Skilled PK being consulted. In summary, largely for the reasons explained by Dr Blakey, the Skilled PK would have concluded that accumulation of mirabegron would not be a problem.

374. However, it is necessary to discuss the issues of solubility and permeability further.

Solubility

375. As mentioned above, Professor Shakesheff referenced a figure for the solubility of mirabegron in his first report, which came from a post-priority source. Professor Craig did not provide a value of the solubility of mirabegron in his first report.

376. In reply, Professor Craig did not take issue with the solubility provided by Professor Shakesheff or his characterisation of that solubility as "*practically insoluble*" Indeed at one point in his second report, he relied on the value provided by Professor Shakesheff.

377. On this issue, Astellas submitted as follows:

i) First, despite having led no evidence on the subject, at trial the Defendants sought to establish that the figure given by Professor Shakesheff in his first report was wrong. This was done by reference to the document provided one day before the start of the trial at **DXX-KS/Tab 17**.

ii) Astellas were highly critical of this document. It was described in the index as an extract from Sandoz' regulatory dossier (although it did not say so on its face) and Astellas submitted that the exact status of the document is unclear.

iii) No CEA Notice had been adduced in relation to it.

iv) Sandoz had provided a sworn PPD of its product in these proceedings which did not contain this data.

378. The document provided values for the solubility of mirabegron at three pH

values: 12.5 mg/ml (at pH 1.2), 14.1 mg/ml (at pH 4.5) and 3.3 mg/ml (at pH 6.8). On the basis of these data mirabegron was classified as having a "*high solubility*" at a dose of 50 mg, it therefore would be classified as BCS Class III (i.e. high solubility but low permeability).

379. Professor Shakesheff was not cross-examined as to the reasons why these figures differed from the figure he had relied on in his first report. Professor Craig suggested the differences related to differences in the pH at which solubility was measured.

380. Ultimately, Astellas submitted the Court is left with two alternative solubilities at mid-level pH (of 0.082 mg/ml at pH 7 and 3.3 mg/ml at pH 6.8) and no basis for preferring one over the other or for determining that either of them is wrong. Astellas submitted that, as a matter of evidence, if the Court has to it should prefer the value given in the FDA document exhibited by Professor Shakesheff.

381. It seemed to me that there was a certain amount of gamesmanship employed by both sides on the issue of the solubility of mirabegron. Sandoz were very late in putting forward the extract from their EMA regulatory dossier. However, Astellas are likely to have possessed detailed (and likely very similar) solubility data for mirabegron. Astellas would also know the relevant BCS class for mirabegron, as Professor Shakesheff accepted, but he did not ask for that data.

382. I confess I remain somewhat suspicious of the partial data which were supplied to and reported by Professor Shakesheff in his first report. In cross-examination, Professor Shakesheff agreed it was CGK that BCS classification is determined by reference to the solubility of the drug in aqueous media at a range of pHs. Indeed, in Aulton (a well-known undergraduate textbook) the BCS classification scheme is described and the following features are pertinent:

    i) The four classes are classified according to their aqueous solubility across the GI pH range and their permeability across the GI mucosa.

    ii) The GI pH range is indicated to be 1-8.

383. Professor Shakesheff also agreed that it would have been routine for the Skilled Formulator to work out the solubility of mirabegron at a range of pHs in aqueous solution in accordance with the BCS.

384. All this left me wondering how Professor Shakesheff had felt able to assume that mirabegron was neither BCS Class I or III, without having data for the solubility of mirabegron at a range of pH values, and why he decided to rely on a figure for solubility in water in the FDA product leaflet. That, in my view, was plainly not the best evidence with which Astellas could have provided him. He was not cross-examined about this aspect of his evidence, however.

385. It seems to me that if the Sandoz data were erroneous, Astellas would have been able to demonstrate that with relative ease. Astellas relied on the figure set out in the FDA product leaflet and contended that it was hardly likely they had put forward an erroneous figure. The same point has at least equal force in relation to the Sandoz filing, not least because the FDA product leaflet serves a different

purpose to the EMA document, which one would expect to contain (as it does) more detailed information.

386. In the light of the unsatisfactory position in which the evidence was left, I was inclined to proceed on the basis of the data set out in the Sandoz EMA filing, being far more pertinent to the issue of BCS classification.

387. However, I should mention developments after conclusion of the trial, which arose out of the controversy surrounding Sandoz's MHRA Public Assessment Report ('PAR') for 25mg and 50mg Sandoz Mirabegron. Astellas' solicitors wrote to my clerk by letter dated 12th August 2022, drawing my attention, inter alia, to the clarification in a letter from Sandoz's solicitors dated 2nd August 2022 that Sandoz did not dispute in these proceedings that mirabegron was 'practically insoluble' in water (at an undisclosed temperature and pH) but disputed that this is the only relevant information on solubility that goes to the issues in this case. The clarification was realistic in view of the fact that the PAR stated as much. However, there was more in the letter dated 2nd August 2022 on the solubility issue, which was drawn to my attention by a further letter dated 16th August 2022 and I quote:

> 'As to your comments on solubility data as noted in the document at DXX-KS tab 17, information that mirabegron is soluble in water between neutral to acidic pH comes directly from your client's Assessment report for Betmiga from the EMA (see page 9 of the Betmiga assessment report). In addition, the information that mirabegron is a BCS class III compound of high solubility and low permeability comes from your client's NDA. Further it is noted in your client's Australian PAR that "data provided by the sponsor indicate that it [mirabegron] is Biopharmaceutical Classification System (BCS) Class 3 agent". We therefore do not see that there is any basis on which to suggest the Sandoz data which demonstrates that mirabegron is soluble in aqueous solutions between neutral and acidic pH is incorrect.'

388. In view of the unsatisfactory position on solubility which existed at the conclusion of the trial, I consider it right to admit these two further statements of technical fact not least because the Skilled Team which started an investigation into formulating mirabegron would ascertain solubility data and BCS classification. Accordingly, I proceed on the basis that the Skilled Team would determine solubility data at different pHs and conclude that mirabegron was likely to be BCS Class III.

389. There are some other pieces of evidence which I should take into account.

390. First, Professor Craig explained that in terms of the influence of solubility, it is a kinetic process and not purely an equilibrium process. For example, a poorly soluble drug does not need wholly to dissolve in a volume of liquid which corresponds to its equilibrium solubility. Otherwise, for a poorly water-soluble drug like ibuprofen, several litres of fluid in the stomach would be required for it to be dissolved and absorbed. The reality is that even with poorly water-

soluble drugs the process is a dynamic one. It is not a question that all of the drug has to dissolve at the same time in one place. If a drug is taken in the form of a hydrogel, the drug will dissolve and release dynamically within that, and then be removed from the surrounding fluid through the GI wall. That is why an ibuprofen tablet works even if the person taking it has not drunk several litres of water.

391. Second, Professor Craig pointed out that both nicardipine and acetaminophen had been marketed for many years by the Priority Date. He said the Skilled Formulator would identify that nicardipine was a BCS Class II compound, meaning it has low solubility. Acetaminophen was known to have reasonable solubility even though there was some debate at the Priority Date as to whether it was BCS Class I or Class III. Given these different solubilities, the Skilled Formulator would be reassured that the OCAS platform could potentially be utilised for drugs which have both high or low / sparing solubility

Permeability

392. Astellas criticised Professor Craig for not having a figure for the permeability of mirabegron in any of his reports. This criticism was dented somewhat by the fact that neither did Professor Shakesheff.

393. Professor Craig explained in XX that permeability is not something that is studied by the Skilled Formulator per se – that is more done by the pharmacokineticist. He also explained in XX that the only information that he now had on permeability is from the Sandoz document, which he only saw a week ago. Previously, he had no information on what the permeability of mirabegron would be, which is why he could not incorporate anything on it in his report. He reiterated that permeability data would not necessarily have been included because permeability studies are not necessarily standard.

394. Overall, the Defendants submitted that Professor Craig's approach was consistent with that taken by Professor Shakesheff and neither of them should be criticised for it. I am inclined to agree. As I said, I detected elements of gamesmanship on both sides in relation to the supply to their experts of information relating to their physicochemical properties.

395. Ultimately, the Defendants submitted that all of the fuss over solubility and permeability were an unnecessary sideshow, particularly in the context of Fix.

396. That, however, leaves open the question of what the Skilled Team would do, having read Fix with interest. As to this, there are some other points to be noted:

    i) As Astellas pointed out, Fix is not concerned with alleviating a food effect observed in a conventional immediate release formulation. Instead, it is concerned with preventing a food effect which might emerge when a drug is formulated as a MR formulation. Professor Craig agreed with this.

    ii) Undoubtedly, Fix does teach 'effective drug release in the colon' and that is plainly one of the aims of the preparation being 'fully hydrated'

as it enters the water-scarce environment of the colon.

iii) Professor Shakesheff suggested the Skilled Formulator might be put off by the fact Fix addresses a positive food effect rather than a negative one. However he accepted that it is not suggested in Fix that OCAS only achieves independence with a positive food effect. He was not prepared to accept that the Skilled Formulator would appreciate that the rapid gelation would have the ability to solve a positive or negative food effect but could not identify any rationale as to why the Skilled Formulator would reject this inference from Fix's teaching. By contrast, Professor Craig said the point of interest for the Skilled Formulator was achieving food independence, not whether the food effect was positive or negative.

iv) Based on some of Professor Shakesheff's evidence, Astellas made the point (both in XX and in submissions) that nicardipine is a different drug with different characteristics. I consider this below.

v) A major part of Astellas' case was that Fix would not be seen as worth pursuing for mirabegron as a drug with low solubility, low permeability and a long half-life. Professor Craig addressed the first two parameters in this answer:

> ..... You mentioned low solubility. I have already mentioned that the solubility of the drug can be dealt with further up the GI tract, so I do not think that would put me off at all and we have already established that mirabegron is not a low solubility drug anyway, but leaving mirabegron out of this, low permeability, yes, I think that is a reasonable statement. Well, it is a reasonable statement that you would not be interested in a low permeability drug for delivery and absorption through the colon. However, it was dependent on whether the skilled formulator was reading this with a mindset whereby they were agnostic about colonic absorption and they were much more interested in the food effect. That being the case, the permeation would not actually be an issue that would put them off-taking this issue further. I have forgotten the third ----
>
> Q. Low colonic absorption.
>
> A. Low colonic absorption, I suspect that again it depends on the motivator of the formulator reading this. If they were interested in the food effect, I strongly suspect they would be agnostic about colonic absorption.

vi) As for long half-life, Professor Craig had earlier accepted that putting a long half-life drug into a controlled release formulation would be an unusual step. As Astellas noted, long half-life was not something that Professor Craig had considered in his written reports.

vii) Astellas also pointed out that the BLOSSOM paper reported mirabegron doses of 200-300mg/day, and a dose of 200mg would result in a tablet of 800mg using the ratios described in Fix. Professor Craig accepted this would be 'on the upper side' and agreed that the Skilled Team might look to make some changes to the formulation. He pointed out that Fix

> would not be read as a blueprint but as a signpost. He said it was important to differentiate between the initial *in vitro* studies which would be done and the subsequent *in vivo* studies. His point was various permutations could be studied *in vitro*, starting with the 1:2 ratio and the PEG/PEO recipe in Fix.

397. Professor Craig's answer (quoted above) raises the further question of whether the Skilled Formulator, having considered Fix, would be agnostic about colonic absorption. In other words, would the Skilled Formulator concentrate just on the teaching in Fix regarding food effects and effectively dispense with the teaching about extending effective drug release into the colon. Astellas submitted that Professor Craig was abandoning the teaching of Fix altogether, but that submission is only true on their erroneous reading of Fix. However, on a correct reading of Fix, the question of whether the Skilled Formulator would be agnostic about colonic absorption remains a valid point.

Third, the nature of the project which the Skilled Team is prepared to undertake

398. This issue is a precursor to the next two. It has two aspects, the second of which concerns expectation of success.

399. First, Professors Shakesheff and Craig were agreed that the process of reformulation is empirical in nature – the Skilled Team would put some intellectual thought into what was likely to work but at some point you are going to have to adjust formulations iteratively and test them.

400. On the second aspect, in cross-examination, Counsel got Professor Craig to accept that what he envisaged was 'a substantial research project'. Professor Craig gave that straightforward answer without appreciating the significance, in legal terms, of that expression. However, it was clear from other clear answers that he gave that he regarded the project overall as being familiar and routine work.

401. In this regard, I refer to the answers which Professor Craig gave when a two-part question was put to him regarding nicardipine hydrochloride, which was the drug for which Fix demonstrated that OCAS provided an improvement in food effect. Professor Craig had just given an answer in which he said the Skilled Formulator would undertake a study applying Fix to mirabegron in the expectation there was a reasonable chance it would work. Counsel challenged that answer: 'How can you possibly say that' on two bases: first, because the skilled team/formulator would have no understanding as to why the nicardipine food effect is being achieved; second, because nicardipine was a different drug with different characteristics.

402. On the first point, Professor Craig gave the answer I have already referenced that the choices were very limited but which culminated in his evidence that the Skilled Formulator would say to his notional Managing Director: 'I cannot guarantee but what I will do is I will look at the options and I will make a professional judgment about which ones can be taken forward.'

403. On the second point, the essence of Professor Craig's answer was that if the

Skilled Formulator is presented with some sort of technology, but given a different drug with different physical properties, they do not throw up their hands and say 'I have no idea how to do this' (his point correctly reflecting the burden of some evidence from Professor Shakesheff). He indicated that 'This is what they do on a routine basis. This is what the formulator is there for.'

Fourth, whether the project could lead to a formulation which fell within claim 1

404. For this stage of the analysis, I am not considering the issue of obviousness. I am simply identifying whether and how the project might lead to a formulation which fell within claim 1.

405. In his first report, Professor Craig explained what, in his view, the Skilled Team would do, and much of this was confirmed under some robust cross-examination.

406. In the context of applying the teaching of Fix to mirabegron, Professor Craig explained that the Skilled Formulator would start with a PEO in the mid-range weight of 2million and PEG6000. They would not use another additive such as D-sorbitol because it is likely to be released from the swollen matrix. They would use the PEO and PEG with the drug in the ratio 1:1:2 ratio described in Fix but would not be at all surprised if they had to change the ratio The skilled formulator would have "*a very very free hand*" to conduct *in vitro* studies, so there would be no real limit on the number of permutations they could look at, such as changing the ratio of PEO to PEG or the weight. Having a larger amount of drug would not be off putting or unusual either.

407. The Skilled Formulator would routinely try approximately 20 variants with the aim of generating a range of dissolution profiles using the dissolution profile of Fig 6 of Fix as a starting point. But they would not aim only to make the profile slower than the profile of Fig 6 even though mirabegron has a lower solubility than acetaminophen because there is no certainty as to whether the dissolution profile is causing the reduction in the food effect. They will not know without testing what the dissolution profile of the new formulations will be but that is the whole point of doing a range of options.

408. Professor Craig was challenged that this all amounted to a substantial research project, but he explained that his undergraduate students would be able to complete this type of work part-time over a few weeks, and on that basis it would present the Skilled Formulator with no difficulty whatsoever.

409. Having conducted the *in vitro* testing, Professor Craig said that 'several' formulations would be taken forward into *in vivo* testing in order to establish *in vivo* PK parameters. In cross-examination, he said that *'going into a dog study with three different formulations seems not unreasonable*.' Professor Shakesheff doubted the figure of three, but I can proceed on that basis.

410. So far as the lower dissolution limit in the claim is concerned, Professor Craig said that nearly all MR products would have that dissolution profile of less than 75% at 1.5 hours. Accordingly, he said that all formulations produced using the OCAS approach in Fix would satisfy the lower limit in the claim.

411. So far as the upper dissolution limit was concerned, Professor Craig acknowledged that some of his 20 variants *in vitro* would fall outside that limit, but that some would fall within it, albeit the Skilled Formulator/Team do not know of this limit or any of the theories as to its significance.

412. At this point, the Defendants' argument faces an obstacle.

413. Professor Craig did not explain any criteria by which some (assume three) *in vitro* dissolution profiles would be selected for *in vivo* testing. They could not be selected by reference to their ability to ameliorate food effects because that can only be shown in the *in vivo* testing itself. So it would be a matter of chance as to whether one of the *in vitro* dissolution profiles taken forward would fall within the claim.

414. Three routes emerged by which Professor Craig's Skilled Team **could** get to a formulation with a dissolution profile within the limits of the claim (I consider whether they **would** do so in the next section).

415. The first was put forward by Professor Craig in his written evidence. It was based on the supposition that in Fig 6A of Fix, 65% of nicardipine hydrochloride was dissolved at 7 hours based on a paddle speed of 50rpm, but that if the paddle speed for the mirabegron formulation was increased to 200rpm, then it would have a dissolution profile within claim 1. Even though this was disputed (because Fix showed the OCAS tablet to be robust, even at 320rpm), I can assume that is true, but Professor Craig provided no reason for this increase in paddle speed – it was contrary to his own evidence as to 'normal' paddle speed. To the same effect, other than the desire to test a range of formulations *in vitro*, no reason was put forward as to why the Skilled Team would favour a faster dissolution profile, either at all or for *in vivo* testing.

416. The second possible route emerged in his cross-examination, when he said the Skilled Team would be *agnostic* about drug release and absorption in the colon. Although this was not spelled out, the reasoning would be that for mirabegron with low permeability, the Skilled Team would not see absorption in the colon as being significant or important, so would concentrate on drug release and absorption in the small intestine. I observe that this reasoning and its significance has only emerged in this trial after rounds of expert evidence and intense cross-examination.

417. The third route (which was only implied) is that the Skilled Team would go on testing formulations *in vivo* with various dissolution profiles until it found one which happened to fall within claim 1. This argument would have gained some support from Astellas' 'sweet-spot' theory but I have rejected that.

Fifth, the Pozzoli analysis.

418. As usual, the first two stages of the Pozzoli analysis can be readily identified:

(1)(a) I have identified the notional person skilled in the art above. I remind myself that s/he is unimaginative, lacking any inventive capacity.

(1)(b) I have identified the relevant common general knowledge above as well.

(2) In this case it is not sensible to try to identify the inventive concept of claim 1, it is better and safer simply to proceed on the wording of the claim.

419. Two key differences were identified between Fix and claim 1 of the Patent (there may be other differences in the individual constituents, but these two will suffice for the purposes of argument):

i) First, that Fix was concerned with acetaminophen and nicardipine hydrochloride, and not mirabegron, but this was not considered an obstacle by Professor Craig and I agree.

ii) Second, the dissolution limits (which themselves were dependent on the combinations of the ingredients).

420. I remind myself of the critical fourth stage: '*Viewed without any knowledge of the alleged invention, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require a degree of invention?'*

421. I was prepared to accept Professor Craig's analysis down to (and including) paragraph 411 above. However, even taking Professor Craig's evidence at its highest, it is clear to me that none of the three routes I discussed above would be obvious to the Skilled Team:

i) As to the first route, it seemed to me to be driven purely by knowledge of the target i.e. hindsight.

ii) As to the second, in my view it would require considerable imagination (not to say, inventive capacity) on the part of the Skilled Team to reason in that way, which would require them to reject one of the key pieces of teaching in Fix (extending drug release into the colon).

iii) As to the third, it would cross the line into a substantial research project in circumstances where, for the Skilled Team to proceed, they would have to depart positively from the teaching in Fix when no reason has been identified as to why they would do so.

422. On my construction of Integer A, claim 1 is not obvious over Fix. However, on Astellas' construction, claim 1 would be obvious, because Professor Craig's Skilled Team would produce a formulation which fell within claim 1, even though they had not yet tested it *in vivo* as to whether it ameliorated food effects.

Michel - with or without Chapple

423. Michel is a paper entitled "The Pharmacokinetic Profile of Tamsulosin Oral Controlled Absorption System (OCAS®)". It was published in European Urology Supplements in 2005. As explained in the Abstract, Michel describes the characteristics of various OCAS formulations containing tamsulosin with respect to single and multiple dose human pharmacokinetics. Michel also

explains that the OCAS technology '*has the potential to better control the release during passage of the gastrointestinal tract including the colon and which may be devoid of a food effect.*'

424. Astellas' position in closing was that there was no material difference between the attacks based on Fix and Michel, whether read with Chapple or not. Professor Craig accepted that Chapple added nothing to Michel other than possibly reinforcing the idea that OCAS was a platform technology and that Chapple would suggest an even slower dissolution profile than Michel.

425. In their closing, the Defendants set out a full analysis of Michel and did not disagree with the two points on Chapple.

426. There were differences between Fix and Michel, of which the most significant were:

i) Michel was concerned with an OCAS formulation for tamsulosin;

ii) Professor Shakesheff was less resistant to the notion that the Skilled Team would take the teaching in Michel forward. Despite his resistance in his written evidence, in cross examination he accepted that the Skilled Formulator would be interested, based on the teaching in Michel, whether the OCAS formulation could solve the food effect problem experienced with the conventional formulation of mirabegron.

427. However, it seemed to me that on Michel, the parties reprised nearly all of the arguments deployed on Fix. I do not believe it is necessary to lengthen this judgment further by discussing the precise disclosure of Michel or the arguments, because the arguments reach the same crux point.

428. So, following straightforward and routine steps based on the S3 formulation in Michel, Professor Craig's Skilled Team would proceed with a matrix of 20 *in vitro* OCAS formulations of mirabegron. Within that matrix there would be some formulations which fell within claim 1.

429. The S3 OCAS formulation of Tamsulosin in Michel showed 60% dissolution at 7 hours. Professor Craig's approach on Michel was essentially the same as on Fix. His reasoning was:

> '…the Skilled Formulator would want to take forwards formulations with a range of dissolution rates into *in vivo* testing. One obvious way to increase the dissolution rate is to decrease the molecular weight of PEO. The next common grade of PEO down has an average molecular weight of 5,000,000. On the basis that the Skilled Formulator would seek to vary the dissolution rates by a material margin, it is not unreasonable to expect that one or more formulations from the routine development may achieve greater than 75% dissolution by 7 hours.'

430. As before, Professor Craig did not identify any criteria by which the three

formulations taken forward into *in vivo* testing would be selected from the 20, nor any reason to prefer faster dissolution rates. It would be a matter of chance whether the Skilled Team would take forward into *in vivo* testing a formulation which fell within the functional requirements of claim 1. If they did so, they would find it ameliorated the food effect.

431. Therefore, my conclusion is the same. On my construction of Integer A, claim 1 is not obvious over Michel (whether with Chapple or not). However, on Astellas' construction, claim 1 would be obvious, because Professor Craig's Skilled Team would produce a formulation which fell within claim 1, even though they had not yet tested it *in vivo* as to whether it ameliorated food effects.

ADDED MATTER

432. I address this topic briefly. In their opening skeleton argument, the Defendants identified two main added matter attacks. I need not explain the first because the Defendants accepted it fell away on claim 1 with Conditional Amendment 1. The second was that claim 1 contains impermissible selections from multiple lists in the application. The Defendants submitted this objection was not solved by any of the proposed amendments, indeed they contended that Conditional Amendment 2 made the situation worse for Astellas.

433. This second attack was addressed by Mr Mitcheson in his oral opening for Astellas. In very brief summary, he relied on T 1621/16 for the proposition that selections from lists of converging alternatives which constitute a limitation on the scope of protection, are allowable.

434. By the time of written closings, it appeared that the added matter attacks were no longer pursued, since the Defendants submitted the added matter attacks had served their purpose in limiting the ways in which Astellas was able to pursue its case. The Defendants explicitly reserved their position in the pending opposition proceedings and in proceedings in other jurisdictions. In these circumstances, I need not say anything further.

INFRINGEMENT - SANDOZ

435. I will relate, as briefly as I can, the events which took place at the very end of the trial and subsequent to it. These events demonstrate that Astellas has failed to prove infringement by the Sandoz Mirabegron product, assuming I am correct on the construction issue above. If I am wrong on the construction issue, then Astellas will have proved that the Sandoz product infringes.

436. In the closing minutes of the trial, the Defendants' complaint about Astellas' new case on [0010] was not the only excitement. After Mr Mitcheson had made his oral closing, he indicated that his junior Ms Edwards-Stuart, would address me on 'a couple of the infringement issues'. Ms Edwards-Stuart proceeded to make an oral application for specific disclosure against Sandoz. This took place at 4.30pm on the last day of the summer term, with no application notice, no evidence and no notice. Sandoz and I were hearing this application for the first time as Ms Edwards-Stuart spoke. However, I heard a brief explanation of the application, which Ms Edwards-Stuart said she had to make before the trial

concluded. I directed that Astellas should make a formal application, explain the basis for it, so that Sandoz could respond and the application would be determined at a later date.

437. Astellas then issued their application notice on 5th August 2022 (filed 12th August and supported by the witness statement of Ms Katie McConnell dated 5th August 2022), seeking an order that:

> 'Sandoz promptly disclose all pharmacokinetic data within their control (per the disclosure requirements in CPR 31 and their ongoing duty of disclosure) relating to their Sandoz 25mg and 50mg products in fed and in fasted studies (as well as any data within their control for any immediate-release mirabegron product(s)), pursuant to the confidentiality club agreed between the parties (the "Sandoz PK Data").'

438. In an accompanying letter, Astellas' solicitors made it clear that:

> 'Astellas' position is that the Sandoz PK data sought in Astellas' Disclosure Application is only relevant on Sandoz's construction of Claim 1 of the Patent. Therefore, the issues in the Disclosure Application will only be 'live' if Mr Justice Mellor finds in favour of Sandoz's claim construction. If Mr Justice Mellor does find in favour of Sandoz's construction, then as Astellas' junior counsel, Ms Anna Edwards-Stuart, explained at the end of trial (transcript reference T5/8082-5), any finding of infringement by Sandoz will need to be subject to the resolution of the PK data issues which are the subject of Astellas' Disclosure Application, and can be dealt with at a separate hearing after judgment.'

439. This was, as Sandoz later submitted, a distinct and very late change of position by Astellas.

440. Before I proceed further, I should mention what had been set out on behalf of Sandoz in the Defendants' Opening Skeleton for trial. In brief summary:

i) Sandoz explained that, until a recent amendment to their Particulars of Infringement Astellas' claim for infringement was premised on an allegation that its own mirabegron product ("Betmiga") was a "*composition for modified release*" within the meaning of claim 1, that Betmiga satisfied the various structural requirements of claim 1, and that Betmiga satisfied the dissolution requirements of claim 1– see original Particulars of Infringement §8(a)-(b). There was then a pleaded inference that any generic mirabegron product that used the Betmiga MA as a reference marketing authorisation would also fall within the scope of claim 1, and that therefore the Sandoz product would infringe - see original Particulars of Infringement (Sandoz) §8(c) and §9.

ii) Sandoz did not admit infringement because the various properties of Betmiga were outside its knowledge. Sandoz then served its PPD which addressed the structural components of its product and provided what

relevant functional data it had i.e. it provided dissolution data but had no measurements at 1.5 and 7 hours. Sandoz also made a contingent admission - – it would admit that its product satisfied the dissolution requirements of the claim if Astellas proved that Betmiga satisfied those requirements. Following protracted correspondence, Sandoz then accepted its product satisfied the dissolution requirements of claim 1.

iii) That left the issue of whether the Sandoz product was a 'pharmaceutical composition for modified release', which depended on the issue of construction.

iv) Sandoz identified an evidential hole in Astellas' case. Sandoz contended that (unlike Sandoz) Astellas can be expected to have plenty of clinical data about its own product, and in particular must have Cmax and AUC data from clinical trials. However, it has chosen not to disclose any clinical data about its own Betmiga product. Sandoz submitted this was particularly surprising given that its infringement case was, until very recently, premised on its own product falling within the claims, and given that it did produce data relating to its own product's dissolution behaviour.

v) Sandoz also pointed out that it might have been the case that Astellas sought to argue that even without having actual clinical data on the Sandoz product, it could demonstrate infringement on the balance of probabilities i.e., it might have argued that based on the structural characteristics of the Sandoz product and their dissolution profiles that it was more likely than not that those products would reduce the effect of food. Sandoz went on to submit that was clearly not Astellas' case as they had led no evidence on this at all (nowhere in Astellas' expert evidence is there any evidence on infringement).

441. Sandoz made it clear they would be submitting that Astellas had simply failed to prove infringement because it had failed to prove (either in fact, or on the balance of probabilities) that the Sandoz products reduce the effects of food as against a conventional formulation, and therefore that they are a "*pharmaceutical composition for modified release*" within the meaning of claim 1.

442. In their Opening Skeleton, Astellas identified the single issue of construction as being the basis of the non-admission of infringement by Sandoz – in other words, infringement rested on the issue of construction. Astellas adopted the same position in their written closing – it was made clear that if I agreed with Astellas' construction, then Sandoz's non-infringement position fell away. Nothing was said about the alternative.

443. In their written closing, Sandoz made their understanding clear – that infringement stood or fell with the issue of construction of Integer A. On Astellas' construction, Sandoz admitted their product fell within the claim. On their construction, Sandoz submitted infringement has not been proved against their product.

444. This remained the position (even in Mr Mitcheson's oral closing) until Ms Edwards-Stuart sought to change it. The purported justification for the very late application was that Sandoz had previously maintained that they had no *in vivo* data, yet Astellas claimed to have discovered that Sandoz did have such data, which, Astellas contended, ought to have been disclosed in the PPD.

445. In due course, Sandoz filed a detailed response to the application, in the second witness statement of Dr Gareth Morgan. I need not relate all the points he made, but key points were that:

i) Astellas had known for a long time that Sandoz did have *in vivo* data relating to their product, because Sandoz had obtained a marketing authorisation on the basis that their product was bioequivalent to Betmiga, and the PPD referred to that *in vivo* data.

ii) However, Astellas had been repeatedly told that Sandoz had no *comparative in vivo* data, and Dr Morgan again confirmed this.

iii) Sandoz did not understand what data Ms Edwards-Stuart was referring to in her oral submissions. This was clarified in a letter sent on that Friday evening. The 'new data' were apparently the bioequivalence data from studies conducted to confirm bioequivalence to Betmiga. These were set out in Sandoz' MHRA Public Assessment Report for Sandoz Mirabegron in the UK, and the studies described in that document (at least for the 25mg product) were set out in the PPD. On 2nd August 2022, Sandoz's solicitors reminded Astellas' solicitors of the content of the PPD.

iv) In that vein, Dr Morgan stated:

> 'Sandoz does not hold any PK data for immediate release mirabegron products (i.e., conventional formulations). The PK data Sandoz does hold are bioequivalence data and it holds no data from a fed/fasted cross-over study. These data (i.e., the Sandoz BE data) are therefore irrelevant whichever way the Court resolves the dispute on construction'.
>
> 'On the Defendants' construction, PK data are only relevant to the extent that they establish the size of the 'gap' between the fed and fasted state of a particular parameter for a modified release formulation, which can then be compared to equivalent data for a conventional formulation. That is the means by which a reduction in food effects is to be assessed. However, Sandoz has not conducted any fed/fasted cross-over study with a modified release formulation and does not have any data relating to any conventional mirabegron formulation. What PK data it has for the Sandoz products relate only to modified release formulations, in each case from a single cohort, in a single study, in a single fed or fasted state. In each case, those data are used to determine bioequivalence of the Sandoz generic mirabegron product to Betmiga.'

446. In due course I was asked to list Astellas' disclosure application for a hearing. After much to-ing and fro-ing on the availability of counsel, the hearing was listed for a date in late February 2023, but withdrawn by Astellas in early February. Sandoz then wrote on 15th February 2023 to contend the application had been an abuse of process. This contention relates to costs which I will deal with at the form of order hearing following the hand down of this judgment.

447. For the sake of completeness, I am conscious that I have rejected the Defendants' insufficiency arguments on the basis that the Patent makes it plausible that a reduction in food effect is achieved across the breadth of claim 1. However, plausibility is a different standard to that required to prove infringement and I have held that, to prove infringement, at least some reduction in food effect must be demonstrated. For Sandoz Mirabegron, Astellas did not attempt to establish this, either directly or by inference via expert evidence.

INFRINGEMENT – TEVA'S REVISED PRODUCT

448. As I indicated, the infringement issue on Teva's revised product could not be ready to be determined at trial. It remains to be seen whether that infringement issue is to be pursued in the light of my decision on construction.

CONCLUSIONS

449. For the reasons set out above, and on my construction of Integer A, I find EP410 (as unconditionally amended) to be valid but not infringed by Sandoz Mirabegron. Teva admitted that their original product infringed, but infringement by Teva's revised product remains to be determined.

450. If I am wrong on my construction of Integer A, EP410 would be invalid for obviousness over Fix and Michel.

451. I did not understand the conditional amendments to claim 1 to be required.

452. Finally, I must sincerely apologise to the parties for the length of time it has taken me to produce this judgment, which falls well short of what the parties are entitled to expect from the UK Patents Court. The root cause was the time taken to produce my FRAND judgment in *InterDigital v Lenovo* which has caused the subsequent backlog.

453. I request the parties to arrange a hearing to determine the form of order arising from this judgment, if it cannot be agreed, within 4 weeks from hand-down.