**High Court Invalidates Shionogi EPC Patent to HIV Drug "Tivicay"**

Today in *Merck Sharp and Dohme Ltd. v. Shionogi & Co Ltd*., [2016] EWHC 2989 (Pat)(High Court 2016)(Arnold, J.), the High Court invalidated Shionogi's European Patent (UK) No. 1 422 218 that covers its anti-HIV drug "Tivicay" thus reaching a conclusion of no infringement on the basis of invalidity as to the MSD drug "Isentress".

The opinion of the High Court is attached.

Regards
Hal

November 25, 2016

Neutral Citation Number: [2016] EWHC 2989 (Pat)

Case No: HP-2015-000040

**IN THE HIGH COURT OF JUSTICE**
**CHANCERY DIVISION**
**PATENTS COURT**

Rolls Building
Fetter Lane, London EC4A 1NL

Date: 25 November 2016

**Before** :

**MR JUSTICE ARNOLD**

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**Between :**

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|---|---|
| **MERCK SHARP AND DOHME LIMITED** | **Claimant** |
| **- and -** | |
| **SHIONOGI & CO LIMITED** | **Defendant** |

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**Piers Acland QC** and **Stuart Baran**, instructed by, and **Laura Whiting** of, **Hogan Lovells International LLP**, for the **Claimant**
**Justin Turner QC** and **Miles Copeland**, instructed by **Bristows LLP**, for the **Defendant**

Hearing dates: 28, 31 October 1-3, 7 November 2016

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# Approved Judgment

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

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MR JUSTICE ARNOLD

## MR JUSTICE ARNOLD :

Contents

## Introduction

1. The Defendant ("Shionogi") claims that the Claimant ("MSD"), which is a subsidiary of Merck Sharp & Dohme Corp (previously known as Merck & Co Inc, "Merck"), has infringed Shionogi's European Patent (UK) No. 1 422 218 entitled "Antiviral agent" ("the Patent"). The allegation of infringement concerns Merck's product raltegravir, which is marketed under the trade mark Isentress. Raltegravir is an anti-HIV therapy which has been on the market since 2007. Shionogi and GlaxoSmithKline developed an anti-HIV therapy called dolutegravir which has been marketed by Viiv Healthcare (a joint venture between Shionogi, GlaxoSmithKline and Pfizer) under the trade mark Tivicay since 2013. It is common ground that dolutegravir does not fall within the claims of the Patent. Both drugs are integrase inhibitors. MSD denies infringement and claims that the Patent should be revoked on the grounds of lack of inventive step, insufficiency and added matter.

2. The application for the Patent ("the Application") was filed on 8 August 2002. Although the earliest claimed priority date is 10 August 2001, and no challenge to priority had been pleaded by MSD, counsel for Shionogi abandoned the claim to priority for the purposes of these proceedings in his opening submissions, thereby avoiding a dispute as to the relevant date(s) of assessment.

3. European Patent No. 1 422 218 was opposed by Merck. The European Patent Office Opposition Division maintained it in amended form for the reasons given in a written decision dated 31 March 2015. That decision is under appeal, and therefore the amendment has been suspended. In the meantime, Shionogi has made an

unconditional application to amend the Patent in accordance with the claims maintained by the Opposition Division. In addition, Shionogi has made two conditional applications to amend.

4. There are parallel proceedings before the courts of Germany and the Netherlands which are ongoing.

5. In addition to the expert witnesses whose evidence is discussed below, there was one factual witness, who was called by Shionogi. Dr Tomokazu Yoshinaga is currently Head of the Anti-virus 1 Group within Shionogi. Between August 1999 and August 2003 he was sub-leader of the Anti-virus 2 Group (except during the period from July 2001 to August 2002 when he was working at the National Institutes of Health in the USA). His evidence concerned experimental work that Shionogi did on compounds falling within the claims of the Patent during that four year period, that being the period covered by the parties' disclosure obligations with respect to validity. He was a straightforward witness.

6. By contrast with Shionogi, MSD did not call any factual witness to speak to the experimental work that Merck did on compounds falling within the claims of the Patent during the four year period, but merely gave disclosure.

Technical background

7. The following account of the technical background is largely reproduced from the technical primer which was sensibly agreed between the parties.

*Viruses*

8. Viruses are pathogens which can infect a wide range of life forms, ranging from animals and plants to bacteria. Viruses can only replicate once they are inside an infected cell.

9. Virus particles (also known as virions) contain genetic information in the form of either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) packaged in a protein coat called the capsid. In some viruses the capsid is further enclosed by a lipid-containing envelope. Viruses with a lipid-containing envelope are also called enveloped viruses.

10. After infecting a cell, viruses can multiply in the infected cell in several ways. In general, however, multiplication involves a number of steps, including the following:

    i) disassembly of the infectious virus particle within the infected cell;

    ii) copying the viral genome with the help of the infected cell (replication of the viral genome);

    iii) reading the viral nucleic acid and synthesis (transcription) of messenger RNA (mRNA) that is required for the production of the viral proteins;

    iv) synthesis of the viral proteins (translation) by the host cell ribosomes; and

v) re-assembly of the viral genomes which have been replicated in the infected cell, and of the translated protein coating into new virus particles.

11. As explained below, in the case of retroviruses (a family of RNA viruses), the additional steps of transcribing the viral RNA genome into double stranded DNA (reverse transcription) and movement of this DNA into the host cell nucleus followed by its incorporation into the DNA of the host cell (integration) are required between steps (i) and (ii) above.

12. In this way, a single virion can produce thousands of progeny from a single infected cell. Such multiplication may eventually kill the host cell.

13. Virions generally use specific receptors on the outside of cells (cell-surface receptors) to enter the host cells. These receptors are often present only on particular cell types, with the consequence that many viruses are only capable of infecting specific types of cell.

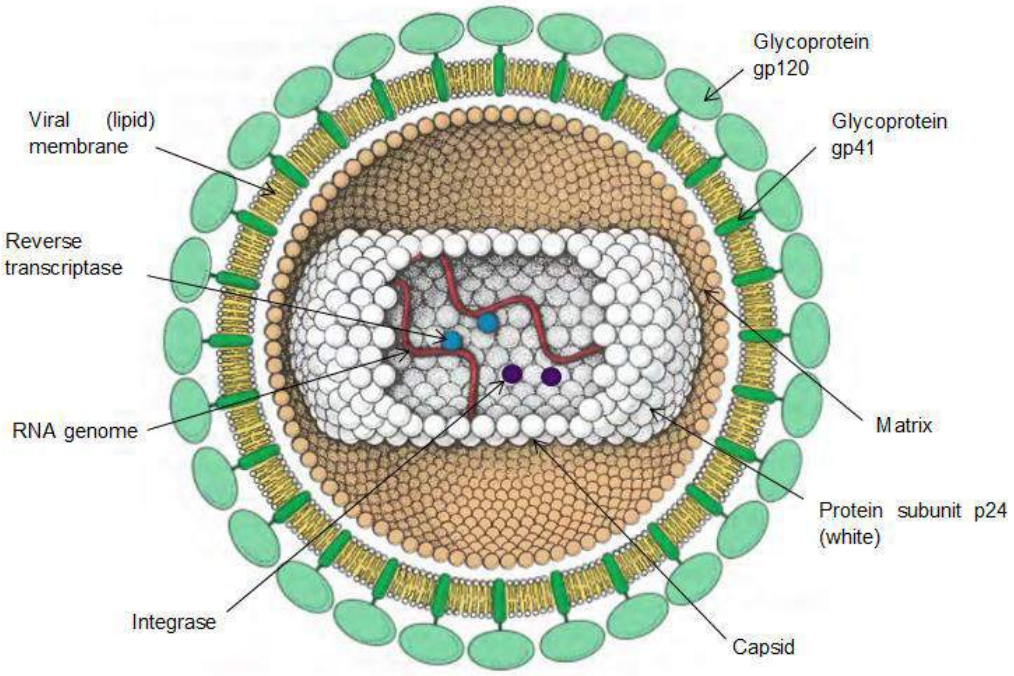
*HIV*

14. Human immunodeficiency virus (HIV) is a retrovirus which primarily infects cells of the human immune system, including CD4+ T cells, which are white blood cells that are an essential part of the human immune system. They are also often referred to as CD4 cells, T-helper cells or T4 cells, and are named after the glycoprotein CD4 which is found on their surface. There are two types of HIV, HIV-1 and HIV-2, of which HIV-1 is the most common.

15. HIV is the causative agent of Acquired Immune Deficiency Syndrome (AIDS). AIDS is a disease in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. An opportunistic infection is an infection caused by a pathogen (e.g. bacteria, viruses) which exploits the weakened immune system of the person suffering from AIDS. Examples of such infections and forms of cancer often seen in AIDS patients are tuberculosis, pneumonia, toxoplasmosis, invasive cervical cancer, Kaposi's sarcoma, lymphoma.

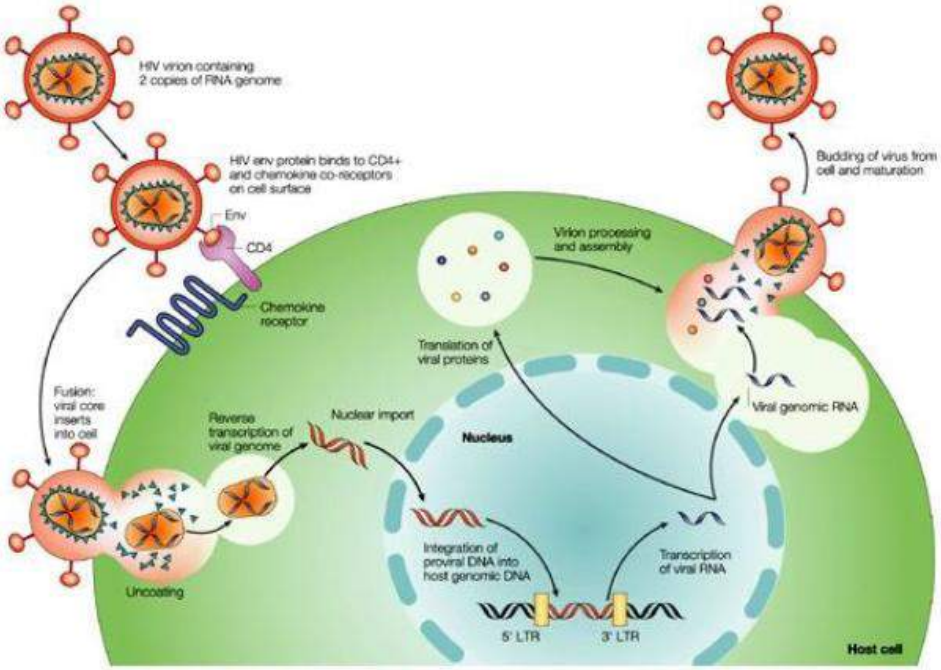
*HIV structure*

16. HIV is transmitted as an enveloped single-strand RNA virus. The viral genome is encoded on two single strands of RNA, contained in the capsid together with enzymes involved in HIV replication. The capsid is surrounded by an envelope comprised of a lipid bilayer in which a number of different proteins necessary for infecting human cells are embedded. An important protein which is involved with the binding of the virus particle to the receptors of the target cell is the HIV protein glycoprotein 120 (also referred to as gp120). The structure of the HIV virion is shown below (adapted from Stryer *et al*, *Biochemistry*, 5th ed (2000)).




*HIV infection and replication cycle*

17. HIV can infect human cells which express the CD4 receptor molecule on their surface, including CD4+ T cells, monocytes, macrophages and dendritic cells. CD4+ T cells express CD4 most frequently and are the main target for the HIV virus in the body. The life cycle of HIV is shown below (from Rambaut *et al*, *Nature Reviews Genetics*, 5, 52-61 (2004)).




18. HIV infects CD4+ T cells by the binding interaction between one of the gp120 proteins on the viral envelope and a CD4 receptor on the surface of the cell. This

initial binding causes a conformational change which allows the gp120 protein to interact with a second molecule on the surface of the cell. Depending on the sub-strain of the HIV virus, this interaction is with either the C-C chemokine receptor 5 (CCR5) or C-X-C chemokine receptor 4 (CXCR4).

19. Following this interaction, the HIV virus fuses to the infected cell using the viral protein gp41 (virus-cell fusion) and the capsid is then taken into the cell.

20. The capsid is then uncoated in the cytoplasm of the cell. The capsid contains a number of viral proteins including reverse transcriptase, integrase, protease and auxiliary proteins such as Vif, Vpr, Vpu and Nef. Reverse transcriptase is responsible for transcribing the viral RNA genome into double-stranded DNA (reverse transcription).

21. The resulting viral DNA is imported into the nucleus of the cell where it is incorporated into the cell's own DNA (integration) by the integrase enzyme. Remaining DNA gaps are repaired by host cell DNA repair enzymes. The integrated viral genome is referred to as a provirus.

22. In active HIV infection (rather than latently infected "resting" CD4+ T cells), the proviral DNA is used to make multiple new copies of the viral mRNA (transcription) by host cell RNA polymerase.

23. The viral mRNA leaves the nucleus and is processed by the cell's own mechanisms to synthesise the proteins and enzymes needed to form new virus particles (translation).

24. HIV proteins are initially expressed as polyproteins named *Gag*, *Gag-Pol* and *Env*, rather than discrete polypeptides. A host cell enzyme (Furin) cleaves the polypeptide *Env* into the proteins gp120 and gp41. Both proteins locate on the cell membrane of infected cells at the site of assembly of new virions. *Gag* and *Gag-Pol* assemble at the surface of the host cell and arrange themselves into new viral capsids around the viral enzymes and viral genomic RNA before "budding" off using part of the cell's own cell membrane as the viral envelope. The newly enveloped virions undergo viral maturation to become infectious. During maturation the HIV protease enzyme cleaves the polypeptides at specific locations to form the component proteins.

25. The HIV-1 genome contains nine genes named *Gag*, *Pol*, *Env*, *Vif*, *Vpr*, *Tat*, *Rev*, *Nef*, and *Vpu* enclosed by two long terminal repeat (LTR) sequences. The *Gag*, *Pol* and *Env* genes code for the major structural proteins and equivalent genes are found in all retroviruses. The *Gag* gene codes for elements of the matrix and capsid. The *Pol* gene codes for the viral enzymes reverse transcriptase, integrase and protease. The *Env* gene codes for the surface glycoproteins gp120 and gp41.

*Treatment of HIV*

26. The first marketed antiretroviral (ARV) was zidovudine (AZT) which was authorised in the USA in 1987. AZT inhibits the reverse transcription step in the viral lifecycle. AZT is classified as a nucleoside reverse transcriptase inhibitor (NRTI): nucleoside because the chemical structure is similar to a DNA nucleotide base; and reverse transcriptase inhibitor because the drug inhibits the viral reverse transcriptase enzyme.

*Classes of anti-retrovirals*

27. Since the authorisation of AZT, further ARVs have been developed. The ARVs currently available (in 2016) can be classified as follows:

    i) NRTIs: these are analogues of natural DNA building blocks which interfere with DNA synthesis. When one of these analogues is added to a growing HIV DNA chain, further elongation of the chain is terminated.

    ii) Non-nucleoside reverse transcriptase inhibitors (NNRTIs): these bind to the reverse transcriptase enzyme, interfering with its ability to convert HIV RNA into HIV DNA, but are not structurally analogous to a DNA base (hence "non" nucleoside).

    iii) Protease inhibitors (PIs): these target the viral protease, whose function is required for the production of infectious virions.

    iv) Integrase inhibitors: these target the viral integrase, and thus interfere with integration of HIV DNA into the DNA of the infected cell.

    v) Entry inhibitors: these interfere with the virus' ability to bind to the host cell membrane by inhibiting the interaction with the cell surface receptors. This class of ARVs includes co-receptor antagonists.

    vi) Fusion inhibitors: these target the virus' ability to fuse to the host cell by inhibiting the process whereby the viral membrane and cell membrane are fused together.

28. As at August 2002, all of the ARVs which had been successfully developed and authorised for use in patients were from one of the first three classes listed above.

29. The typical treatment paradigm in 2002 was a combination therapy known as HAART (highly active anti-retroviral therapy). At the time, this therapy typically comprised a combination of three ARVs chosen from the first three classes above.

30. As at August 2002, no integrase, entry or fusion inhibitor had been approved for marketing. The first integrase inhibitor (raltegravir) was authorised by the US Food and Drug Adminisration in 2007. At present three integrase inhibitors have been approved for marketing: raltegravir, dolutegravir and elvitegravir (Gilead).

*Integrase*

31. Integrase is an enzyme found in retroviruses. It is essential for integration of the viral DNA into the host cell DNA. Not all retroviral integrase enzymes are identical, although all integrases share a number of highly conserved regions.

32. The first integrase was isolated in 1978 from avian myeloblastosis virus and Rous sarcoma virus. The protein, named p32 (based on its molecular weight), was observed to bind nucleic acids as well as exhibiting endonuclease activity, nicking plasmid DNA in the presence of magnesium ($Mg^{2+}$) or manganese ($Mn^{2+}$) ions.

33. It was speculated that p32 could be involved in replication, proviral integration or processing of viral message, but its involvement in the integration process (and essentiality for viral replication) was only confirmed after further genetic studies had been performed.

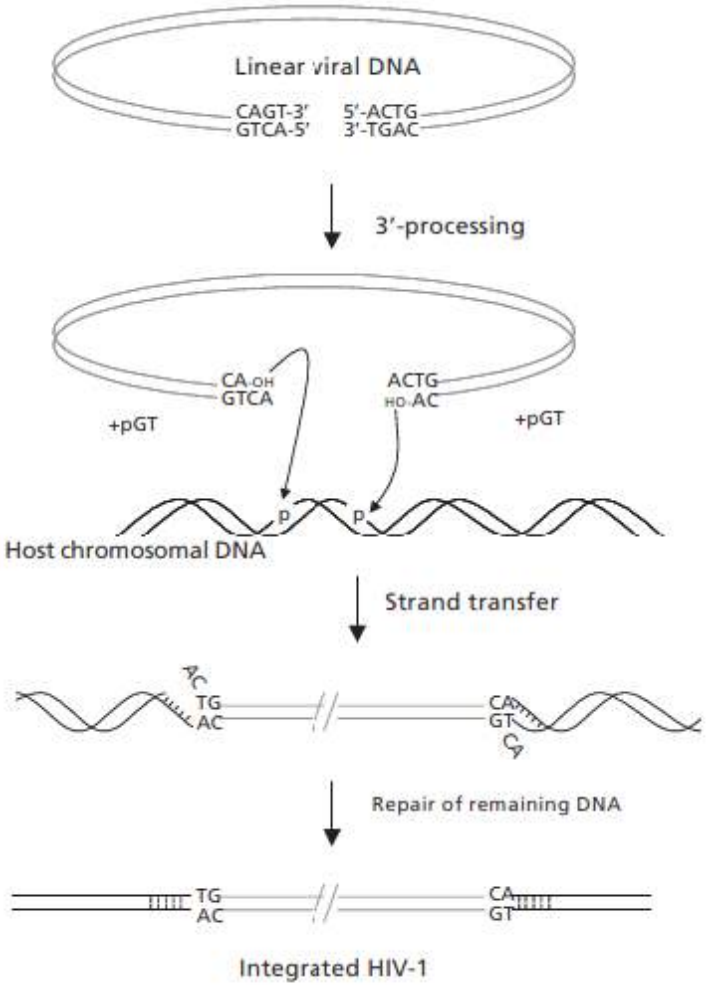
34. p32 was given the acronym IN based on its functionality as an integration protein in 1988, but it was not until 1990 that it was established that IN or integrase alone was necessary and sufficient for the integration of HIV DNA into the genome of the host cell.

35. The first firm indication that a functional integrase enzyme was a requirement for HIV virions to retain their infectivity was published in 1992.

*Mechanism of action of integrase*

36. After reverse transcription of the viral RNA genome, the double-stranded DNA copy is transported into the nucleus and inserted into the host cell genome. The only viral protein required for this process is integrase. Integration is accomplished by a set of reactions that result in the cutting and ligating of DNA sequences mediated by integrase and the host cell's DNA repair machinery.

37. Integration of the viral DNA into the host chromosome depends on two activities of integrase: (i) 3' processing and (ii) strand transfer. These processes are shown schematically below (from Debyser *et al*, *Antiviral Chemistry & Chemotherapy*, 13, 1-15 (2002), "Debyser 2002").




38. 3' processing involves cleavage of the terminal dinucleotide pair (GT) from each 3' end of the proviral DNA, thereby exposing a 3' hydroxyl group and generating a two-base pair (CA) overhang at the 5' end of the complementary strand. This reaction is carried out within the cytoplasm of the cell concurrently with or directly after reverse transcription.

39. Following 3' processing, integrase remains bound to the proviral DNA as a complex that bridges both ends of the processed viral DNA, referred to as the pre-integration complex (PIC). The PIC also contains reverse transcriptase, matrix protein p17 and capsid protein p24, and it is in this complex that the viral DNA is imported into the nucleus where integrase catalyses the strand transfer reaction.

40. During strand transfer, integrase catalyses the staggered nicking of the chromosomal DNA, to which the CA-3'OH viral DNA ends are joined. The viral 5' ends, as well as the chromosomal 3' ends, remain non-joined in the intermediate. Repair of the remaining gaps is accomplished by the host cell's DNA repair machinery. The result of the strand transfer reaction is that the genome of the host cell is expanded to include the proviral DNA.

*Measuring integrase inhibition and antiviral activity*

41. In August 2002 the following techniques were known as methods for measuring integrase inhibition and antiviral activity respectively: (a) biochemical (enzymatic) *in vitro* assays; and (b) cellular assays.

42. *Biochemical assays*. In the early days of HIV-1 integrase research, integrase activities were measured by low throughput gel assays involving radioactively labelled oligonucleotides which detected both the 3' processing and strand transfer reactions. They used short synthetic oligonucleotides representing the LTR ends of the viral DNA (i.e. a small piece of DNA with the CAGT motif on one end and radioactive phosphorus ($^{32}$P or $^{33}$P) on the other end).

43. In this assay, the DNA resembling the ends of the viral DNA functions as the substrate. Other molecules of the same oligonucleotides serve as integration targets. Therefore the products of the 3' processing reaction (if it occurs) are joined to the 5' end of a nick made on another oligonucleotide. As many different nucleotide positions can be used as target sites, the resulting strand transfer products are heterogeneous in length. The products of the 3' processing and strand transfer reactions are visualised by autoradiography after separation of the products in denaturing gel electrophoresis. This produces a ladder pattern of strand transfer products of varying lengths. As not all 3' processed substrates become joined to another oligonucleotide, typically a band two nucleotides shorter than the original substrate is also detected after electrophoresis. The gel assay was run using either $Mg^{2+}$ or $Mn^{2+}$ as the co-factor in the reaction solution.

44. Using this method, the $IC_{50}$ (half maximal inhibitory concentration) of the compound can be determined. The $IC_{50}$ is a measure of the effectiveness of a substance in inhibiting a particular biochemical reaction, in this case integration. The lower the $IC_{50}$, the more potent the substance is.

45. The gel assay was slow and time consuming. It also required researchers to work with radioactive products.

46. In 1997 a pre-cut DNA assay was published that looked only at strand transfer using a high-throughput microtiter plate-based assay to screen for integrase inhibition. A microtiter plate contains 96 small wells which can each contain a reaction mixture, and allows the testing of large numbers of compounds at once. The assay method was optimised for non-radioactive detection of the strand transfer reaction using a colorimetric avidin-linked alkaline phosphatase reporter system. This assay speeded up the screening process significantly and removed the hazards associated with handling radioactive compounds.

47. *Cellular assays*. For inhibitors targeting HIV-1, there were several cellular assays which could be used to test the antiviral activity of a potential inhibitor, including MTT/MT4, HeLaP4, and HIV breakthrough assays measuring p24.

48. The MTT/MT4 assay is a colorimetric assay for assessing cell metabolic activity. MTT, a yellow tetrazolium dye, is reduced to insoluble blue/purple formazan dye in living cells (by specific cellular enzymes). A solubilising solution is added to dissolve

the blue/purple product. The absorbance of this coloured solution can then be quantified at a specific wavelength using a spectrophotometer.

49. The target MT4 cells are infected with HIV-1 and grown for five days (HIV-1 has a 24 hour replication cycle, and this allows multiple generations of HIV-1 to replicate). In the absence of an effective inhibitor, HIV will kill the cells and the solution will remain yellow. However, if the cells do not die as a result of HIV infection (or cytotoxicity of the test compound), the solution will be blue/purple. The control wells (no HIV, no inhibitor added) should also be blue/purple. The effect of an inhibitor can be seen by the extent to which the HIV infected wells turn purple at different concentrations. MTT/MT4 dye assays can also be used to measure cytotoxicity.

50. The MTT/MT4 assay was developed in the 1980s. The results produced from an MTT/MT4 assay can be used to determine the following information:

    i) $CC_{50}$ (half maximal cytotoxic concentration): this is the concentration of compound resulting in the death of 50% of the uninfected tested cells.

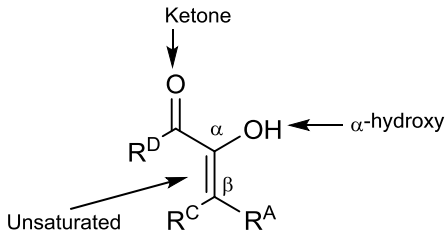
    ii) $EC_{50}$ (half maximal effective concentration): this is the concentration of compound at which 50% of its maximum response is observed.

51. The less toxic a compound is, the higher its $CC_{50}$. The more potently antiviral the compound, the lower its $EC_{50}$. From these results it is possible to calculate the therapeutic index (TI) for the compound (in relation to the cells used) using the formula TI = $CC_{50}/EC_{50}$. This value indicates the relationship between its effectiveness and toxicity. A high TI value is desirable.

52. In August 2002 it was best practice to include a reference compound of known activity (and mechanism of action) in order to provide a control for the experiment and to allow researchers to gauge the effectiveness of the compounds under investigation and to assess the sensitivity of the assay.

The Patent

53. The specification starts by stating at [0001] that the invention relates to "an antiviral agent, especially, a compound having an α-hydroxy-α, β unsaturated ketone as a partial structure and a pharmaceutical composition as an integrase inhibitor containing the same". The skilled team would understand that a structure containing an α-hydroxy-α, β unsaturated ketone was as shown below:



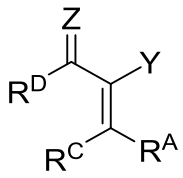

54. The specification then describes the background art. Having explained at [0002]-[0003] that the development of anti-HIV agents other than reverse transcriptase inhibitors and protease inhibitors is desired, the specification acknowledges the disclosures of a number of patent applications at [0004] in the following terms:

> "Examples of the integrase inhibitor include 1,3-dioxobutanoic acids and 1,3-propanediones described in W099/50245, W099/62520, W099/62897, W099/62513, W000/39086, and W001/00578. Another integrase inhibitor is acrylic acid derivative described in W001/17968. The other recently reported types are aza- or polyazanaphthalenylcarboamide derivatives described in W02002/30426, W02002/30930, W02002/30931, and W02002/36734."

55. The specification goes on at [0005]-[0006] to acknowledge prior publications of certain compounds having similar structures to those of the invention in other contexts.

56. After a consistory clause corresponding to claims 1 and 8, the specification states at [0009] that the compounds and pharmaceutical compositions of the invention "are useful as antivirus agent, antiretrovirus agent, anti-HIV agent, anti-HTLV-1 (Human T cell leukemia virus type 1) agent, anti-FIV (Feline immunodeficiency virus) agent, and anti-SIV (Simian immunodeficiency virus) agent, esp., anti-HIV agent and an integrase inhibitor". The specification goes on at [0010] to say that that they "are useful as anti-HIV agent as well as anti-AIDS agent for diseases such as AIDS, its related clinical syndrome, e.g., AIDS related complication (ARC), persistent generalized lymphadenopathy (PGL), Kaposi sarcoma, pneumocystis carini pneumonia, sudden thrombocy topenic purpura, AIDS related neurological symptom, for example, AIDS dementia complications, AIDS-associated encephalopathy, multiple sclerosis or tropical spastic paraparesis, and anti-HIV antibody positive and HIV positive symptom in asymptomatic patients".

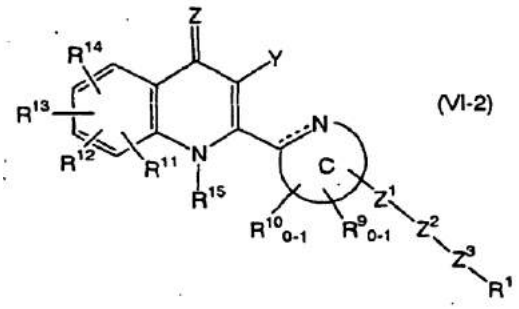
57. The specification then states that the invention relates to the use of the class of compounds of formula (I) and of six sub-classes that form the subsidiary claims. Formula (I) is a Markush formula as follows:




The permissible substituents $R^A$, $R^C$, $R^D$, Y and Z are defined in claim 1 which is set out below.

58. The subsidiary claims divide up the territory covered by Formula (I) by reference to the different forms that the $R^CR^D$ ring can take. Thus, for example, claim 2 covers 5-membered rings containing nitrogen (N) hetero atoms and claim 6 covers 6-membered rings containing N hetero atoms.

59. Thereafter the specification sets out at [0014]-[0028] preferred examples of the $R^CR^D$ rings, the $Z^1$-$Z^2$-$Z^3$-$R^1$ groups ("Z tail-rings" or "Z chains") and the C ring. Then the specification sets out at [0029]-[0033] certain "reference compounds". Preferred embodiments some of which fall within the claims are set out at [0034]-[0040]. Of significance for MSD's allegations of insufficiency are the classes of compounds described by formulae VI-2, VII-1 and VII-2 on pages 19 and 20:



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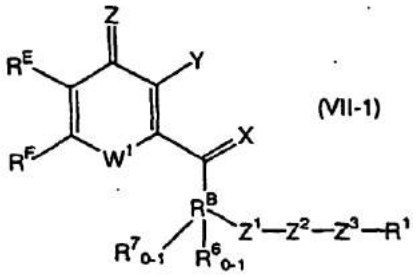

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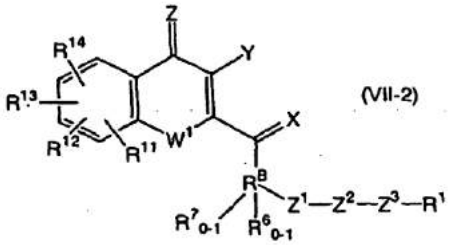


(VII-2)

60. The definitions of each substituent of these compounds are set out at [0041]-[0052].

61. Various terms used in the Patent are defined at [0053]-[0087]. In particular, in explaining the meaning of various terms which incorporate the phrase "optionally substituted", the specification states in [0084]:

> "The substituent is selected from those which do not interfer [sic] with the integrase inhibitory activity, as well as the case of above mentioned 'non-interfering substituent'."

62. At [0088] the specification states that keto/enol tautomers of formula (I) are included in the compounds of the invention. At [0089] it refers to the design of prodrugs of the compounds of the invention.

63. From [0099]-[0230] methods for use in the synthesis of the compounds of the invention are set out. None of this detail is material for present purposes.

64. The specification then states:

> "[0232] The present invention is useful for preparing a pharmaceutical composition such as antivirus agent. The present invention compounds, possessing a remarkable inhibitory activity on integrase of virus, is expected to exhibit a preventing or treating effect for diseases caused by viruses which grow at least via production of integrase in infected animal cells, thus being useful as an integrase inhibitor against a retro-virus (e.g. HIV-1, HIV-2, HTLV-1, SIV, FIV) as well as an anti-HIV agent.
>
> [0233] Further, the present invention compound can be used in combination with other anti-HIV agents having a different action of mechanisum such as a reverse transcriptase inhibitor and/or a protease inhibitor. Since any of the integrase inhibitors have not been on sale, a combination therapy of the

present invention compound with a reverse transcriptase inhibitor and/or a protease inhibitor is very useful.

[0234] Further, the present invention compound can be used as a combined agent for enhancing the anti-HIV activity of other HIV agents, as shown in the cocktail therapy.

[0235] Further, the present invention compound can be used in gene therapy in order to prevent a retrovirus vector derived from HIV or MLV from spreading over non-targeted tissues. In particular, in a case that cells infected with a vector in vitro is put back to a body, administration of the present invention compound in advance can prevent an unnecessary infection in the body."

65. The specification addresses formulation and dosing at [0236]-[0242].

66. A considerable number of examples are described at [0243]-[0425]. These consist of the synthesis and chemical characterisation of 234 compounds in classes A to M comprising both reference compounds and compounds falling within the claims. Again, none of this detail matters for present purposes. It should be noted, however, that classes A to M are distinguished by the nature of the $R^CR^D$ ring, including the number and position of heteroatoms, if any, in the ring, the presence or absence of a benzene ring fused to the $R^CR^D$ ring and the nature of the $R^A$ group. Whilst classes B, C, D, G and K fall within the scope of formula (I), classes A, E, F, H, I, J, L and M all fall outside formula (I). This is because they include a ketone functional group at $R^A$, or looked at another way $R^B$ is not amino.

67. Certain preferable combinations of substituents are set out by reference to various coding schemes at [0425]-[0435].

68. At [0436]-[0444] the specification sets out what is described an "experimental example". It describes an assay by which the ability of test compounds to inhibit integrase activity has been determined. Utilising the streptavidin-biotin binding system, which is commonly deployed in biochemical assays owing to the extremely high affinity of streptavidin for biotin, biotinylated substrate DNA is bound to a streptavidin-coated plate. Into each well target DNA, labelled with digoxygenin, is added, together with integrase, buffer containing $Mn^{2+}$ and a test compound. For positive and negative controls, no test compound and no integrase are added, respectively. In the absence of integrase inhibition, the plate-bound substrate DNA will be integrated into the digoxygenin-labelled target DNA by the action of the integrase enzyme, thereby attaching the digoxygenin-labelled target DNA via the plate-bound substrate DNA to the plate. Conversely, in the absence of integrase activity, integration will not occur and the target DNA will not be covalently attached to the substrate DNA. A colorimetric assay in which optical density (OD) is measured is then used to determine levels of immobilised digoxygenin and the resultant OD values converted into $IC_{50}$ values according to the formulae set out at [0440]-[0441]. The description of the assay does not specify the integrase used.

69. Table 1 contains the results from this assay for a number of compounds expressed as $IC_{50}$ values. Some of these (identified by asterisks) are reference compounds. I

reproduce Table 1 below with the $IC_{50}$ values also expressed in µM (micromolar) to facilitate comparison:

| **Compound No.** | **$IC_{50}$ (µg/ml)** | **$IC_{50}$ µM** | **Compound No.** | **$IC_{50}$ (µ g/ml)** | **$IC_{50}$ µM** |
|---|---|---|---|---|---|
| A-7* | 0.76 | 2.2 | C-26 | 0.36 | 1.1 |
| A-12-a* | 0.33 | 1.0 | C-39 | 0.23 | 0.63 |
| A-17* | 0.80 | 2.4 | D-5 | 0.45 | 1.3 |
| A-17-c* | 0.94 | 2.6 | E-8 | 0.14 | 0.45 |
| A-50 | 0.16 | 0.51 | E-16 | 0.12 | 0.37 |
| A-141-k* | 0.68 | 1.8 | F-4 | 0.57 | 1.8 |
| A-158* | 0.67 | 1.7 | G-7 | 0.48 | 1.5 |
| B-6-a | 1.6 | 5.4 | H-7 | 0.68 | 2.2 |
| B-6-d | 2.4 | 6.6 | I-4 | 0.50 | 1.5 |
| B-12 | 0.29 | 0.98 | J-4 | 0.26 | 0.79 |
| B-12-b | 0.21 | 0.67 | K-4 | 0.57 | 1.9 |
| B-29 | 0.12 | 0.40 | L-4 | 0.49 | 1.6 |
| B-68 | 0.22 | 0.70 | M-6 | 2.9 | 8.9 |
| C-22 | 0.48 | 1.3 | | | |

70. There are 27 compounds disclosed as having been tested. MSD contends that only 10 of these compounds fall within the claims, whereas Shionogi contends that the 12 compounds highlighted above fall within the claims. Neither side suggests that it matters whether the correct figure is 10 or 12, however, and I will assume that Shionogi is right about this. In each case a single data point is reported. There is no statement as to whether this represents a single experiment or an average of a number of experiments. If it is a mean, no standard deviations are reported. No data from any cellular assay are reported.

71. The experimental example concludes with the following statements:

> "[0443] The compounds of the present invention except the above compounds had the same or more integrase inhibitory activities.
>
> [0444] And the compounds of the present invention have high stability against metabolism and they are superior inhibitory agents against integrase."

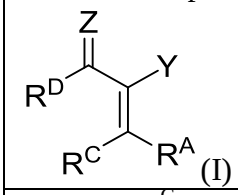
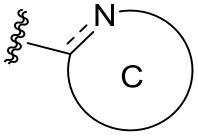
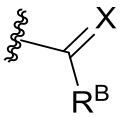
72. Thereafter there are some formulation examples at [0445]-[0460].

73. The specification concludes at [0461] with the statement: "The compounds of the present invention have inhibitory activities against integrase and [are] useful for treatment of AIDS as an antiviral and an anti-HIV agent."

The claims

74. Claims 1 to 7 are in Swiss form while claims 8 to 14 are corresponding purpose-limited product claims. Claims 1 and 6 are alleged to be independently valid and infringed, as are claims 8 and 14. It is not suggested by either side that anything turns for present purposes on the difference between the Swiss form claims and the product claims. Accordingly, I shall focus on claims 1 and 6.

75. Claim 1 as unconditionally proposed to be amended may be broken down as follows:

| |
|---|
| Use of a compound of formula (I) :<br>  <br><br>(I) |
| wherein, $R^C$ and $R^D$ taken together with the neighboring carbon atoms form a 5- to 6-membered ring which may contain (a) heteroatom(s) of N and/or O and may be condensed with a benzene ring, |
| Y is hydroxy; |
| Z is O; |
| $R^A$ is a group shown by<br>  <br><br>(wherein, C ring is a 5- to 6-membered N-containing aromatic heterocycle which may contain 1 to 4 of O, S and/or N atom(s), wherein at least one atom neighboring to the atom at the bonding-position is non-substituted N atom; the broken line shows the presence or absence of a bond), or by<br>  <br><br>(wherein, X is O ; $R^B$ is amino); |
| at least one of the ring formed by $R^C$ and $R^D$, C ring and $R^B$ is substituted with a group of $-Z^1-Z^2-Z^3-R^1$, wherein $Z^1$ and $Z^3$ are each independently a bond, alkylene or alkenylene ; $Z^2$ is a bond, alkylene, alkenylene, -CH(OH)-, -S-, -SO-, $-SO_2-$, $-SO_2NR^2-$, $-NR^2SO_2-$, -O-, $-NR^2-$,$-NR^2CO-$, $-CONR^2-$, -C(=O)-O-, -O-C(=O) or -CO-; $R^2$ is hydrogen, alkyl, alkenyl, aryl or heteroaryl; $R^1$ is cycloalkyl, aryl, or heteroaryl, with $R^1$ being optionally substituted by one or two substituents selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, halogen or $C_1$-$C_6$ alkoxy; |
| the ring formed by $R^C$ and $R^D$ is optionally substituted with a non-interfering substituent selected from hydrogen, halogen, $C_1$-$C_6$ alkyl, $C_3$-$C_6$ cycloalkyl, phenyl or naphthyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy($C_1$-$C_6$)alkyl, amino, $C_1$-$C_6$ hydroxyalkyl, |

| |
|---|
| $C_2$-$C_8$ alkenyl, or hydroxyl, and the C ring or $R^B$ is optionally substituted with a non-interfering substituent selected from hydrogen, $C_1$-$C_6$ alkyl, amino, halogen and hydroxyl, at any position other than that where the group of $-Z^1-Z^2-Z^3-R^1$ (wherein, $Z^1$, $Z^2$, $Z^3$ and $R^1$ are the same as defined above) locates; |
| or a pharmaceutically acceptable salt or solvate thereof, |
| for the preparation of a pharmaceutical composition |
| for use as an integrase inhibitor |
| for preventing or treating a viral disease. |

76. Claim 6 limits the ring formed by $R^C$ and $R^D$ to a 6-membered ring which contains one or more hetero atoms of N.

77. Shionogi's first conditional amendment limits claim 1 to "for preventing or treating ~~a viral disease~~ HIV".

78. Shionogi's second conditional amendment limits claim 1 by adding the restriction "but where $Z^1$, $Z^2$ and $Z^3$ are not bonds at the same time" to the integer which begins with the words "at least one of the ring formed by $R^C$ and $R^D$".

The skilled team

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

80. In the present case it is common ground that the Patent is addressed to a team, and that the team would have expertise in three fields:

    i) medicinal chemistry, including experience in organic synthesis and drug design;

    ii) biochemistry, including experience of running assays like the one disclosed in the Patent; and

    iii) virology, including experience of cell culture assays for antiviral activity and/or toxicity.

81. It is also common ground that these sets of skills may be found in two people rather than three, which is why both parties were able to manage with two experts rather than three. For convenience, these may be referred to as the medicinal chemist and the virologist. It should be appreciated there would be some overlap between the knowledge of the medical chemist and that of the virologist. For example, both would be likely to have knowledge about biochemical assays, whereas organic synthesis and the devising of structure-activity relationships would be more the domain of the medicinal chemist and cell culture assays would be more the domain of the virologist.

82. Although Shionogi tended to focus upon a skilled team working in industry, it was common ground between the experts that they could be working in the context either of a pharmaceutical company or an appropriate academic research department or a government-funded laboratory. Moreover, counsel for Shionogi expressly accepted in closing submissions that they could be academics. Each member of the team would be educated to undergraduate level in his respective subject, would also have a PhD and would have some post-doctoral experience.

83. Despite this common ground, there is a narrow, but not insignificant, dispute, between the parties as to the attributes of the skilled team. MSD contends that the members of the skilled team would have experience in the field of integrase inhibition, whereas Shionogi disputes this.

84. The correct approach to identifying the skilled person to whom a patent is addressed was considered in detail by Jacob LJ, with whom Sullivan and Waller LJJ agreed, in *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819, [2010] RPC 33 at [30]-[70]. The issue under discussion was whether the addressee is the same, and has the same common general knowledge, when considering both obviousness and insufficiency. In the course of that discussion, however, Jacob LJ drew at [42] the following conclusion from the decision of the Court of Appeal in *Dyson Appliances Ltd v Hoover Ltd* [2001] EWCA Civ 1440, [2002] RPC 22:

> "I think one can draw from this case that the Court, in considering the skills of the notional 'person skilled in the art' for the purposes of obviousness will have regard to the reality of the position at the time. What the combined skills (and mind-sets) of real research teams in the art is what matters when one is constructing the notional research team to whom the invention must be obvious if the Patent is to be found invalid on this ground."

While there can be differences when it comes to insufficiency, in a case such as the present these observations are equally pertinent in both contexts.

85. In my judgment the evidence shows that, whatever may have been the position at earlier dates, by August 2002 real research teams in the field to which the Patent is directed were teams whose members had acquired experience with integrase inhibition.

The expert witnesses

86. As noted above, each side called two expert witnesses, a virologist and a medicinal chemist. Shionogi called Professor Matthias Götte and Professor Youla Tsantrizos. MSD called Professor Zeger Debyser and Professor Nouri Neamati. Before considering their evidence, I wish to say a few words about the cross-examination of expert witnesses in patent cases.

*The cross-examination of expert witnesses in patent cases*

87. In a passage in *Medimmume Ltd v Novartis Pharmaceuticals UK Ltd* [2011] EWHC 1169 (Pat) at [99]-[114] which I believe is fairly well known, I considered the preparation of experts' reports in patent cases. I explained that not only did expert witnesses owe the court a duty to be independent and impartial, but also the lawyers who assisted the experts to prepare their reports bore a heavy responsibility for ensuring that expert witnesses were not put in a position where they could be made to appear to have failed in their duty to the court even though they conscientiously believed that they had complied with that duty. I concluded by observing:

> "It is also important that courts should be cautious about criticising an expert witness purely on the basis of omissions from his report unless it is clear that the fault lies with the expert rather than those instructing him, bearing in mind that the court will not usually be privy to the expert's full instructions (whatever may be the effect of CPR r. 35.10(4), which it is not necessary to go into for present purposes)."

88. What I did not explicitly say, but should have been clear, is that advocates who cross-examine expert witnesses in patent actions should also be cautious about criticising an expert witness purely on the basis of omissions from his (or her) report unless it is clear that the fault lies with the expert rather than those instructing him.

89. More generally, in my experience too much time is spent by cross-examiners in patent cases on *ad hominem* attacks that are unfair to the witness, unhelpful to the court and waste expensive time. It is, of course, both legitimate and helpful to explore such matters as the witness' qualifications and experience, and hence the extent to which the witness has relevant expertise and/or is representative of the skilled person; the basis upon which the witness considers that information was or was not common general knowledge (which may include whether the witness has correctly understood the concept); the witness' approach to issues such as obviousness (which may include whether the witness has fully appreciated the need to avoid hindsight and whether he or she has actually avoided hindsight); and so on. But cross-examiners must refrain from using the fact that the expert has not mentioned something in their report as a stick to beat the witness with unless the cross-examiner has real grounds for suggesting that this reflects on the witness' impartiality, competence or approach to the issues rather than upon the instructions they have been given. (If the witness has been wrongly instructed, that is, of course, a highly relevant matter, but it is a point for submissions rather than criticism of the witness.)

90. A particular difficulty which often arises in multiple expert cases is the distribution of responsibilities between the experts. As noted above, the law recognises that some patents are addressed to skilled teams rather than skilled individuals. As the label implies, a skilled team is deemed to function as a team. In practice, however, it is extremely difficult for lawyers to instruct multiple experts as a team. The experts will often be busy people with limited availability, and whose schedules frequently do not coincide. Moreover, the steep learning curve for the lawyers in understanding the technical issues pushes them towards compartmentalisation. This means that, all too often, parties give insufficient attention to the interface between the different areas of expertise and between the different members of the expert team.

91. This difficulty is exacerbated where there is an overlap between the expertises of the experts, as in the present case. In such circumstances the lawyers will usually be conscious of the need to avoid duplication between the experts' reports. This will often lead to the lawyers deciding to ask one expert to deal with a particular topic even though another expert is equally well-placed to address it. Such decisions may be taken when the lawyers have an incomplete understanding of the issues, and may subsequently turn out to have been mistaken in the sense that it would have been better if the second expert had dealt with it.

92. In such cases it may well be legitimate and helpful for the cross-examiner to explore the division of responsibility between the experts and the extent to which, collectively, they have approached matters in a manner which reflects the approach of the notional skilled team. What will rarely be legitimate or helpful is to criticise a witness for failing to deal with a point which he or she could have dealt with when it has been addressed by another expert, because this is unlikely to have been a decision made by the witnesses. Nor does it become any more legitimate or helpful if the cross-examiner either expressly asks the witness about the point or (more usually) asks the witness a question which leads the witness to bring it up.

93. Finally, it should go without saying that cross-examiners should question experts fairly. In the present case experts on both sides were subjected to cross-examinations parts of which were in my view unfair even disregarding the points I have made above. Counsel for MSD expressed incredulity when Prof Tsantrizos said that she could not remember when she was first instructed and tackled her at some length on a couple of paraphrases of sentences in other reports which, while not completely accurate, were not materially inaccurate. Counsel for Shionogi intervened in the cross-examination to object to this line of questioning. Although it was not necessary for me to rule upon the objection at the time, since counsel for MSD was willing to move on, having considered the matter, I consider that the objection was well founded. Rightly, counsel for MSD did not pursue these criticisms in closing submissions. Counsel for Shionogi asked Prof Debyser a number of questions in the form "Did you consider the toxicity data in Hazuda [2000]?". I intervened to stop this form of questioning because, apart from the fact that counsel had not taken the witness to the paper when asking the question, the point being put was that there was no toxicity data in it when the question implied that there were. (In fact, as Prof Debyser explained in re-examination, Hazuda 2000 did contain toxicity information; but that is a separate point.) Again, no criticism was made in closing submissions based on these questions.

*Virologists*

94. *Virologists*. Shionogi's virology expert was Prof Götte. He is Professor and Chair of the Department of Medical Microbiology and Immunology at the University of Alberta in Canada, a position he has held since July 2014. He studied chemistry at undergraduate level at the University of Kiel and then the Technical University of Munich from 1984-1991, and obtained the equivalent of an MSc degree in 1991. He obtained a PhD from the Ludwig Maximilian University of Munich in 1997 for studies on the reverse transcriptase (RT) enzyme of HIV-1. He was a postdoctoral researcher at the Lady Davis Institute for Medical Research at the Jewish General Hospital, Montreal, Canada between 1997 and 2000. During this time, he turned his attention to mechanisms of action and resistance associated with nucleoside analogue

RT inhibitors. He started his own lab at the Lady Davis Institute for Medical Research in 2000 working on HIV as well as HCV and related viruses. In 2005 Prof Götte moved to the Department of Microbiology and Immunology at McGill University, Montreal, Canada. In 2007 he was promoted to Associate Professor and in 2011 to Full Professor. His interests over the last 16 years have covered a broad range of viruses, including HIV, HCV, BVDV, and human herpes viruses. He has published his work on viral polymerases and related enzymes in approximately 100 peer reviewed papers. He is also the co-editor/co-author of a number of books and book chapters.

95. Prof Götte had not worked on integrase inhibition in August 2002, nor has he since then. He had, however, been interested in the field since mid-1999 when he attended a presentation by Daria Hazuda of the work which was later published in Hazuda 2000 (as to which, see below). As a result, he stated in his first report that he "would have been broadly familiar with the work of the major contributors in this field". In cross-examination he explained that, for the purposes of preparing his report, he had conducted a literature search. He accepted that his selection of papers was influenced by his own interest in the metal ion-binding of related enzymes.

96. Rightly, counsel for MSD made no criticism of Prof Götte's evidence and accepted that he did his best to assist the court. Moreover, counsel for MSD accepted that Prof Götte was able to give evidence on the technical issues in the case. He submitted, however, that Prof Debyser was better placed to give evidence of the knowledge and perceptions of virologists engaged in integrase research in August 2002. I accept that submission.

97. MSD's virologist was Prof Debyser. He is a Full Professor and Head of Division of Molecular Virology and Gene Therapy in the Department of Pharmaceutical and Pharmacological Sciences at the Katholieke Universiteit Leuven ("KU Leuven") in Belgium, a position he has held since 2012. He graduated from Medical School at KU Leuven and Kulak in 1990. He obtained a PhD from KU Leuven on non-nucleoside inhibitors of HIV-1 reverse transcriptase in 1994. From 1992 to 1993 he was a post-doctoral fellow at Harvard Medical School in Boston, USA. From 1994 to 1997 he undertook speciality training in Laboratory Medicine/Clinical Biology in KU Leuven and University Hospitals Leuven with a focus on Clinical Virology. From 1997 to 1998 he was a post-doctoral Fellow at the Rega Institute in Leuven studying HIV-1 integrase and integrase inhibitors. From 1998 to 2003 he was a post-doctoral fellow working on HIV-1 integrase as a target for antiviral therapy and as a tool for gene therapy with lentiviral vectors. From 2000 to 2006 he taught at Kulak, first as a special guest lecturer on gene transfer and gene therapy (2000-2003), and then as an Associate Professor in Biochemistry (2003-2006). From 2006 to 2011 he was Head of the Division of Molecular Medicine at KU Leuven. He has been a Full Professor at KU Leuven since 2009. Between 1995 and 2010 he mainly focussed on HIV integrase research. Since 2010 he has expanded his focus to include drug discovery and target validation in the fields of HIV, leukaemia and cystic fibrosis. He has published over 250 peer reviewed papers and contributed two chapters to the textbook *HIV-1 Integrase: Mechanism and Inhibitor Design* (Wiley, 2011) among other book chapters.

98. It can be seen that, unlike Prof Götte, Prof Debyser had considerable experience of working in the HIV integrase field by August 2002. Indeed, he had by then published

a number of research papers on the topic, two review articles and a book chapter on methods for evaluating integrase inhibitors. Counsel for Shionogi pointed out that Prof Debyser had had little experience in industry at that date. This is correct, but irrelevant.

99. Counsel for Shionogi advanced three criticisms of Prof Debyser's evidence. First, he submitted that Prof Debyser had slipped into being an advocate for MSD's case. I do not accept this. Prof Debyser struck me as a very knowledgeable witness who was trying to assist the court, and I did not perceive any lack of impartiality on his part.

100. Secondly, counsel submitted that Prof Debyser had not been even-handed in assessing the data in the Patent and equivalent data in the literature. This criticism overlooks an important point made by Prof Debyser in his evidence, namely that the field was rapidly evolving in the years prior to August 2002 and therefore it was not appropriate to apply the same standards in August 2002 as might have been acceptable a few years before. I have no doubt that Prof Debyser gave me his honest opinion about the data in the Patent. The merits of his criticisms are a separate matter which I will consider below.

101. Thirdly, counsel submitted that Prof Debyser had gone beyond the limits of his expertise in relation to the issue of serum binding. I do not accept this. Prof Debyser explicitly stated in paragraph 31 of his second report that "[t]he detailed pharmacokinetics would not be within the knowledge of the Virologist". His discomfort with questions of pharmacokinetics in cross-examination was consistent with this. On the other hand, it is fair to say that the evidence he gave on this topic in cross-examination was somewhat more limited and nuanced than that in his report.

*Medicinal chemists*

102. Shionogi's medicinal chemist was Prof Tsantrizos. Prof Tsantrizos is a Full Professor of Chemistry at McGill University in Montréal, Canada. She obtained a Bachelor's degree in Biochemistry from McGill University in 1977 and a Master's degree in Synthetic Organic Chemistry from the same institution in 1979. From 1979 to 1987 she taught at Vanier College in Quebec. In 1990 she obtained a PhD in Organic Chemistry from McGill. From 1990 to 1991 she was a post-doctoral fellow at Brown University, Rhode Island, USA. From 1991 to 1996 she was first Assistant Professor and then Associate Professor at Concordia University in Montreal. From 1997 to 1998 she was a visiting scientist first at Stanford University and then at Boehringer Ingelheim (Canada) Ltd ("BI Canada"). From 1998 to 2007 she was employed by BI Canada successively as Senior Research Scientist, Group Leader and Distinguished Scientist. During that time, she participated in the review process of all projects within BI Canada as well as international review meetings within BI worldwide. She particularly worked on HCV NS3/4A protease inhibitors and HCV NS5B polymerase inhibitors, but from some time in about 2004 she also began participating in a new project on HIV integrase inhibitors and was appointed chemistry project leader for this project in 2005. In 2009 she was appointed as an Associate Professor at McGill and in 2011 as Full Professor. She has published over 65 peer-reviewed papers.

103. Prof Tsantrizos had not undertaken any research into integrase inhibitors in August 2002. Her knowledge of the field at the time was derived from discussions at BI about antiviral targets generally, which would have included integrase. Like Prof Götte, she

had undertaken a literature search for the purposes of preparing her report, but she did not identify in it any papers beyond those mentioned by Prof Götte.

104. Counsel for MSD made no criticism of Prof Tsantrizos' evidence and accepted that she did her best to assist the court. Moreover, counsel for MSD accepted that Prof Tsantrizos was able to give evidence on the technical issues in the case. He submitted, however, that Prof Neamati was better placed to give evidence of the knowledge and perceptions of medicinal chemists engaged in integrase research in August 2002. I accept that submission.

105. A completely different point about Prof Tsantrizos' evidence is that it is unfortunate that, through no fault of hers, she was not asked to consider either Grobler or Pais (as to which, see below) in her third report, which responded to Prof Neamati's second report. This was despite the fact that Prof Neamati said in his second report that, if the relevant date was August 2002 rather than August 2001 (as he had been instructed to assume for the purposes of his first report), then the medicinal chemist would have been familiar with those publications, which would have affected his common general knowledge and hence his reading of the Patent. As a result, Prof Tsantrizos' views on those publications only became known when she was cross-examined. Time would have been saved if these had been put in writing.

106. MSD's medicinal chemist was Prof Neamati. He is Professor of Medicinal Chemistry at the University of Michigan. He obtained BS and MS degrees in Chemistry from the University of Alabama in Huntsville, USA, followed by a second MS degree in Medicinal Chemistry from the University of Houston, Texas. He obtained a PhD in Biomedical Sciences from the University of Texas MD Anderson Cancer Center. This was followed by a postdoctoral position at the National Cancer Institute in Bethesda, Maryland where his research focused on the design and discovery of small-molecule inhibitors of HIV-1 integrase. He was then successively Assistant, Associate, and Full Professor at the University of Southern California College of Pharmacy, where his research was broadly concerned with the design and discovery of small-molecule inhibitors of HIV-1 integrase as well as anticancer drugs. He has over 20 years of experience in the design and discovery of small-molecule HIV-1 integrase inhibitors. He has published over 220 manuscripts in peer-reviewed journals relating to HIV-1 integrase and other medicinal chemistry related fields. He edited the book *HIV-1 Integrase: Mechanism and Inhibitor Design* to which many of the world's leading integrase scientists (including Prof Debyser) contributed.

107. Again, it can be seen that, unlike Prof Tsantrizos, Prof Neamati had considerable experience of working in the HIV integrase field by August 2002. Again, he had by then published a number of research papers and review articles on the topic. Again, counsel for Shionogi pointed out that Prof Neamati had had little or no experience in industry. Again, this is correct, but irrelevant.

108. Counsel for Shionogi advanced two criticisms of Prof Neamati's evidence. First, he criticised Prof Neamati for failing to mention the importance of using magnesium rather than manganese as a co-factor when assaying for integrase inhibition in his first report given that Prof Neamati stressed this in his oral evidence. This criticism is unfair to the witness for three reasons. The first is that the criticism assumes that the fault, if fault there was, lay with the witness rather than those instructing him, whereas

no reason was ever advanced by counsel for Shionogi for supposing that it was Prof Neamati's fault.

109. Secondly, this is a good illustration of the difficulties caused by the division of labour between experts discussed above. Prof Neamati expressly stated in paragraph 127 of his first report that the medicinal chemist would not disagree with any of the reasons given by Prof Debyser for not regarding it as plausible that the compounds tested in Table I of the Patent would be effective as integrase inhibitors for preventing or treating viral disease. Prof Debyser discussed the magnesium/manganese issue in some detail in his first report (at paragraphs 52-56 and 103). Counsel for Shionogi pointed out that Prof Debyser did not expressly refer back to those passages when addressing the question of plausibility, but it is fairly plain from reading his report as a whole that it was part of his reasoning (the same goes for the question of statistics, in relation to which counsel for Shionogi raised no criticism). At the very least, Prof Neamati could be forgiven for having read it in that way.

110. Thirdly, the criticism overlooks the fact that Prof Neamati referred at paragraph 16 of his first report, and exhibited, a declaration that he had made in connection with the EPO proceedings and confirmed that its contents were true. In that declaration, he explained that it was well known to the skilled person that the use of manganese had a tendency to generate false positives; that it was a less reliable predictor of *in vivo* activity than magnesium; and that the reported $IC_{50}$ tended to be higher in magnesium than in manganese.

111. I would emphasise that I am not questioning the legitimacy of counsel for Shionogi exploring the reasons for Prof Neamati's opinion and the cogency of those reasons, matters I will consider below. What concerns me is the criticism of the witness.

112. Counsel for Shionogi's second criticism of Prof Neamati concerned a review of the patent literature written by Prof Neamati, "Patented small molecule inhibitors of HIV-1 integrase: a 10 year saga", *Expert Opin. Ther. Patents,* 12(5), 709-724 (2002) ("Neamati 2002"). Counsel criticised Prof Neamati for failing to mention Neamati 2002 in his reports. This criticism is unfair for three reasons. First, Neamati 2002 was written in early 2002, and published in about May 2002, that is to say, well after the August 2001 date addressed in Prof Neamati's first report. While the second report also considered the position as at August 2002, it was still mainly focused on August 2001.

113. Secondly, Neamati 2002 was written for a very different purpose, as is made clear at 709-710:

> "Although numerous inhibitors have been claimed, there are no reported antiviral activities or chemical characteristics for several of these agents. Moreover, a large number of these compounds may inhibit multiple viral and nonviral proteins *in vitro*. For example, hydroxylated aromatics such as chicoric acid, claimed as IN inhibitors were in fact proven to inhibit gp120 binding [22, 23]. This this review will not address any controversy in the field, but simply compile these data so that this wealth of information can be used for the future drug design targeting IN [sic]."

As Prof Neamati explained, he was provided with the patents and patent applications that he reviewed by the publisher, and he wrote the review to help workers who did not have ready access to the patent literature (for example, those in academia) to see what had been reported in it.

114. Thirdly, Prof Neamati explained in cross-examination that he had drawn Neamati 2002 to the attention of MSD's legal team. Thus the fault for not mentioning it, if fault there be, lies at the door of the legal team. In my view, however, their decision not to ask him to consider it in his reports is understandable having regard to the first two points.

115. Counsel for Shionogi also submitted that Prof Neamati's assessment of the patent literature in Neamati 2002 was inconsistent with, or otherwise undermined, his evidence about the patents applications referred to in the Patent at [4]. This is a different point, and I will consider it in context.

Common general knowledge

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

117. It is common ground that everything I have set out in the technical background section of this judgment (except where I have explicitly referred to developments after August 2002) formed part of the skilled team's common general knowledge. Although there is no substantial dispute between the parties as to the remainder of the common general knowledge, except with respect to a couple of points, there are differences of emphasis and nuance. In the circumstances I do not propose to review the rival contentions, but simply to set out my findings. As will appear, I have largely accepted MSD's submissions which I consider to be supported by the evidence of the respective experts.

*Common general knowledge of the virologist*

118. It was common ground between the experts that integrase had long been regarded as an ideal target for therapeutic intervention, but that it had proved to be a very difficult target. Prior to 2000, no authentic antiviral integrase inhibitor (that is to say, one which achieves antiviral activity by virtue of inhibiting integrase) had been identified. In Debyser 2002, Prof Debyser and his co-authors noted that all of the HIV integrase research up to that date had led to only one series of compounds that selectively inhibit the integration step during HIV replication, namely the diketo acids. (These were the subject of Hazuda 2000, which is discussed below.) On page 7, Prof Debyser and his co-authors considered the question "Why is it so difficult to find selective integrase inhibitors?" They explained that the molecular biology and biochemistry of integration made it a difficult process to target effectively with drugs, and that existing biochemical assays made it difficult, if not impossible, to dissociate activity and toxicity of the compounds.

119. As Prof Debyser explained, the virologist would have known that evidence of enzymatic integrase inhibition in a biochemical assay was not sufficient to identify an

effective antiviral agent, and that antiviral activity in cell culture was also required. He would not merely have known this as a matter of scientific principle, but would also have been aware of many published examples of compounds shown to inhibit enzymatic integrase activity which were not effective as antivirals. These included compounds such as chicoric acid and the so-called "G-quartets". As Prof Götte accepted, a positive result in a biochemical integrase inhibition assay merely indicates that the compound being studied can inhibit integrase *in vitro* and it remains necessary to conduct antiviral testing.

120. Prof Debyser explained that, having identified a compound that showed enzymatic inhibition of integrase, the virologist would know the following would also be needed:

i) an antiviral assay in cell culture – to show whether there was in fact antiviral activity, as discussed above;

ii) toxicity testing (ordinarily as part of the antiviral assay) - to see whether the compound was toxic to the host cells; and

iii) validation work – to correlate any observed antiviral effect with the integrase inhibition and hence establish the mechanism of action.

121. As Prof Debyser explained, toxicity testing is part of performing a proper antiviral assay. A compound which kills the virus, but is also toxic to the host cells, is not meaningfully an antiviral agent. Furthermore, an integrase inhibitor which is toxic is not suitable for use to prevent or treat viral disease. Some degree of toxicity may be acceptable, however, providing it arises at concentrations much greater than those needed for effective antiviral activity. Prof Götte agreed that toxicity testing is not just important, but is essential. Moreover, he agreed that the first indication of toxicity can come in the antiviral assay. As Dr Yoshinaga also confirmed, an $EC_{50}$ greater than the $CC_{50}$, either measured both in HeLa cells or both in MTT/MT4 assays, indicates that the compound in question is more toxic than it is active.

122. More specifically, Prof Debyser explained that assessing toxicity was particularly important when testing for antiviral activity arising from integrase inhibition because it was hypothesised that chelation of a divalent metal ion, probably magnesium, might play an important role in the catalytic activity of the enzyme. Several other physically-important enzymes were known to use magnesium as a co-factor, however. Thus the less specific a candidate compound's inhibitory activity was to integrase, the greater the risk that it would inhibit other cellular processes and hence give rise to problematic toxicity.

123. Moreover, cellular assays only provide information about the toxicity of the compound under investigation to the type of cells used in the assay. Thus they do not predict toxicity in other cell types or on a systemic level. Indeed, as Prof Tsantrizos emphasised from her perspective, toxicity is extremely unpredictable.

124. Prof Debyser also explained the requirement for validation work. He described three methods: quantitative polymerase chain reaction (qPCR) studies; time of addition studies; and resistance selection studies. Prof Götte accepted that validation work was necessary. He explained that the need for validation work arises because, even if

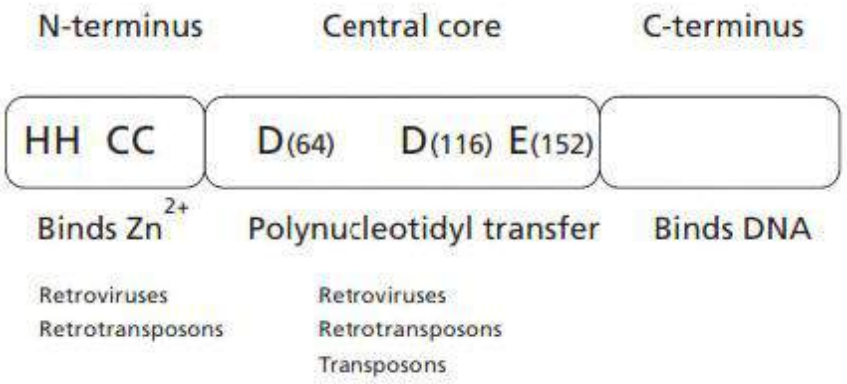
integrase inhibition by a particular compound is observed in an enzymatic assay, and antiviral activity is seen in an antiviral assay, the compound may not have targeted the integration step of HIV. Subject to a small qualification as to the relative usefulness of qPCR as against the other techniques he discussed, Prof Götte agreed with Prof Debyser's account.

125. Finally, Prof Debyser explained that identifying a compound that showed positive integrase inhibition in an enzymatic assay, adequate antiviral activity and no (or sufficiently limited) toxicity, and verifying that the antiviral effect was due to integrase inhibition, would not be enough to produce a viable drug for clinic use. In addition, the compound would have to have suitable pharmacokinetic properties.

*Common general knowledge of the medicinal chemist*

126. *The structure of HIV-1 integrase*. HIV-1 integrase's full structure in the presence or absence of DNA had not been established by August 2002. What was known was the enzyme's primary structure and the tertiary structures of its three domains. This was described by Prof Neamati and Prof Götte in very similar terms. My description is based on that of Prof Neamati.

127. HIV-1 integrase is a 32,000 Da protein comprised of 288 amino acid residues made up of three domains: the N-terminus, the C-terminus and the central core. This is shown schematically below (from Debyser 2002):




128. In 1997, the structure of the N-terminal domain (residues 1-50) was shown by NMR studies to be composed of three α-helices. By 2001 it had been determined that the domain contained a conserved HHCC (histidine, histidine, cysteine, cysteine) motif which bound zinc ($Zn^{2+}$) and appeared to be required for 3' processing and strand transfer activity.

129. It was also known that the central core domain (residues 51-212) of HIV-1 integrase contained a highly conserved "triad" of amino acids labelled "DD(35)E": aspartic acid (D) at number 64, aspartic acid (D) at number 116 and glutamic acid (E) at number 152. The label "(35)" referred to the number of amino acids between the second aspartic acid and the glutamic acid. The crystal structure of a soluble mutant of the isolated core domain of HIV-1 integrase was resolved in 1994 showing that the two aspartic acid residues of the DD(35)E motif lie in close proximity. In 2000, crystallisation of a two-domain integrase protein was obtained. The structure of the

central core linked to the C-terminus was resolved and found to be nearly identical to the structure resolved in 1994.

130. The C-terminal domain (residues 212–288) structure of HIV-1 integrase was solved by NMR and shown to be a dimer of parallel monomers. The structure of each monomer consists of five anti-parallel β strands that fold into a β-barrel. The C-terminal domain was suggested to bind non-specifically to DNA.

131. The lack of structural information meant that rational structure-based design of inhibitors of HIV-1 integrase (let alone HIV-2 integrase) was not readily feasible.

132. *The nature of the HIV-1 integrase binding site*. Equally, the exact structure and shape of the binding site of HIV-1 integrase were not fully known in August 2002.

133. In 1999, a crystal structure had been published for the core domain of HIV integrase complexed with an inhibitor called 5-CITEP (Goldgur *et al*., "Structure of the HIV-1 integrase catalytic domain complexed with an inhibitor: A platform for antiviral drug design", *PNAS*, 96(23), 13040-13043 (9 November 1999). 5-CITEP was shown to locate within the integrase active site between the three catalytic residues Asp-64, Asp-116 and Glu-152. However, there was no indication that the inhibitor co-ordinated with $Mg^{2+}$. Instead, the $Mg^{2+}$ ion remained complexed to Asp-64 and Asp-116 and 5-CITEP appeared to be hydrogen-bonded to a number of residues near the active site which were known to be critical for binding to viral DNA (Lys-156, Lys-159 and Gln-148). This led the authors to suggest that the interaction between 5-CITEP and integrase might interfere with the normal binding between the enzyme and substrate DNA. As Prof Neamati, Prof Götte and Prof Tsantrizos agreed, however, Goldgur's structure was obtained without any viral DNA being bound to the integrase (as it would be *in vivo*), and therefore the knowledge of this structure was known to be of limited use in any attempt to design a candidate drug structure.

134. Thus, although it was known that the catalytic triad of amino acid residues in HIV-1 integrase was, like a number of other polynucleotidyl transferases, DDE, the conformation of those residues in the active site, in the presence of bound DNA, was not known in August 2002. Furthermore, Prof Götte accepted that it was generally known by that time that there was considerable flexibility of the positioning of the glutamic acid (E) at residue 152 in HIV-1 integrase.

135. *Knowledge of HIV-1 integrase inhibitors.* It is common ground that by August 2002 the skilled team would be aware of several categories of compounds that had been shown to achieve enzymatic inhibition of HIV-1 integrase. Two such categories are of particular relevance to this case.

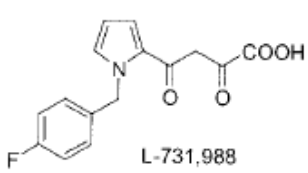
136. The first category is hydroxylated aromatics. These were a diverse group of published integrase inhibitors. They are compounds possessing aromatic rings substituted with more than one hydroxyl (-OH) group. Many (but not all) were catechols (i.e. those with two hydroxyl groups on adjacent carbons of the benzene ring). Biscatechols (formed of two catechols joined by a linker) were shown to be generally more potent *in vitro* enzymatic inhibitors.

137. It was generally assumed that they worked by co-ordinating metal cations in the integrase active site, though this was not definitively shown. Indeed, it was also

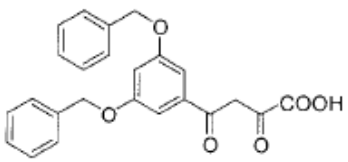
speculated that they might work by participating in hydrogen bonding within the enzyme. A number of hydroxylated aromatics are among the examples cited by Prof Debyser (as explained above) of compounds that showed positive enzymatic inhibitory activity, but were not effectively antiviral and/or were toxic. The non-specificity and/or toxicity were generally attributed to the catechol functionality.

138. The second group is diketo acids. These came to light as a result of work by a group at Merck led by Dr Hazuda. Four key papers were published by this group prior to 8 August 2002. In chronological order, they are Hazuda *et al*, "Inhibitors of Strand Transfer That Prevent Integration and Inhibit HIV-1 Replication in Cells", *Science*, 287, 646-650 (28 January 2000) ("Hazuda 2000"); Espeseth *et al*, "HIV-1 integrase inhibitors that compete with the target DNA substrate defined a unique strand transfer conformation for integrase", *PNAS*, 97(21), 11244-11249 (10 October 2000) ("Espeseth"); Wai *et al*, "4-Aryl-2,4-dioxobutanoic Acid Inhibitors of HIV-1 Integrase and Viral Replication in Cells", *J. Med. Chem.*, 43(26), 1-4 (28 December 2000) ("Wai"); and Grobler *et al*, "Diketo acid inhibitor mechanism and HIV-1 integrase: Implications for metal binding in the active site of phosphotransferase enzymes", *PNAS*, 99(10), 6661-6666 (14 May 2002) ("Grobler"). It is common ground that the contents of each of these were common general knowledge by 8 August 2002.

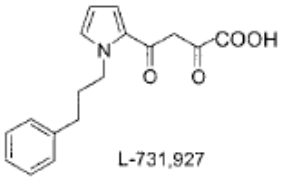
139. Hazuda 2000 reported the results of a screen of some 250,000 compounds. It identified two compounds (L-731,988 and L-708,906) which were potent enzymatic integrase inhibitors and also had potent antiviral activity results in a cellular assay. A third compound (L-731,927) was demonstrated to be a potent enzymatic integrase inhibitor with moderate antiviral activity results. The virologist would not have considered a fourth compound (L-731,942) for which data was provided to be active or worth pursuing. The paper included validation work of the sort described above. I reproduce part of Fig 1 showing the structures of L-731,942, L-708,906 and L-731,927 below. The structure of L-731,942 was identical to that of L-731,988 save that it had a benzyl substituent instead of the fluorine substituent.




L-731,988




L-708,906




L-731,927

140. All the witnesses agreed that Hazuda 2000 was a landmark paper: it disclosed the first authentic integrase inhibitors which not only had antiviral activity, but had also been subject to mechanism of action validation firmly to establish that such activity stemmed from the inhibition of integration. Prof Debyser explained that Hazuda 2000 set the standard for validation of antiviral activity by integrase inhibition thereafter.

141. In cross-examination Prof Tsantrizos expressed the view that, despite the inclusion in Hazuda 2000 of biochemical assay data, antiviral assay data, PIC data, and various validation experiments, more data would be needed before the medicinal chemist would be happy to draw any conclusions going beyond the numbers stated for the four compounds disclosed. (Indeed, she raised an issue not canvassed in any of her three

expert reports (or in any of the other experts' reports or in any of the literature in the case), namely the lack of aggregation data in Hazuda 2000.)

142. In any event, it is clear that Hazuda 2000 did not teach the medicinal chemist that all compounds containing a diketo acid moiety will be authentic integrase inhibitors suitable for treating HIV-1. On the contrary, the authors state expressly on the first page that: "The diketo functionality is an intrinsic feature of these inhibitors but is not sufficient for activity …" Prof Tsantrizos accepted that the medicinal chemist would know from Hazuda 2000 that the diketo acid functionality was not sufficient for antiviral activity, and that this would form part of his common general knowledge in August 2002.

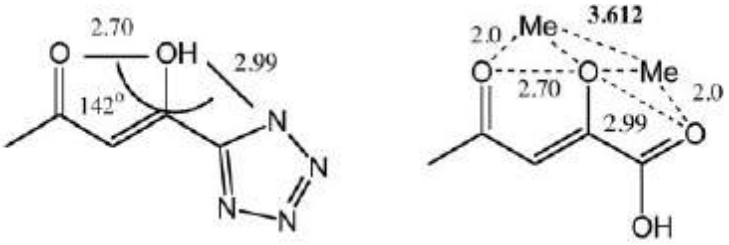
143. Espeseth suggested that the target DNA and inhibitor occupied the same or overlapping sites, thought to arise from a conformational change in the enzyme induced by the substrate DNA. Consistently with this, Prof Götte accepted that it was part of the common general knowledge of the virologist in August 2002 that there was considerable flexibility in the catalytic triad, and in the positioning of the glutamic acid at residue 152, in HIV integrase.

144. Wai was a structure-activity relationship study containing both biochemical and antiviral data in which a compound having greatly enhanced antiviral activity was identified. This structural study confirmed that, for the diketo acids (as for many other medicinally interesting compounds), making small changes in the chemical structure of a compound can have a significant impact on activity. In particular, Prof Tsantrizos accepted that one of the take-home messages of Wai was that the antiviral activity was very sensitive to the orientation of the hydrophobic group.

145. Grobler evaluated the integrase binding affinity and inhibitory activity of chimeric molecules based on 5-CITEP and the most potent of the diketo acids reported in Hazuda 2000 (L-731,988). The authors also synthesised a number of L-731,988 derivatives and found that those compounds which retained the diketo substituents, but lacked the acid functionality, were inactive. As they put it in the abstract:

> "We demonstrate that an acidic moiety such as a carboxylate or isosteric heterocycle is not required for binding to the enzyme complex but is essential for inhibition and confers distinct metal-dependent properties on the inhibitor."

Grobler proposed a model for the binding of diketo acid analogues to HIV-1 integrase. It involved co-ordination of two divalent metal cations in the integrase active site and was in part based upon the crystal structure of Goldgur, which (as discussed above) was limited in that it was a structure of the complex without bound DNA. This model is shown in Fig 5 of Grobler, which I reproduce below. The right-hand diagram shows two metal ions coordinated with three oxygen atoms in a diketo acid, while the left-hand diagram shows the corresponding positions of two oxygens and a nitrogen in 5-CITEP.




146. Prof Götte gave evidence in his first report that this model was part of the common general knowledge of the virologist in August 2002, and Prof Tsantrizos accepted that it was also part of the common general knowledge of the medicinal chemist.

147. Prof Tsantrizos stated in cross-examination that in her opinion the data contained in the paper did not support the generality of the statement from the abstract quoted in paragraph 145 above. She accepted, however, that Grobler had advanced a plausible explanation for the reduction in antiviral activity seen when the carboxylate functionality in L-731,988 (compound I in Table 2) is substituted by a tetrazole (compound III). As she accepted, the explanation put forward in Grobler as to the different respective levels of activity observed with the carboxylate and the corresponding tetrazole corresponds to the well-known HSAB (Hard and Soft Acids and Bases) theory in organic chemistry.

148. In addition to the four papers published by the Merck group, MSD relies upon a paper published by a group from the Center for Cancer Research at the National Institutes of Health in the USA, Pais *et al*, "Structure Activity of 3-Aryl-1,3-diketo-Containing Compounds as HIV-1 Integrase Inhibitors", *J. Med. Chem.*, 45, 3184-3194 (18 July 2002) ("Pais"). Pais was published just three weeks before 8 August 2002. MSD contends that it had nevertheless become part of the common general knowledge of the medicinal chemist involved in integrase research by the latter date. Shionogi disputes this. At first blush, it appears unlikely that a paper published only three weeks before the relevant date could have been generally known and generally accepted as a good basis for further action by the bulk of those in the field in such a short space of time. Counsel for MSD relied upon the following evidence as showing that this was the case, however.

149. First, it was common ground between Prof Neamati and Prof Tsantrizos that *Journal of Medicinal Chemistry* was a leading journal in the field. Secondly, Prof Neamati and Prof Tsantrizos were agreed that the medicinal chemist would have read Pais by 8 August 2002. (Indeed, counsel for Shionogi accepted this when cross-examining Prof Neamati.) Thirdly, as Prof Neamati explained, Pais built upon Grobler (which itself built upon the earlier publications by Hazuda's group). Thus it was not advancing a new concept. Fourthly, it is clear from the evidence that the field of integrase research was a relatively small and close-knit field in August 2002, such that new papers by reputable authors in leading journals were rapidly absorbed. Thus Prof Götte gave evidence in paragraph 4.7 of his second report about the common general knowledge of the virologist as at 8 August 2002 based upon a paper by Prof Debyser and co-authors published in *Current Biology* on 23 July 2002, just two weeks before that date. He accepted in cross-examination that this demonstrated the speed with which such papers were absorbed by workers at the time. I also note that Pais was referred to by Prof Debyser in paragraph 16(e) of his second report as being part of the common general knowledge of the virologist without challenge.

150. In these circumstances, I conclude that the core findings of Pais, albeit not the fine detail, would have formed part of the common general knowledge of the medicinal chemist. In any event, it is clearly a paper that would have been turned up if the medicinal chemist had done a routine literature search into integrase inhibition preparatory to embarking upon a project to synthesise and test suitable compounds, and as a recent publication by reputable authors in a leading journal it would have been of particular interest.

151. Pais used an enzymatic activity assay to investigate the 3'-processing and strand transfer inhibitory activities of 5-CITEP and several of its derivatives. Those showing strand transfer activity were then taken forward to test their antiviral activity and/or toxicity in a cell-based assay. Table 1 of the paper collates the results. Prof Neamati summarised the core findings of Pais in unchallenged evidence as follows:

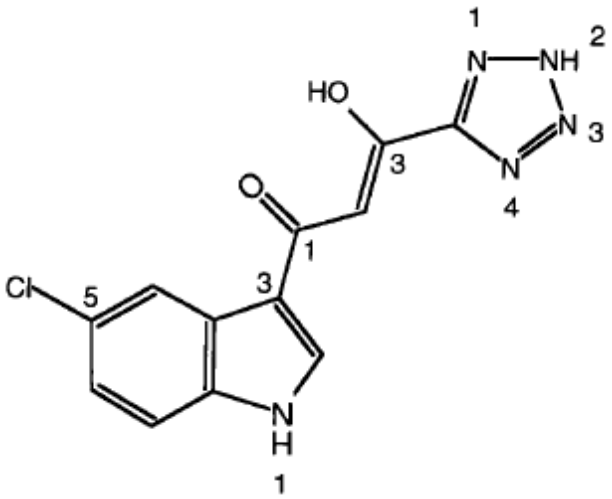
i) 5-CITEP showed potent enzymatic integrase inhibition, but was "essentially inactive" as an antiviral agent;

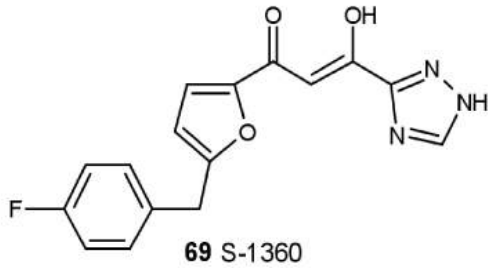
ii) most of the compounds with an acidic moiety were potent strand transfer inhibitors in the enzymatic assay, but only two out of all those showed appreciable antiviral activity; and

iii) activity was highly sensitive to the nature of the hydrophobic group.

152. Prof Tsantrizos agreed that the medicinal chemist would see that Pais includes enzymatic integrase inhibition data and antiviral data, and that it showed that 5-CITEP (which possesses a triazole ring in place of the carboxylic acid group in the diketo acids) does not possess antiviral activity.

153. *5-CITEP and S-1360*. These are two specific integrase inhibitors developed by Shionogi. Both contain an α,γ-diketo moiety (like MSD's diketo acids), but have a nitrogen-containing heterocycle instead of the carboxylic acid group (triazole and tetrazole, respectively). Neither falls within the formula (I) as defined in the Patent. I reproduce below the structures of 5-CITEP and S-1360 as set out in Goldgur and Neamati 2002:






**69** S-1360

154. It is common ground that 5-CITEP was part of the common general knowledge of the medicinal chemist. As discussed above, it featured in Goldgur, Grobler and Pais. Both medicinal chemistry experts discussed it in their reports (as did both virology experts). It is also common ground that, as discussed above, 5-CITEP had been shown to be inactive in an antiviral assay by Pais.

155. It was not suggested by either of Shionogi's experts in their reports that S-1360 was common general knowledge. Indeed, the only reference to S-1360 in Shionogi's expert reports was in paragraph 2.15 of Prof Götte's second report, where he said that "A close derivative of [5-CITEP], S-1360, advanced into clinical trials although this would not necessarily have been well known at the time." It was not contended to be common general knowledge in Shionogi's opening skeleton argument either. Despite this, counsel for Shionogi submitted in his closing submissions that S-1360 was part of the common general knowledge. MSD disputes this.

156. Prof Debyser was asked a number of questions about S-1360's chemistry, which he considered to be outside his expertise. He did note, however, that "there was a lot of mystery about this kind of compounds [sic] and the work from Shionogi" since little data was published by Shionogi.

157. Counsel for Shionogi put it to Prof Neamati that it was announced by Shionogi at the 9th Conference on Retroviruses and Opportunistic Infections ("CROI") in Seattle, USA in February 2002 that S-1360 was going into Phase II clinical trials. Prof Neamati replied that he had not attended that conference, but had heard about the announcement from Prof Debyser afterwards. It may have been as a result of this that Prof Neamati contacted a scientist at Shionogi for details of the presentation, information from which he then included in Neamati 2002 with acknowledgement. The presentation is not itself in evidence. (It is not even apparent from the evidence whether an abstract of the presentation was made available to attendees of CROI.) Nor is there any other reference to it in the evidence or in the literature which is in evidence. Consistently with what he had said in Neamati 2002, Prof Neamati accepted that it was "public knowledge" that S-1360 was in clinical trials and showed antiviral activity. It was not directly put to Prof Neamati that this information was common general knowledge in August 2002, however, although that was assumed in one question that was put to him.

158. In these circumstances I am not persuaded that it has been established by Shionogi that information as to S-1360's structure and activity was common general knowledge by 8 August 2002. Nor has it been shown that the presentation at CROI would, or even could, have been turned up through a routine literature search.

159. If it is assumed, contrary to the conclusion I have just reached, that the structure and activity of S-1360 was common general knowledge, or would have been found through a literature search, then the medicinal chemist would have appreciated from the disparity in activity between S-1360 and 5-CITEP that replacement of a carboxylic acid group with a nitrogen-containing heterocycle did not necessarily result in an active compound. This would be consistent with the medicinal chemist's common general knowledge derived from Grobler and Pais.

160. *Pharmacophores and structure-activity relationships*. There was a rather odd dispute between Prof Neamati and Prof Tsantrizos in their reports as to the meaning of the term "pharmacophore" to a medicinal chemist. Prof Neamati defined a pharmacophore in his first report as "the three dimensional arrangement of a molecule necessary for its interaction with a biological target". Prof Tsantrizos criticised this definition in her second report and preferred the following definition given by Patrick, *An Introduction to Medicinal Chemistry* (2nd ed, 2001) at 177-178:

> "The pharmacophore summarizes the important functional groups which are required for activity and their relative positions in space with respect to each other."

161. As counsel for MSD observed in his closing submissions, it is not clear why Prof Tsantrizos chose Patrick as a reference, as it became clear in her oral evidence that she had never come across it prior to this case and considered it to be over-simplified. In any event, she accepted that there was little difference between her preferred definition and that of Prof Neamati. As Prof Neamati explained, whichever definition one takes, a key aspect is the relative positions in space of the important functional groups.

162. Prof Neamati described how a pharmacophore is determined, and the role of studies of structure-activity relationships, in a drug discovery program in his first report. Such programs involve a sequence of steps which can be summarised as follows:

i) A lead compound with activity in the relevant biological assay is identified. As Prof Neamati emphasised, it is important that the activity of the lead compound be firmly established.

ii) Structure-activity relationship (SAR) studies are undertaken in which the effect of changes to particular functional groups or parts of the lead compound on its activity are studied to ascertain which groups or parts of the molecule are important for biological activity and which are not. SAR studies are necessarily empirical since it is well known that even small changes made to a compound can have significant effects on biological activity. These studies sometimes reveal a compound with enhanced potency, which then becomes the new lead compound.

iii) Once sufficient SAR studies have been performed, it may be possible to define a pharmacophore.

iv) Thereafter, lead optimisation can be performed to improve the activity and properties of the lead compound(s). Again, the effect of each type of

> modification on biological activity is frequently unpredictable and requires testing in the relevant biological assay(s).

163. Prof Tsantrizos' oral evidence was entirely consistent with this. Five points merit emphasis. First, Prof Tsantrizos explained that "just looking at the activity of compounds was not sufficient … to develop a structure-activity relationship model".

164. Secondly, Prof Tsantrizos confirmed the accuracy of the following statement she and a number of co-authors from BI made in a paper published in July 2001:

> "Understanding the structure-activity relationship between a chemical probe and its biological target is often a very challenging task in medicinal chemistry. This is primarily due to the fact that even minor structural modification of a compound may lead to the introduction of a large number of variable factors that cannot be easily identified or quantified."

She went on to explain that this depended on the reliability of the SAR that had been developed. As she emphasised a number of times, "the hallmark of drug discovery is based on establishing a reliable structure-activity relationship model".

165. Thirdly, Prof Tsantrizos was at pains to distinguish between the predictive ability of a SAR model with respect to enzymatic potency and with respect to cell-culture potency. If one had a validated SAR model, then one could make reasonable predictions of enzymatic potency; but the medicinal chemist would not try to predict cell-culture potency.

166. Fourthly, Prof Tsantrizos agreed that structure-activity relationship information was the essential starting point to come up with a pharmacophore.

167. Finally, Prof Tsantrizos accepted that defining a pharmacophore also requires structural information as to how the molecule binds to the active site from x-ray measurements or failing that NMR measurements. Computer-based modelling would also be of assistance in August 2002 for this purpose.

168. For his part, Prof Neamati emphasised that having identified the key features of a class of molecules or a lead compound which are positively required for activity is not enough to draw conclusions that every member of the defined class will show activity.

Construction

169. There is no dispute as to the applicable principles which were summarised by Jacob LJ in *Virgin Atlantic v Premium Aircraft Interiors* [2009] EWCA Civ 1062, [2010] RPC 8 at [5] and by Floyd LJ in *Actavis v Eli Lilly* [2015] EWCA Civ 555, [2016] RPC 2 at [42].

170. It is common ground that the skilled team would understand the term "integrase inhibitor" to mean a compound which inhibits integrase in the type of biochemical assay described in the Patent.

171. MSD contends that the requirement that the compounds be "for preventing or treating a viral disease [or HIV]" would be understood as follows:

i) the claimed compounds are effective (in the sense of having a beneficial therapeutic effect) in preventing or treating a viral disease or HIV;

ii) for any compound to be effective in this sense, it must also be sufficiently well tolerated to be capable of clinical use; and

iii) the claim only covers those compounds whose efficacy derives from integrase inhibitory activity (rather than having their antiviral effect by another mechanism).

172. So far as the criterion by which efficacy is to be judged is concerned, MSD's position is that the compound must at least be sufficiently effective to be taken forward into clinical trials. MSD does not go so far as to contend that the compound must have been successful in a Phase III trial, or even that success in such a trial would be predicted.

173. Shionogi does not dispute that the compounds must be effective and tolerated, but it takes issue with MSD as to the criteria for efficacy and tolerability. So far as efficacy is concerned, Shionogi contends that all that is required is that the compound has the potential to reduce viral replication. Counsel for Shionogi described this as efficacy at the level of a working prototype, rather than being good enough to be in the clinic. As to tolerability, Shionogi contends that the compound may have some level of toxicity, provided that the toxicity is not so great that it would not be considered suitable for use.

174. As I see it, there is little of substance between the parties' positions with regard to toxicity, since I did not understand counsel for MSD to contend that no level of toxicity would be regarded as acceptable. What is more important is the criterion for therapeutic efficacy. As I understand it, in practical terms, the difference between MSD's formulation and Shionogi's formulation is that Shionogi effectively treats a positive result in a biochemical assay as a sufficient demonstration of efficacy, whereas MSD requires (at minimum) not only a positive result in the biochemical assay, but also a positive result in a cell-culture antiviral assay and validation that the antiviral activity is due to integrase inhibition.

175. As I observed in *Eli Lilly & Co v Janssen Alzheimer Immunotherapy* [2013] EWHC 1737 (Pat), [2014] RPC 1 at [190]-[201], the criterion by which therapeutic efficacy is to be judged depends on the context, and in particular the disclosure of the patent specification. Counsel for MSD relied on [0010], [0232]-[0235] and [0444] of the Patent and upon the common general knowledge of the virologist as supporting MSD's position. In my judgment, having regard to those passages and my findings as to the common general knowledge, MSD is correct as to the applicable criterion. The skilled team would appreciate that a positive result in a biochemical assay simply showed that the compound was an integrase inhibitor, and was insufficient to demonstrate a likelihood of efficacy in preventing or treating viral disease.

176. There is also a dispute as the meaning of the term "a non-interfering substituent" which appears twice in the last part of the definition of formula (I) in claim 1. There is no difficulty with the word "substituent", which refers to a substitutable part of a molecule. The question is what is meant by the qualification "non-interfering". It is common ground that there is no definition or explanation of the meaning of this

expression in the specification. Nor it is suggested by either side that it is a term of art with a settled meaning. Thus the skilled team must try to ascertain its meaning from its context in the claim and the specification.

177. Shionogi contends that "non-interfering" means that the substituent must not interfere with the integrase inhibitory activity of the compound, that is to say, it must not prevent the compound from acting as an integrase inhibitor. Since the claim requires the compound to be an integrase inhibitor anyway, however, the effect of this interpretation is to render the word "non-interfering" redundant. As is common ground, the skilled team would be slow to conclude that a word in the claim was redundant, because the skilled team would ordinarily think that each word had been included for a reason; but such a conclusion is not impossible.

178. MSD contends that the meaning of the term is so unclear that the claim is ambiguous, and hence the Patent is both invalid for insufficiency and incapable of being infringed. MSD argues that "non-interfering" cannot simply mean the substituent does not interfere with the integrase inhibitory activity of the compound, both because that would render the word redundant and because the sentence from [0084] quoted in paragraph 61 above suggests that something else is meant. Accordingly, it must mean that the substituent does not reduce the activity of the compound with respect to a compound which lacks that substitution. But in that case, MSD argues, it is unclear what activity is meant not to be inferfered with, against what non-substituted standard the activity of the compound in question is to be compared and what degree of reduction of activity is permitted before a substituent ceases to be "non-interfering". Furthermore, MSD argues, the non-substituted comparator cannot be the only obvious comparator, namely a compound with a hydrogen substituent because hydrogen is listed among the possible non-interfering substituents.

179. In my judgment the skilled team would conclude that the expression "non-interfering" cannot mean that the substituent does not reduce the activity of the compound with respect to a compound which lacks that substitution for precisely the reasons identified by MSD: it is unclear what the comparator would be or how the comparison should be made. In those circumstances I consider that the skilled team would be driven to the conclusion that it must mean that the substituent does not prevent the compound from being an integrase inhibitor even though the result is to make the word "non-interfering" redundant. As for the passage at [0084] relied upon by MSD, in my view this is capable of being read the other way round, that is to say, as indicating that "non-interfering" does simply mean that the substituent does not interfere with integrase inhibition. At all events, I do not think it would dissuade the skilled team from adopting Shionogi's interpretation.

Inventive step

180. MSD contends that all of the claims of the Patent, both as granted and as proposed to be amended, are invalid on the ground that they lack an inventive step. MSD's case is not the more conventional kind of case that it would be obvious to take the step from a specific item of prior art to the claimed invention, but rather that the claimed invention is not inventive because it makes no technical contribution to the art (so-called "*AgrEvo* obviousness", after the decision of the Technical Board of Appeal of the European Patent Office in the leading case of T 939/92 *AgrEvo/Triazoles* [1996] EPOR 171).

*The law*

181. The relevant law has been considered in detail by the Court of Appeal in two recent cases: *Generics (UK) Ltd v Yeda Research & Development Co Ltd* [2013] EWCA Civ 925, [2014] RPC 4 and *Idenix Pharmaceuticals Inc v Gilead Sciences Inc* [2016] EWCA Civ 1089. In *Generics v Yeda* Floyd LJ said at [39]:

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

182. In *Idenix v Gilead* Kitchin LJ cited this passage and added at [107]:

> "It follows that the scope of the monopoly claimed must correspond to and be justified by the technical contribution or, put another way, everything falling in the scope of the claim must be inventive. In the case of a claim to a new class of chemical compounds, the selection of those compounds must not be arbitrary but justified by a technical effect which distinguishes the claimed compounds from many other compounds. Moreover, this technical effect must be shared by substantially all of the claimed compounds."

183. Having reviewed *AgrEvo*, T 1329/04 *Johns Hopkins/Factor-9* [2006] EPOR 8, *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] RPC 28 and *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co Ltd* [2009] EWCA Civ 1362, [2010] RPC 9, Floyd LJ summarised the applicable principles in *Generics v Yeda* at [49] as follows:

> "(i) Article 56 of the EPC is in part based on the underlying principle that the scope of the patent monopoly must be justified by the patentee's contribution to the art.
>
> (ii) If the alleged contribution is a technical effect which is not common to substantially everything covered by a claim, it cannot be used to formulate the question for the purposes of judging obviousness.
>
> (iii) In such circumstances the claim must either be restricted to the subject matter which makes good the technical contribution, or

> a different technical solution common to the whole claim must be found.
>
> (iv) A selection from the prior art which is purely arbitrary and cannot be justified by some useful technical property is likely to be held to be obvious because it does not make a real technical advance.
>
> (v) A technical effect which is not rendered plausible by the patent specification may not be taken into account in assessing inventive step.
>
> (vi) Later evidence may be adduced to support a technical effect made plausible by the specification.
>
> (vii) Provided the technical effect is made plausible, no further proof of the existence of the effect is to be demanded *of the specification* before judging obviousness by reference to the technical effect propounded."

184. Having cited this passage, Kitchin LJ went on in *Idenix v Gilead* to consider what was meant by "plausible" in this context. Having considered *Human Genome Sciences Inc v Eli Lilly & Co* [2011] UKSC 51, [2012] RPC 6 and *Warner-Lambert Company LLC v Generics (UK) Ltd* [2016] EWCA Civ 1006, he concluded at [114]:

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

185. Counsel for Shionogi submitted that where, as in the present case, the claims of the patent included a functional limitation, no objection of *AgrEvo* obviousness could arise. I do not accept this. In *Idenix v Gilead*, the claims were on their face expressed to be pure compound claims, but it was common ground between the parties that they should be interpreted as claims to compounds with anti-*Flaviviridae* activity (see Kitchin LJ at [116]). I nevertheless concluded that the claims lacked an inventive step because it was not plausible that substantially all of the compounds covered by the claim had anti-*Flaviviridae* activity, and that conclusion was upheld by the Court of Appeal. This is because the technical problem which was required plausibly to be solved if the claimed invention was to make a technical contribution to the art was the provision of compounds which had such activity. The identification of a very large class of compounds only some of which had such activity would not make a technical contribution to art, and it made no difference that the claim was limited to the compounds which did have activity. As Kitchin J (as he then was) put it (albeit in the context of insufficiency) at first instance in *Novartis AG v Johnson & Johnson Medical Ltd* [2009] EWHC 1671 (Pat) at [244]:

> "… a claim to a class of products said to possess a useful activity must be based upon the identification of a common

> principle which permits a reasonable prediction to be made that substantially all the claimed products do indeed share that activity. Further, it is not permissible to by-pass that requirement simply by adding a functional limitation which restricts the scope of the claim to all the products which do have the relevant activity, that is to say all those which 'work'. …"

*Assessment: claim 1 as unconditionally proposed to be amended*

186. I shall preface my consideration of this issue with three preliminary points. The first is that MSD was content to argue its case by reference to the Patent, rather than to the Application. As I shall discuss when I come to consider MSD's added matter objection, formula (I) was defined even more broadly in the Application than in the Patent. It was open to MSD to argue that, if the claimed inventions were only plausible in the light of the disclosure of the Patent and not in the light of the disclosure of the Application, then the Patent must be invalid for added matter. But given the breadth of formula (I) in the Patent, MSD evidently did not feel the need to advance its case in that way.

187. Secondly, it is Shionogi's case that substantially all the compounds covered by the claims can be made by the skilled team and assessed for integrase inhibition (and antiviral activity, if necessary) without undue burden. For the purposes of assessing inventive step, I shall assume that this is correct. I shall consider whether it is in fact correct when I come to consider insufficiency.

188. Thirdly, counsel for MSD submitted that, when considering inventive step, it was not open to Shionogi rely upon information cross-referenced in the specification which was not common general knowledge to bolster its case in plausibility, and in particular the patent applications referred to at [0004]. He accepted that it was open to Shionogi to rely upon this information in the context of insufficiency, however. Counsel for Shionogi did not take issue with the correctness of this analysis as a matter of law. While I am not entirely sure that it is correct, it is convenient to assume that counsel for MSD is right, because that will enable me to make findings upon both bases.

189. *The number of compounds covered by formula (I).* The starting point for MSD's case is the staggeringly vast number of compounds covered by formula (I) as defined in claim 1 of the Patent. Prof Neamati's unchallenged conservative estimate was that formula (I) covers some $10^{39}$ compounds. To put this into context, it exceeds the total number of unique chemical substances ever registered in the CAS Registry (a register of chemical substances administered by the American Chemical Society) by a factor of approximately $10^{31}$.

190. Counsel for Shionogi made a number of points about this figure. First, he submitted that it was not open to MSD to rely upon it because counsel for MSD had not put to Shionogi's witnesses that the claimed inventions lacked plausibility because of the number of compounds falling within the scope of formula (I). This is not MSD's case, however. Rather, MSD's case is that the number of compounds failing within the scope of formula (I) provides the context in which the question of plausibility falls to be considered. Moreover, that context was not in dispute between the experts. Prof

Neamati set out the estimate in his first report, and Prof Tsantrizos accepted it in paragraph 16 of her second report. Consistently with this, Prof Neamati's estimate was not challenged in cross-examination.

191. Secondly, counsel for Shionogi pointed out that many patent claims cover large numbers of products. That is undoubtedly true, but it is beside the point. The question is not about the number of products covered, but about the plausibility of the claim. It cannot sensibly be contended that the breadth of the claim is irrelevant to this question.

192. Thirdly, counsel for Shionogi pointed out that claim 1 (both as granted and as proposed to be amended) is not a claim to the compounds which satisfy the structural requirements of formula (I) as defined, it is a claim to those compounds which both fulfil those structural requirements and satisfy the functional requirements of the claim. This is correct, but for the reasons explained above it does not detract from the proposition that the question of plausibility must be assessed having regard to the number of compounds which fulfil the structural requirements.

193. Fourthly, counsel for Shionogi pointed out that in certain respects formula (I) was defined narrowly, while allowing for more variation in other parts of molecule. He submitted that this accorded with the function of the formula, which was to define the key features which were necessary for the compounds to have the desired activity while permitting variation elsewhere in the molecule. In principle, I accept that this is a relevant consideration. Thus MSD was right not to contend that the claims are invalid purely because of the number of compounds covered by the formula. But it remains necessary to consider the extent to which the claim does in fact define a pharmacophore and hence renders the claim plausible.

194. *The data in the Patent*. MSD contends that the data in the Patent are both very limited in extent and suffer from a number of defects. Counsel for Shionogi submitted in his closing submissions that one of the defects relied upon by MSD, namely the absence of data using magnesium as a cofactor in the assay (as opposed to manganese) was not open to MSD because it had not been pleaded in MSD's Re-Amended Grounds of Invalidity. I do not accept this submission for the following reasons.

195. It is fair to say that MSD's pleading on this point is cast in very general terms:

> "The biological results presented in the specification are confined to the integrase inhibitory activity of a small number of compounds when tested using a particular *in vitro* assay. The person skilled in the art could not, from such results and/or his common general knowledge … make a reasonable prediction (nor does the specification make it plausible) that substantially all the compounds claimed would be effective as integrase inhibitors for preventing or treating a viral disease or HIV."

(The same plea is relied upon by MSD in support of its case on insufficiency, and I shall have to come back to it in that context.)

196. It does not appear that Shionogi ever requested further information from MSD as to the limitations in the data relied upon. In MSD's evidence in chief, however, a

number of limitations were identified by MSD's witnesses, and in particular Prof Debyser. One of the matters to which Prof Debyser drew attention was the lack of any magnesium data (see paragraph 109 above). He also drew attention to the other defects which I shall consider below, such as the absence of statistical information. Shionogi raised no objection when it received MSD's experts' reports that they were raising unpleaded points, rather it sought to address the points on their merits. Counsel for Shionogi did not contend in his written closing submissions that it was not open to MSD to rely upon the other defects (although he did so in his oral closing submissions when I queried this). I cannot see any reason why the complaint about the absence of magnesium data should stand in a different position.

197. Furthermore, there can be no question of Shionogi having been taken by surprise on this question. Prof Götte replied to Prof Debyser's comments about the absence of magnesium data in paragraph 2.13 of his second report. In paragraphs 132-135 of Shionogi's opening skeleton argument, counsel for Shionogi noted that "Prof Debyser has a number of criticisms of the data in the Patent" and submitted that the criticisms were unfounded. While the criticisms which were specifically addressed did not include the magnesium point, it was one of Prof Debyser's criticisms. The point about magnesium was expressly relied upon by MSD in paragraph 71 of MSD's opening skeleton argument, but no protest was made about this by counsel for Shionogi in his oral opening submissions.

198. I turn therefore to consider the various criticisms raised by MSD. The first is the limited number of compounds for which any data at all is reported. There is little dispute about this. I have reproduced Table 1 in paragraph 69 above. As noted in paragraph 70 above, there are only data for 27 compounds, of which at most 12 fall within the claims.

199. Secondly, MSD points out that in each case a single data point is reported. There is no statement as to whether this represents a single experiment or an average of a number of experiments. If it is a mean, no standard deviations are reported. MSD relies on the evidence of Prof Debyser and Prof Neamati as to the desirability of this information being reported and on the acceptance by Prof Götte that it would have been better if this had been done. Shionogi's answer to this point is four-fold. First, Shionogi contends that the skilled team would assume that the experiments were competently done and therefore had at least been carried out in duplicate. As Prof Götte accepted, however, the skilled team has no way of knowing whether this was so or not. Secondly, Shionogi says that the skilled team would not regard the absence of standard deviations as significant given that a standard deviation from a sample size of two would not be very meaningful. Thirdly, Shionogi points to certain papers in the field which also appear to report single experiments without statistical analysis. This is a fair point, although the tenor of Prof Debyser's evidence was that standards had risen over the period leading to August 2002. Fourthly, Shionogi points out that it is clear from the evidence that such results are inherently rather imprecise. (Indeed, Dr Yoshinaga explained that the results could vary two or three-fold.) I accept that, at least for the second and fourth reasons, the skilled team would not be particularly concerned about the absence of information about the number of repetitions (if any) or statistics; but by the same token the skilled team would appreciate that the precise numbers given in Table 1 were not reliable.

200. Thirdly, MSD points out that, although the experiment included negative and positive controls, it did not include any reference compound. As stated in paragraph 6.11 of the technical primer agreed between the parties (reproduced in paragraph 57 above), albeit in relation to cellular assays, it was best practice to include such a reference compound. Prof Debyser explained that this was because of the problems that had been experienced in the field with false positives – compounds that gave positive results in biochemical assays that were not true integrase inhibitors. Shionogi's answer to this is to rely on the fact that that there was no reference compound in Hazuda 2000. As Prof Debyser explained, however, the whole reason why Hazuda 2000 was so important was that it provided the first examples of validated authentic integrase inhibitors. Prior to Hazuda 2000, researchers just had to do the best they could. After the publication of those results, however, it was important to compare the activity of any new compound with one that had been established to be an authentic integrase inhibitor. Prof Götte accepted that it would have been better if this had been done, although he considered that it was not absolutely necessary. Strikingly, Dr Yoshinaga's evidence was that, for the testing underlying the Table 1 data, Shionogi in fact used not one, but two, benchmark compounds (one of which was S-1360) to ensure the validity and accuracy of the assay; but this data is not included in the Patent.

201. Fourthly, MSD points out that the Patent does not include any information about the integrase used in the assay. It does not even state that the integrase was HIV-1 integrase. Prof Götte explained, and Prof Debyser accepted, that it would be possible to use the substrate DNA sequence on page 261 of the specification to work out that it was appropriate for HIV-1 (although Prof Debyser did not know whether the sequence was exclusive to HIV-1). More importantly, however, as Prof Debyser explained, the Patent does not identify the source, type or method of purification of the integrase. In particular, it does not specify whether the integrase was wild-type or a soluble mutant. This was significant because some compounds were active against soluble mutants, but inactive against wild-type integrase.

202. Fifthly, MSD points out that the data in the Patent were generated using manganese as a co-factor and that no results are reported using magnesium. MSD contends that the skilled team would want to see confirmation of the results using magnesium. A considerable amount of time was spent on this topic at trial, and counsel for Shionogi chose to make it his first point of attack on MSD's case in his closing submissions. I have already considered the pleading point he raised. I now turn to the evidence.

203. Prof Debyser's evidence in his first report was that it was well known that biochemical assays gave different results when performed with manganese and with magnesium and that, as a general rule, integrase activity was more easily observed *in vitro* with manganese than with magnesium. Accordingly, some researchers would first assay with manganese, since the assay was easier to run. But the prudent approach was to repeat the assay using magnesium for those compounds which gave a positive result with manganese, since magnesium was believed to be the co-factor *in vivo*. Prof Debyser maintained this evidence in cross-examination. It was suggested to him that an experimental protocol using manganese described in Debyser *et al*, "Assays for the Evaluation of HIV-1 integrase inhibitors" in Schein (ed), *Methods in Molecular Biology, vol 160: Nuclease Methods and Protocols*, 139-155 (2001) was inconsistent with his evidence, but he did not accept that and nor do I. Prof Debyser

was clear that it was perfectly acceptable to screen for activity using manganese, but that the risk of false positives meant that the results should be confirmed with magnesium. Equally, it was pointed out to Prof Debyser that some of the patent applications referred to in the Patent at [0004] report tests carried out using just manganese, but the answer is the same. Moreover, many of those applications were filed, and/or claimed priority from applications filed, several years before August 2002. As I have already noted, standards were rising in the field over that period.

204. Prof Götte accepted that, as a general rule, integrase activity was more easily observed *in vitro* with manganese than with magnesium and that it was widely assumed that the co-factor for integration *in vivo* was magnesium. Moreover, Prof Götte himself cited Grobler in his evidence, and stated that it formed part of the virologist's common general knowledge. Grobler states at 6666 that:

> "IN mutations that confer virologic resistance *in vitro* reduce the affinity and activity of DKAs in $Mg^{2+}$ but not $Mn^{2+}$. These results illustrate the importance of assessing integrase activity in the appropriate metal and provide evidence supporting $Mg^{2+}$ as the relevant cofactor. … $Mn^{2+}$ is compatible with a wider range of reactive group geometries than $Mg^{2+}$ (35) and thus $Mn^{2+}$-catalyzed IN reactions and inhibition may be less sensitive to changes in reactive group geometries."

205. Although Prof Götte did not agree with the first two sentences quoted when they were put him, I understood his point to be that one could detect activity using manganese and therefore it was not essential to test with magnesium. But that is not what Grobler is saying, which is that testing with magnesium is important to obtain reliable results.

206. It emerged in Prof Neamati's oral evidence that he considered that the absence of data obtained with magnesium to be the most significant weakness in the data in the Patent. He accepted that workers in the field might screen compounds for activity with manganese first, but he considered it essential to carry out a follow-up assay with magnesium on those compounds which were active with manganese because it was well known by August 2002 that results with manganese were unreliable. As noted above, counsel for Shionogi criticised Prof Neamati for raising this point during cross-examination when he had not mentioned it in his written evidence. I do not accept the criticism of the witness for the reasons I have already explained. Furthermore, the substance of his evidence was entirely consistent with the evidence of Prof Debyser, although Prof Neamati expressed it in stronger terms.

207. Given their experience in the field at the time, and given the support it receives from papers such as Grobler, I have no hesitation in preferring the evidence of Prof Debyser and Prof Neamati to that of Prof Götte to the limited extent that they differed on this topic. Accordingly, I conclude that the skilled person would be concerned by the absence of any data from tests with magnesium.

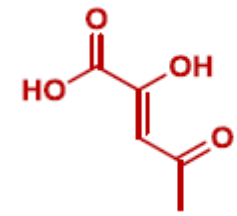
208. Sixthly, MSD points out that, as was common ground between the experts, the data reported in Table 1 are "flat". That is say, they simply show that a number of compounds had integrase inhibitory activity in the assay. The data do not show the effect of the presence or absence of any particular features of compounds in question. To make matters worse, the majority of the compounds fall outside the claim.

209. MSD does not contend that any of the limitations discussed above, either individually or collectively, mean that the skilled team would not regard the data in the Patent as credible so far as they go. Thus MSD does not contend that the skilled team would not regard it as plausible that the compounds in Table 1 had integrase inhibitory activity. Rather, MSD contends that the very limited and imperfect data in Table 1 did not make it plausible, as at August 2002, that substantially all the other compounds covered by formula (I) had integrase inhibitory active in a biochemical assay. This contention was strongly supported by the evidence of Prof Debyser and Prof Neamati. Before expressing my conclusion on this point, however, I need to consider Shionogi's response to it.

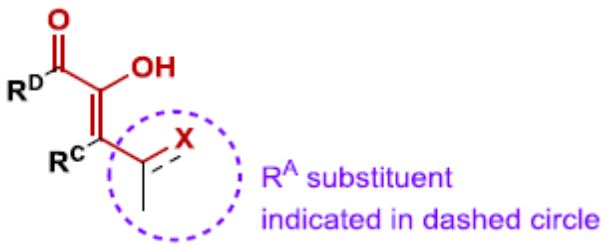
210. *The pharmacophore relied upon by Shionogi*. Nowhere in the Patent is there is any explanation as to why it is suggested that the compounds covered by formula (I) are likely to possess integrase inhibitory activity (let alone antiviral activity). The skilled team is simply presented with the formula, the data in Table 1 and the assertion that the compounds of the invention have inhibitory activity (and are useful for preventing or treating viral disease). There is not a word on the subject of the relationship between the structures of those compounds and the activity they are asserted to possess.

211. In an attempt to meet this difficulty, Shionogi relied upon the evidence of Prof Tsantrizos. In paragraphs 42 and 43 of her first report, Prof Tsantrizos said that the skilled team (and, implicitly, the medicinal chemist in particular) would recognise the compounds claimed in formula (I) of the Application to possess four shared structural features which were also present in the compounds claimed in formula (I) of the Patent, albeit with a more limited range of substituents. These features were as follows:

i) a diketo-acid like motif with a triad of heteroatoms as shown below:

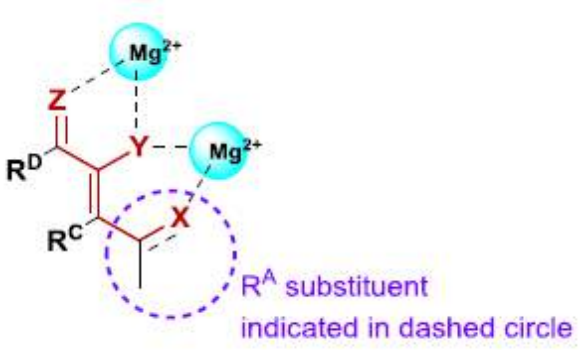



DiKeto Acid (DKA)

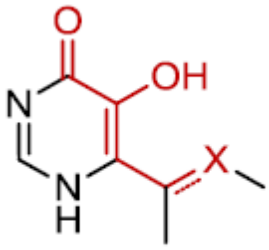



DKA-like structural motifs

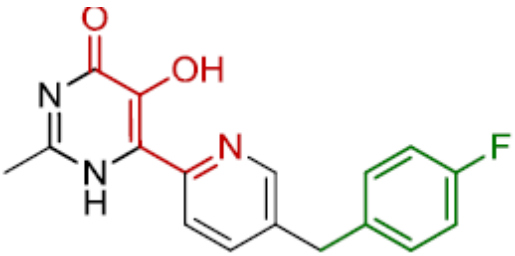
ii) the heteroatoms being arranged in a geometry capable of chelating two divalent metal atoms as shown below:




iii) the triad being on a scaffold of a ring structure which provided rigidity and co-planarity as exemplified by the ring structure of Group G as shown below; and




iv) at least one terminal ring attached to the main scaffold of the molecule by a variable linker region such as the part of compound G-7 highlighted in green below.




212. Although Prof Tsantrizos did not describe these four features as defining a pharmacophore in her first report, she did so in her second report, where she also set out a more simplified depiction of these features.

213. Counsel for MSD submitted that in cross-examination Prof Tsantrizos had resiled from the suggestion that features (iii) and (iv) above were defining features of the pharmacophore. Counsel for Shionogi disputed this. I am bound to say that I understood Prof Tsantrizos to accept that not all of the claimed compounds possessed features (iii) and (iv); but, having re-read the transcript, I accept that it is possible that she simply got confused.

214. But even if Prof Tsantrizos did not intend to concede the point, I found the evidence of Prof Neamati that the medicinal chemist would not consider that all of the claimed compounds shared feature (iii) more convincing. As he explained, there would be rigidity and co-planarity with an aromatic $R^CR^D$ ring, but not with a non-aromatic system.

215. As for feature (iv), this is simply a description of a structural feature of molecules falling within the claim. It does not define the three-dimensional position of any key functional groups.

216. More fundamentally, as counsel for MSD submitted, there is nothing in the Patent that defines a true pharmacophore. Not only is there no information about the position of the key functional groups in space, but also there is no structure-activity relationship information which could be used to define a true pharmacophore. There is not even any mention in all of the 261 pages of the specification (excluding the cover pages and the claims) of metal chelation.

217. The skilled team already knew from the work of Hazuda's group (in particular from Hazuda 2000, Espeseth, Wai and Grobler) that the diketo functionality appeared to be necessary for integrase inhibition, but not sufficient. Furthermore, as discussed above, Grobler had proposed a model for the binding of diketo acids to HIV-1 integrase involving co-ordination of two divalent metal cations in the integrase active site. Prof Götte accepted that the model proposed by Grobler was speculative. On the other hand, as counsel for MSD accepted, it was regarded as sufficiently plausible to be accepted for publication in a leading peer-reviewed journal.

218. I would add that, even if the skilled team was aware of S-1360 from their common general knowledge, that would not assist Shionogi both for the reasons given above and because S-1360 does not fall within the claim.

219. Thus although the specification presents the skilled team with (rather poor quality) data about the integrase inhibitory activity of a small number of compounds, it teaches the skilled team nothing about the relationship between the structures of those compounds and their activity. To the extent that the skilled team was able to draw any conclusions about that relationship – and Prof Neamati was sceptical that the medicinal chemist would have concluded that the compounds of formula (I) were capable of coordinating two $Mg^{2+}$ ions without being prompted – such conclusions would be based on the common general knowledge they brought to their reading of the Patent and not on anything in the Patent itself.

220. Furthermore, reading the Patent with their common general knowledge, the skilled team would appreciate that small changes in the claimed structures not merely could, but would be likely to, have an impact on the activity of the compounds. Thus, as noted above, Prof Tsantrizos accepted that a take-home message of Wai was that the antiviral activity was very sensitive to the orientation of the hydrophobic group. It follows that changes in the hydrophobic group itself would also be expected to have an impact upon the activity. Prof Tsantrizos also accepted that even the small change of a fluorination to the hydrophobic benzene ring could have a significant effect on activity.

221. Accordingly, I conclude that the specification does not make it plausible that substantially all the compounds covered by formula (I) possess integrase inhibitory active in a biochemical assay. At best, it is plausible that a tiny fraction of that class of compounds in addition to the specific compounds for whom data is reported in Table 1 may do, but that plausibility derives from the skilled team's common general knowledge and not from the Patent. It follows that the scope of the monopoly claimed

is not justified by the extent of the technical contribution to the art. Accordingly, claim 1 as proposed unconditionally to be amended lacks an inventive step.

222. *The absence of any antiviral data, toxicity data or validation work*. Even if it is assumed, contrary to the conclusion I have just reached, that the specification does make it plausible that substantially all the compounds covered by formula (I) possess integrase inhibitory activity in a biochemical assay, in my judgment it does not begin to make it plausible that substantially all the compounds covered by formula (I) possess antiviral activity, whether against HIV or any other virus. Still less does it make it plausible that substantially all the compounds covered by formula (I) would be effective for preventing or treating a viral disease applying the criterion for efficacy discussed above.

223. The specification does not report any antiviral data, toxicity data or validation work for even a single compound. There is abundant evidence that a compound showing enzymatic activity in a biochemical assay may not show antiviral activity, that a compound which shows antiviral activity may not achieve that activity through integrase inhibition and that a compound which shows antiviral activity may be toxic. As discussed above, by August 2002, a considerable number of promising compounds and classes of compounds had failed for one or other of these reasons. Thus a positive result in a biochemical assay was not sufficient to make a reasonable prediction that that compound would have antiviral activity, still less that it would have antiviral activity due to integrase inhibition and not be toxic. An antiviral assay, toxicity testing and validation work would still be required. Toxicity in particular was difficult to predict. As discussed above, there was little between the virology experts on this. Prof Debyser's evidence was clear and consistent, and Prof Götte substantially agreed with Prof Debyser's account in cross-examination. Moreover, the evidence of the medicinal chemists was also consistent with this.

224. As Prof Debyser pointed out, it was not as if it was not possible to provide proper data in support of such a claim. On the contrary, Hazuda 2000 had shown that it was possible to demonstrate that compounds had integrase inhibitory activity and antiviral activity, that one was due to the other and that they did not appear to be unduly toxic (although further toxicity studies would be required). Moreover, Grobler had started the work on building up a structure-activity relationship that would enable predictions to be made about activity.

225. Even if it was plausible that the Table 1 compounds would possess antiviral activity due to integrase inhibition and would be sufficiently non-toxic, in the absence of any structure-activity relationship information in the specification, it would remain utterly implausible that substantially all of the compounds covered by formula (I), or even a tiny fraction of them, would do so.

226. In short, the claim to antiviral activity in the Patent is entirely speculative and the claim to therapeutic efficacy is, if that is possible, even more speculative.

227. *Conclusion*. For the reasons given above, I conclude that claim 1 as unconditionally proposed is invalid on the ground that the claimed invention lacks an inventive step.

*Claim 1 as conditionally proposed to be amended*

228. Neither of Shionogi's proposed amendments affects the conclusions reached above. The first amendment limits the claim to HIV, but since there is no more support for the claim that the compounds would be useful for preventing or treating HIV than for any other viral disease, this makes no difference. The second amendment narrows that scope of formula (I), but only very slightly. Again this makes no difference.

*Claim 6*

229. The limitation in claim 6 does not affect the conclusions reached above either. Again, it narrows the scope of formula (I), but not to any extent which makes any real difference for this purpose.

Insufficiency

230. MSD contends that all of the claims of the Patent, both as granted and as proposed to be amended, are invalid on the ground of insufficiency. In broad terms, MSD advances two separate contentions. First, MSD contends that the specification does not enable the claimed inventions to be performed over the whole scope of the claim without undue burden. As part of this objection, MSD contends that the disclosure of the Patent does not make it plausible that the invention will work across the scope of the claims. Secondly, MSD contends that the specification does not enable the claimed inventions to be performed because the claims are ambiguous. Since I have concluded that the claims are not ambiguous, however, this objection must be rejected. Accordingly, I shall say no more about it.

*The law*

231. The law relating to MSD's first objection has been reviewed in a number of recent Court of Appeal decisions. In *Eli Lilly & Co v Human Genome Sciences Inc* [2012] EWCA Civ 1185. [2013] RPC 22 at [11] Sir Robin Jacob, and in *Idenix v Gilead* at [133] Kitchin LJ, cited the following summary of the basic principles given by Kitchin J (as he then was) at first instance in the former case [2008] EWHC 1903 (Pat), [2008] RPC 29 at [239]:

> "The specification must disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. The key elements of this requirement which bear on the present case are these:
>
> (i) the first step is to identify the invention and that is to be done by reading and construing the claims;
>
> (ii) in the case of a product claim that means making or otherwise obtaining the product;
>
> (iii) in the case of a process claim, it means working the process;

> (iv) sufficiency of the disclosure must be assessed on the basis of the specification as a whole including the description and the claims;
>
> (v) the disclosure is aimed at the skilled person who may use his common general knowledge to supplement the information contained in the specification;
>
> (vi) the specification must be sufficient to allow the invention to be performed over the whole scope of the claim;
>
> (vii) the specification must be sufficient to allow the invention to be so performed without undue burden."

232. So far as the requirement that the invention be capable of being performed over the whole scope of the claim is concerned, Kitchin LJ explained in *Regeneron Pharmaceuticals Inc v Genentech Inc* [2013] EWCA Civ 93, [2013] RPC 28 that:

> "98. … 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 claim. …
>
> …
>
> 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."

233. Accordingly, the court must undertake a two-stage enquiry. The first stage is to determine whether the disclosure of the patent, read in the light of the common general knowledge of the skilled team, makes it plausible that the invention will work across the scope of the claim. At this stage, it is not permissible for either the patentee or the party attacking the patent to rely upon evidence which post-dates the patent. If

the disclosure does make it plausible, the second stage is to consider whether the evidence establishes that in fact the invention cannot be performed across the scope of the claim without undue burden. In some cases, it is convenient to divide the second stage into two parts, first considering whether the invention can be performed without undue burden at all and then whether the claim is of excessive breadth. At this stage, evidence which post-dates the patent is admissible.

234. As noted above, in *Idenix v Gilead* the Court of Appeal held that the criterion of plausibility was the same in this context as in the context of inventive step. There must be a real reason for supposing that the claimed invention will indeed have the promised technical effect.

235. So far as the question of undue burden is concerned, in *Regeneron v Genentech* Kitchin LJ repeated at [97] what he had said at first instance in *Novartis v Johnson & Johnson* at [236]:

> "Whether the specification discloses an invention clearly and completely enough for it to be performed by a person skilled in the art involves a question of degree. It is impossible to lay down any precise rule because the degree of clarity and completeness required will vary depending on the nature of the invention and of the art in which it is made. On the one hand, the specification need not set out every detail necessary for performance. The skilled person must be prepared to display a reasonable degree of skill and use the common general knowledge of the art in making routine trials and to correct obvious errors in the specification, if a means of correcting them can readily be found. Further, he may need to carry out ordinary methods of trial and error, which involve no inventive step and generally are necessary in applying the particular discovery to produce a practical result. On the other hand, he should not be required to carry out any prolonged research, enquiry or experiment: *Mentor Corporation v Hollister Inc.* [1993] R.P.C. 7."

236. He went on to consider the requirement that the specification should enable the skilled person to perform the invention without undue burden in the context of a claim to the use of a product to make a medicine for a particular therapeutic purpose:

> "102. … patentees not infrequently seek to avoid the possibility that a claim covers products or methods which do not work by inserting a functional limitation. Such a claim may be allowed by the EPO if the invention can only be defined in such terms or cannot otherwise be defined more precisely without unduly restricting its scope. But, it must still be possible to perform the invention across the scope of the claim without undue effort. As I said in *Novartis v Johnson & Johnson* at [244]:
>
> > '… In the case of a claim limited by function, it must still be possible to perform the invention across the scope of the scope of the claim without undue effort.

> That will involve a question of degree and depend upon all the circumstances including the nature of the invention and the art in which it is made. Such circumstances may include a consideration of whether the claims embrace products other than those specifically described for achieving the claimed purpose and, if they do, what those other products may be and how easily they may be found or made; whether it is possible to make a reasonable prediction as to whether any particular product satisfies the requirements of the claims; and the nature and extent of any testing which must be carried out to confirm any such prediction.'

103. … the Boards of Appeal of the EPO have recognised that in the case of a claim to the use of a product to make a medicine for a particular therapeutic purpose it would impose too great a burden on the patentee to require him to provide absolute proof that the compound has approval as a medicine. Further, it is not always necessary to report the results of clinical trials or even animal testing. Nevertheless, he must show, for example by appropriate experiments, that the product has an effect on a disease process so as to make the claimed therapeutic effect plausible. It was put this way in T609/02 *Salk* at [9]:

> '… It is a well-known fact that proving the suitability of a given compound as an active ingredient in a pharmaceutical composition might require years and very high developmental costs which will only be borne by the industry if it has some form of protective rights. Nonetheless, variously formulated claims to pharmaceutical products have been granted under the EPC, all through the years. The patent system takes account of the intrinsic difficulties for a compound to be officially certified as a drug by not requiring an absolute proof that the compound is approved as a drug before it may be claimed as such. The boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical. It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or

> demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (T 241/95, OJ EPO 2001, 103, point 4.1.2 of the reasons, see also T 158/96 of 28 October 1998, point 3.5.2 of the reasons) or, as decision T 158/96 also put it, if there is a "clear and accepted established relationship" between the shown physiological activities and the disease (loc. cit.). Once this evidence is available from the patent application, then post-published (so-called) expert evidence (if any) may be taken into account, but only to back-up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on their own.'"

237. It has been held in a number of cases that a patent will be insufficient if the specification requires the skilled person to undertake a substantial research project in order to perform the invention (either at all or across the breadth of the claim) and claims the results: see e.g. *Halliburton Energy Services Inc v Smith International (North Sea) Ltd* [2006] EWCA Civ 1715 at [18] (Jacob LJ), *American Home Products Corp v Novartis Pharmaceuticals UK Ltd* [2001] RPC 8 at [41]-[47] (Aldous LJ), *Novartis AG v Johnson & Johnson Medical Ltd* [2010] EWCA Civ 1039, [2011] ECC 10 at [50]-[92] (Jacob LJ) and *Idenix v Gilead* at [197] (Kitchin LJ).

*Assessment: claim 1 as unconditionally proposed to be amended.*

238. *Plausibility as at August 2002*. Counsel for Shionogi submitted that MSD's plea of lack of plausibility, which I have set out in paragraph 195 above, was bad in law since the claim was limited to compounds which were suitable for preventing or treating viral disease. I do not accept this submission. As explained above, the mere fact that a claim contains a functional limitation to products which "work" does not avoid the issue. Moreover, the Patent promises at [0009]-[0010], [0232]-[0235] and [0461] that the compounds covered by formula (I) will be suitable for preventing or treating HIV.

239. The findings I have made in relation to inventive step above lead to the conclusion it was not plausible that substantially all of the compounds covered by formula (I) would possess integrase inhibitory activity, still less that they would be suitable for preventing or treating viral disease unless the information cross-referenced in the Patent makes a difference. I therefore turn to consider that question.

240. It can be seen that the specification refers at [0004] to a number of types of integrase inhibitor described in identified patent applications (some of which were Shionogi applications and some were Merck applications):

    i) 1,3-dioxobutanoic acids and 1,3-propanediones described in international applications numbers W099/50245, W099/62520, W099/62897, W099/62513, W000/39086 and W001/00578;

ii) an acrylic acid derivative described in international application number W001/17968; and

iii) aza- or polyazanaphthalenylcarboamide derivatives described in international applications W02002/30426, W02002/30930, W02002/30931 and W02002/36734.

241. There is no suggestion in the specification that the information contained in these patent applications is relevant to the claimed inventions other than as background. In particular, there is no suggestion that the compounds of formula (I) have common structural features with these compounds described in the patent applications or that the patent applications shed light on the relationship between the structures of the compounds or formula (I) and their claimed activity as integrase inhibitors and antivirals.

242. All that Prof Tsantrizos said in her first report was that "At [0004], the Patent then refers to examples of integrase inhibitors in prior art publications which would be of interest to the Skilled Team". She did not suggest that any of the information contained in the cited patent applications was relevant to the question of plausibility. Prof Götte did not comment on this part of the specification at all.

243. Prof Debyser noted in his first report that, of seven applications published before August 2001, all but two contained "results from some compounds" from an antiviral assay as well from a biochemical integrase assay.

244. Prof Neamati expressed the opinion in his first report that the medicinal chemist "would not derive any meaningful assistance from [the applications published before August 2001] in relation to the biological activity of the Formula I, Table 1 compounds" for the reasons he went on to explain. In relation to four Merck applications, he noted that they contained statements in the form "representative compounds tested in the integrase assay demonstrated $IC_{50}$s in the range from 0.01 to 5 micromolar" and said:

> "Presenting biological data in this general way does not assist the Medicinal Chemist. Each application discloses a large number of different compounds but gives the Medicinal Chemist no information about which of them were tested, or their activity."

He went on to conclude that there was "nothing in … the publications referred to in the Patent which would affect the Medicinal Chemist's conclusion" with respect to plausibility which he had previously set out.

245. In her second report, Prof Tsantrizos disagreed that the medicinal chemist would not learn anything from the applications. She considered the contents of the applications and concluded as follows:

> "Taking the background patent applications cited in [0004] of the Patent together, the Skilled Team would appreciate, in keeping with its expectations from the common general knowledge and what it learns from the Patent, that the α,γ-

> diketo acid moiety is important for integrase inhibitory activity and more particularly it is the geometry of the three heteroatoms in which the activity resides, most likely as a consequence of being involved in the chelation of divalent metal ions. The Skilled Team would also appreciate that the α,γ-diketo acid moiety can be adapted by replacing the carboxylic acid functional group and/or the γ-carbonyl with various bioisosteric groups, and that there is some diversity of choice in these replacements, as long as there is an O or N atom in the same geometry, and in other parts of the molecule substitutions can be made more freely."

246. Counsel for Shionogi submitted that Prof Neamati's evidence about the patent applications in his report was inconsistent with, or otherwise undermined by, what he had said about some of the same applications in Neamati 2002. In this regard counsel relied on the fact that, in Neamati 2002, Prof Neamati had summarised the disclosure of the applications without adverse comment. Indeed, in relation to one of the Merck applications (WO/0100578), he said:

> "Merck's representative compounds inhibited strand transfer activity with $IC_{50}$ value range of 0.01 - 5 M and showed antiviral activity within similar dose [sic]. These latter compounds are perhaps the most potent diketo-containing inhibitors of IN discovered to date."

Moreover, this was one of a number of patent applications highlighted in the bibliography as being of "considerable interest to readers" and described as an "Important patent describing diketoacids as integrase inhibitors".

247. Prof Neamati did not accept that he had been inconsistent and neither do I. As explained above, Prof Neamati's purpose in Neamati 2002 was simply to summarise and report the contents of the patent literature he was asked to survey. It was not a critical review. On the contrary, Prof Neamati included a very clear "health warning" to the reader at the outset. In his report, Prof Neamati was considering a different question, which was whether the patent applications referred to at [0004] added to the plausibility of the claimed inventions. His opinion was that they did not. Moreover, as Prof Neamati pointed out during cross-examination, the applications in question did at least report antiviral activity for representative compounds, even if in a rather uninformative way, whereas the Patent does not.

248. Furthermore, I do not consider that Prof Tsantrizos' evidence in her second report, even taken entirely at face value, demonstrates that the applications did add to the plausibility of the claimed inventions. All she says is that the applications help to confirm that "the α,γ-diketo acid moiety is important for integrase inhibitory activity and more particularly it is the geometry of the three heteroatoms in which the activity resides, most likely as a consequence of being involved in the chelation of divalent metal ions". But the skilled team knew that from their common general knowledge anyway. I infer that it was for that reason that Prof Tsantrizos did not say anything about the applications in her first report.

249. Accordingly, I conclude that, even if the applications referred to at [0004] are taken into account, it was not plausible that substantially all of the claimed compounds would possess integrase inhibitory activity, still less would be useful for preventing or treating a viral disease.

250. *Plausibility in the light of later evidence*. MSD contends that, even if it was plausible as at August 2002 that substantially all of the claimed compounds would possess integrase inhibitory activity and be suitable for preventing or treating viral disease, subsequent evidence has made it clear that this is not plausible and that, on the contrary, it is more likely than not that large numbers of compounds covered by formula (I) are not suitable for preventing or treating viral disease. In this regard, MSD relies on three main strands of evidence.

251. First, only one compound falling within the claims of the Patent (in accordance with my conclusions) has been advanced into clinical trials, namely raltegravir. Dr Yoshinaga gave evidence that 11 compounds falling within the claims of the Patent, including a compound with the reference number 210-0249 (B-12-b in the Patent), had been tested in a mouse/MT4 HIV-1 model and gave positive results, but he did not suggest that any of these compounds were progressed further. He also gave evidence that a related compound which fell outside the claims, 210-0319, was progressed to *in vivo* testing in SIV-infected monkeys and gave positive results. It was put to Prof Debyser that certain Shionogi documents showed that 210-0249 had also been progressed into the monkey SIV study, but the context of this question was Prof Debyser's evidence about impact of human serum albumin (as to which, see below) and the purpose of the test may have been to provide a comparator for 210-0139. This would explain why Dr Yoshinaga said that 201-0139 "advanced furthest in testing". The compounds which Shionogi ultimately took forward into clinical trials are not within the claims. It progressed other leads in preference to these compounds, and ultimately abandoned the project altogether in favour of dolutegravir.

252. Secondly, subsequent evidence shows that the nature of the integrase hydrophobic pocket rules out activity for many of the formula (I) compounds. It was not until 2010 that a structure was obtained for full-length integrase in complex with viral DNA and strand transfer inhibitors (Hare *et al*, "Retroviral intasome assembly and inhibition of DNA strand transfer", *Nature*, 464, 232-237 (11 March 2010)). This work (and similar studies by the same group and others) demonstrated that the halobenzyl group of integrase-inhibitors such as raltegravir and other related compounds fits within a tight pocket within the enzyme's active site in complex with the viral DNA. As Prof Neamati explained, the halobenzyl group participates in π–π interactions with the penultimate deoxycytidine of the displaced viral DNA. It was not disputed by Shionogi's experts that this hydrophobic pocket existed or that integrase inhibitors needed to be able to interact with it in order to be effective.

253. In order for a compound to interact with that pocket, three things are required. First, the molecule must contain a hydrophobic group which is by its nature capable of performing the required interactions. Secondly, that hydrophobic group must be of the appropriate size: too small and it is unlikely to be capable of making the required interactions; too big and it will not "fit" in the constrained pocket. Thirdly, it must be connected to the rest of the inhibitor molecule by a flexible linker which allows the hydrophobic group to assume the correct orientation within the pocket.

254. Prof Tsantrizos agreed that, looking through the prism of today's technical knowledge, in order for a compound of Formula (I) to be suitable for use as an integrase inhibitor for preventing or treating HIV, it must have an $R^1$ group which is able to interact with the hydrophobic pocket by π-stacking. As she explained, an aromatic ring would be the best choice for this. She also agreed that a species for which $R^1$ is cyclohexyl could not achieve such interaction, and that it was more likely than not that an aromatic terminal ring was needed to render a given Formula (I) compound suitable for such use. It follows from this evidence that a species for which $R^1$ is cycloalkyl (whatever the ring size) will not be suitable for the claimed use. That rules out one third of the options for $R^1$.

255. Prof Tsantrizos also appeared to accept that, whilst a smaller group might not be fatal to activity, a substituent which exceeded the size of the pocket would not be suitable. Thus her evidence on this point was consistent with that of Prof Neamati: large or bulky groups are unsuitable. That rules out compounds with such groups.

256. Furthermore, Prof Tsantrizos accepted that, in order for π-stacking to take place, it was more likely than not that a flexible linker was required. That rules out compounds which do not have a flexible linker. This is the case for compounds in which none of $Z^1$, $Z^2$ or $Z^3$ comprises an $sp^3$ carbon atom (that is to say, a carbon atom which can form four single covalent bonds in a tetrahedral configuration). (It may be noted that it was this point that prompted Shionogi's second conditional amendment application at the beginning of trial.)

257. Thirdly, the medicinal chemistry experts were agreed that formula (I) includes a number of types of compound that the medicinal chemist would regard as "red flags" in the sense that they would be expected to render the compounds ineffective. These include compounds which are toxic due to particular substituents (such as iodine), metabolically unstable compounds, highly lipophilic compounds and high molecular weight compounds.

258. It is sufficient for present purposes to exemplify this point by reference to the last of these categories. Prof Neamati explained in his first report that compounds over 600 molecular weight would be suspect as they would be unlikely to cross the cell membrane. Similarly, Prof Tsantrizos explained that Lipinsky's rules showed that compounds varied in cell membrane permeability. Thus the skilled team would not expect high molecular weight compounds to be effective. Shionogi argues that the skilled team would therefore not try to make and test such compounds, but the fact remains that formula (I) includes them.

259. In my judgment it is plain from the three strands of evidence summarised above that, given today's knowledge, it is not credible that substantially all of the compounds covered by formula (I) possess integrase inhibitory activity and are suitable for preventing or treating a viral disease. On the contrary, formula (I) covers large groups of compounds that are unlikely to possess integrase inhibitory activity and be suitable for preventing or treating a viral disease.

260. *Examples of compounds which don't "work"*. MSD also contends that, even if (contrary to the conclusion I have reached above) it was plausible to the skilled team reading the Patent with their common general knowledge as at 8 August 2002 that substantially all of the compounds claimed would possess integrase inhibitory activity

and antiviral activity and not be unduly toxic, subsequent evidence shows that various specific compounds falling within the claim don't "work" in this sense.

261. Both parties gave disclosure of relevant experimental work done on compounds falling within formula (I) in the four years around the earliest priority date. Data for a total of 104 compounds from Shionogi and 139 compounds from Merck were disclosed.

262. As counsel for MSD pointed out, these 243 compounds do not represent either a random selection of compounds or a selection which traverses the full breadth of the claim. On the contrary, they represent sub-classes of compounds which Shionogi and Merck's scientists thought were most likely to have suitable activity. Thus it is no surprise that much of MSD's disclosure is centred around developing the SAR which ultimately led Merck to raltegravir. Moreover, it is clear from the structures of the tested compounds that they represent microscopic islands of closely-related compounds within the broad ocean of the claims.

263. MSD contends that a significant proportion of the compounds which were tested fail in one of the following assays:

i) a biochemical integrase assay in the presence of either manganese or magnesium;

ii) one or more cell-based antiviral HIV-1 assays; or

iii) an MTT/MT-4 assay in the presence of human serum or human serum albumin ("HS/HSA").

264. Prof Neamati's evidence in his first report was that 34 of the 139 Merck compounds failed in one or more of these ways. His evidence in his second report was that 54 of the 104 Shionogi Compounds failed in one or more of these ways. The relevant data derived from MSD's disclosure are collated in exhibit NN16 to Prof Neamati's first report. The relevant data from Shionogi's disclosure are contained in exhibit NN24 to Prof Neamati's second report.

265. A general point which applies to both sets of data is that they contain results reported in the form "> x" where x is a molar concentration representing the $IC_{50}$ or $EC_{50}$. What these results show is that the experimenter gave up at a certain point, with x being the last concentration tested. They do not show what the true value is, and it is possible in such cases that, had the experimenter continued the experiment, he would have found that the $IC_{50}$ or $EC_{50}$ value was only slightly larger than x. But the inference to be drawn in such cases is that the experimenter took the view that the value was going to be larger than was worth their time measuring. The evidence is that, in practical terms, such a result indicates a failure as perceived by the experimenter.

266. So far as the Merck compounds are concerned, counsel for Shionogi pointed out that 24 of the 34 had $IC_{50}$ values of 1 μM or below in the biochemical assay, while three were not tested. Accordingly, counsel for Shionogi submitted that 24 compounds had satisfactory activity in this assay and three had unknown activity. Furthermore, he relied upon Prof Debyser's acceptance that there were no firm cut-offs with respect to

activity in such assays as showing that four other compounds were likely to have had at least some activity. I do not accept the point regarding the four other compounds, but in any event this submission overlooks the fact that the compounds which did possess activity in the biochemical assay failed the cell culture assay in the sense explained in the preceding paragraph.

267. Turning to the Shionogi compounds, I shall put on one side for the moment 24 compounds that are only said by MSD to fail in HS/HSA tests. That leaves 30 which are said to fail on other grounds. So far as the biochemical assays are concerned, counsel for Shionogi submitted that Prof Neamati had pointed to only one compound that he considered to be inactive with magnesium and further submitted that that compound had shown some activity even if not very good activity. I am not sure that Prof Neamati was given a proper chance to identify other compounds that he considered to be inactive, but I will assume that counsel for Shionogi is right that all 30 compounds showed activity in a biochemical assay.

268. As for the cell culture assays, Shionogi tested the compounds in both HeLa and MTT/MT4 assays. Counsel for Shionogi pointed out that in 11 cases the experimenter had given up in both assays. He submitted that this did not establish that those compounds were failures. But as discussed above, it is clear from the evidence that, in practical terms, such compounds were regarded as failures by the experimenter. Certainly, in the case of Shionogi's experiments, Dr Yoshinaga's evidence confirms that that was how they were regarded by Shionogi.

269. In three cases, the experimenter gave up in one assay, but got a positive result in the other. Thus the results for these compounds are equivocal.

270. Finally, in 12 cases the results showed that compound had antiviral activity, but was toxic in one assay or the other although not both. Counsel for Shionogi submitted that this did not matter, because the experts were agreed that toxicity in one cell line was not predictive of toxicity in other cell types. That is correct, but beside the point. Prof Debyser's evidence was that toxicity in one cell line would probably lead to the compound being discarded even if it was not found to be toxic in the other.

271. Overall, I conclude that the evidence demonstrates that a significant proportion of the compounds for which there are experimental data either did not possess antiviral activity or possessed antiviral activity but were unduly toxic.

272. Finally, I turn to consider the 24 compounds that are only said by MSD to fail in HS/HSA tests. (Three of the 30 that were said to fail on other grounds are also contended to fail for this reason, but it is unnecessary to consider these separately.) In these tests an antiviral cellular assay was repeated in the presence of HS or HSA rather than foetal bovine serum (FBS). As Prof Debyser explained, certain drugs bind to protein in the blood, and that fraction of the drug is therefore taken out of useful circulation. Normally, only the free drug will go to the appropriate active site and exert its pharmacological activity. The free drug concentration in the blood clearly depends upon how much of the drug is bound to protein. An HS/HSA assay measures the effect on a compound's activity when HS/HSA is added. Where there is a high degree of protein binding, the amount of free, active drug is significantly reduced when the HS/HSA is introduced – and so the measured activity reduces (i.e. the $EC_{50}$ value goes up).

273. Prof Debyser's evidence in his second report was that the prevailing attitude in the integrase field at that time was that a high degree of protein binding was seen as a bad thing and therefore compounds whose activity was greatly reduced when the HS/HSA was introduced was discounted. In cross-examination he maintained that "protein binding was felt at the time as something you tried to avoid". He accepted, however, that it was not a black and white issue, but rather a factor to be taken into account.

274. For his part, Prof Götte accepted that he was not a position to comment on this issue since it was an issue of pharmacokinetics and he was not in the field at the time, although he had no recollection of it being voiced as a major concern.

275. In addition to the evidence of Prof Debyser, counsel for MSD relied on the evidence of Dr Yoshinaga. He testified that HSA tests were implemented as a matter of routine at Shionogi as of the end of 2001. He explained that there was a hypothesis that activity reduction by serum-binding was not a problem if the protein-adjusted $EC_{50}$ exceeded the trough concentration of the drug. But he was clear that this was a hypothesis known to pharmacologists which medicinal chemists did not know about. Indeed, he suggested that it was for this reason that Dr Kiyama and Dr Fuji of Shionogi, both of whom were medicinal chemists, had characterised the serum binding as a problem.

276. Considering the evidence as a whole, I am not persuaded these 30 compounds should be categorised as failures. This is for two reasons. First, I am not satisfied that this is how they would have been regarded in August 2002. I accept that the evidence shows that high HS/HSA activity would have been regarded as a concern, but I do not consider that it shows that investigation of such compounds would have been abandoned. Secondly, as Prof Debyser himself explained in his second report, it is now considered by some groups that a relatively high degree of protein binding is positively advantageous since it provides a sort of *in vivo* slow-release mechanism. Thus, viewed with today's knowledge, such compounds would not be considered to be failures.

277. It follows that these 24 compounds do not advance MSD's case; but that does not detract from the conclusion I have reached in paragraph 271 above.

278. *Undue burden to perform across the scope of the claim*. MSD contends that, even if the compounds which were the subject of MSD's and Shionogi's disclosure "work", or at least have not been shown not to "work", nevertheless the specification does not allow the invention to be performed across the scope of the claim without undue burden.

279. MSD does not contend that the medicinal chemist would have difficulty in synthesising compounds falling within formula (I) following the guidance given in the specification and using his common general knowledge. But MSD points out that synthesising such compounds was a time-consuming activity. Prof Tsantrizos gave evidence about a high-throughput screening project at BI in 2004. By that time, she explained, it was possible for a small team of medicinal chemists and technicians to synthesise something like a hundred compounds a week, but only if a year's tedious work had first been undertaken to establish a suitable modular synthesis. Thus even on this basis, it would take over a year to synthesise a hundred compounds which were structurally sufficiently closely related to be susceptible of modular synthesis. It

is clear from the evidence that, in August 2002, it would have taken longer than that, and even longer to synthesise the same number of structurally diverse compounds. Prof Neamati's estimate was that one medicinal chemist could synthesise about 50 compounds a year provided no difficulties were encountered. Thus a team of three could make 150 compounds in a year.

280. Nor does MSD contend that the skilled team would have any difficulty in screening the compounds for enzymatic and antiviral activity. Prof Debyser's evidence was that carrying out biochemical and antiviral assays on a single compound would take a month, and verification would add an extra month. As he accepted, it was possible, using microtiter plates for the antiviral assay, to test a number of compounds in parallel, which would enable 100-200 compounds to be in tested a week if they had all been synthesised.

281. But as counsel for MSD pointed out, even if one assumes that compounds could be synthesised sufficiently quickly to enable a constant testing rate in both assays of 200 compounds/week, it would take $9.6 \times 10^{30}$ years to assay just 0.01% of the claimed compounds, which is about $2 \times 10^{21}$ times the age of the Earth.

282. Shionogi's answer to this, as I understand it, is that the skilled team should not be deemed to be trying to make and test compounds across the breadth of formula (I), but only to make and test a sample with a view to finding at least one that "works". I do not accept this contention is well founded as matter of law. But I will consider the facts in case I am wrong about that.

283. Prof Debyser thought that the starting point would be to try to synthesise and test 150 structurally diverse compounds which were representative of the different possibilities encompassed by formula (I). Based on what is now known, it is more likely than not that some of these compounds would fail to exhibit integrase inhibitory activity. It is also more likely than not that some of the compounds that did exhibit integrase inhibitory activity would not exhibit antiviral activity. It is also more likely than not that some of the compounds that exhibited activity in both assays would be unduly toxic. It is also more likely than not that some of the compounds that exhibited activity in both assays and were not unduly toxic would fail in validation work. It is a matter for speculation as to whether the skilled team would be able to identify even one compound which was worth taking forward into clinical trials. But given that Shionogi did not itself succeed in identifying such a compound, the likelihood is that the skilled team would not do so.

284. The upshot is that, on any view, the Patent presents the skilled team with a vast research project with a high likelihood of failure, but claims the results if they happen to succeed – even if (as in the case of raltegravir) such success has nothing to do with the teaching of the Patent. Accordingly, it is not possible to perform the claimed inventions across the scope of the claim.

285. *Conclusion*. For the reasons given above, I conclude that claim 1 as unconditionally proposed to be amended is invalid on the ground of insufficiency.

*Claim 1 as conditionally proposed to be amended*

286. Neither of Shionogi's proposed amendments affects the conclusions reached above. The first amendment limits the claim to HIV, but this makes no difference. The second amendment addresses the flexible linker point, but not the other problems discussed above.

*Claim 6*

287. The limitation in claim 6 does not affect the conclusions reached above either. Again, it narrows the scope of formula (I), but not to any extent which makes any real difference for this purpose.

Added matter

288. As is common ground, formula (I) was more broadly defined in the Application than it is in the Patent. MSD contends that the amendments not merely narrowed the claims, but also resulted in added matter.

*The law*

289. The law with regard to added matter has been expounded in a series of decisions of the Court of Appeal over the last 10 years, including *Vector Corp v Glatt Air Techniques Ltd* [2007] EWCA Civ 805, [2008] RPC 10 at [4]-[9] and *Nokia Corporation v IPCom GmbH & Co KG* [2012] EWCA Civ 567, [2013] RPC 5 at [46] to [60]. Despite this, it is necessary to say a little more about the law in so far as it relates to selections from the disclosure of the application, specifically selections from lists of possible compounds or substituents.

290. Where a selection is made of a specific item from a single list, the established case law of the Boards of Appeal of the EPO law is that the selection does not individualise a new disclosure. Thus in T 1357/06 *Takeda Pharmaceutical Co Ltd/Treatment of diabetes* (unreported, 16 September 2008) the combination of pioglitazone with each individual compound of a list was held to have been specifically disclosed in each of the earlier application as filed and the divisional application as filed, since it was in each case only a single list. As the Board put it at [2.1]:

> "Despite the fact that this list comprises a considerable number of compounds, the combination of pioglitazone with each individual compound of this list is considered to be specifically disclosed in view of the fact that only one selection has to be made."

Thus limiting the claim from pioglitazone in combination with a second agent to pioglitazone in combination with metformin did not add matter in circumstances where metformin was among the list of possible second agents.

291. The position may be different where the selection is made from multiple lists. Where a specification contains a series of lists of variables, but does not point to a particular combination of choices from the respective lists, an amendment that narrows to that

particular combination will ordinarily add matter. As counsel for MSD submitted, this principle is traceable back to the important early decision in T 12/81 *Bayer/ Diastereomers* [1979-85] EPOR B308. In that case, the Board was considering the novelty of a selection from two lists. It held at [13]:

> "However, the disclosure by description in a cited document of the starting substance as well as the reaction process is always prejudicial to novelty because those data unalterably establish the end product. If on the other hand two classes of starting substances are required to prepare the end products and examples of individual entities in each class are given in two lists of some length, then a substance resulting from the reaction of a specific pair from the two lists can nevertheless be regarded for patent purposes as a selection and hence as new."

Such a selection from two lists can be novel for the purposes of patentability, and by the same logic it will also constitute added matter if it was not disclosed in the application as filed.

292. An important factor in the analysis is the degree of narrowing that is effected by the selection. The case law is summarised in the *Case Law of the Boards of Appeal of the European Patent Office* (8th edition) at 420-425. It is sufficient for present purposes to cite the following passage at 421:

> "According to the boards consistent case law, the guiding principle is that **deleting** meanings of residues in a generic chemical formula must not lead to the selection, in the respective lists, of a particular combination of single, specific but originally undisclosed meanings of residues (see **T 615/95** and **T859/94**).
>
> In **T 942/98** precisely this had occurred through the deletion of all other meanings, residues X1, X2 and R5 had been narrowed down to a single meaning, leading to a combination of specific meanings of residues not disclosed in the application as filed. Consequently, claim 1 as filed did not itself provide adequate support for claim 1 as amended (cited by **T2013/08** in connection with the established case law concerning '**singling out**').
>
> In **T 615/95** there were three independent lists of sizable length specify distinct meanings for three residues in a generic chemical formula in a claim. One originally disclosed meaning was deleted from each of the three independent lists. The board stated that the present deletions did not result in singling out a particular combination of specific meanings, ie any hitherto nor specifically mentioned individual compound or group of compounds, but maintained the remaining subject-matter as a generic group of compounds differing from the original group only by its smaller size. Such a **shrinking of the generic group** of chemical compounds was not objectionable under Art.

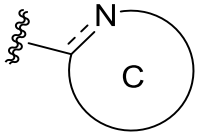
> 123(2) EPC 1973, since these deletions did not lead to a particular combination of specific meanings of the respective residues which was not disclosed originally or, in other words, did not generate another invention (see also **T948/02**, which refers in detail to this case law and which did not allow the amendment of a generic chemical formula; see also **T659/97, T894/05, T 888/08**).
>
> In **T150/13** the board, referring to **T948/02**, summarised that a deletion of genes from a list of specific genes was allowable if it fulfils two conditions: First, the deletion must not result in singling out any hitherto not specifically mentioned individual compound or group of compounds, but maintains the remaining subject-matter as a generic group of compounds differing from the original group only by its smaller size. Second, the deletion does not lead to a particular combination of a specific meaning which was not disclosed originally, ie it does not generate another invention, or in other words it merely restricts the required protection but does not provide any technical contribution to the originally disclosed subject-matter."

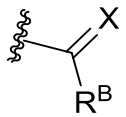
293. In *GlaxoSmithKline UK Ltd v Wyeth Holdings LLC* [2016] EWHC 1045 (Pat) Henry Carr J held at [119] that the rule against selections from multiple lists was not a "rigid" one. He said that "the whole contents of the application as filed must be considered, including its general disclosure", and that a "mechanistic approach" to the question was to be avoided. I would agree with this, but nevertheless the case law of the Boards of Appeal provides useful guidance as to the correct approach.

*The Application*

294. Both sides argued the case by reference to the Application as published, rather than as filed, it being common ground that there is no material difference between the two for these purposes.

295. The differences between formula (I) as defined in the Application and as defined in the Patent are shown below:

| |
|---|
| wherein, $R^C$ and $R^D$ taken together with the neighboring carbon atoms form a 5- to 6-membered ring ~~which may be a condensed ring~~ which may contain (a) heteroatom(s) of N and/or O and may be condensed with a benzene ring, |
| Y is hydroxyl~~, mercapto or amino~~; |
| Z is O~~, S or NH~~; |
| $R^A$ is a group shown by   (wherein, C ring is a 5- to 6-membered N-containing aromatic heterocycle which may contain 1 to 4 of O, S and/or N atom(s), wherein at least one atom neighboring to the atom at the bonding-position is non-substituted N atom; the broken line shows the presence or absence of a bond), or by |

| |
|---|
|  <br>(wherein, X is O~~, S or NH~~; $R^B$ is ~~a substituent selected from substitution group A~~ amino); |
| at least one of the ring formed by $R^C$ and $R^D$, C ring and $R^B$ is substituted with a group of $-Z^1-Z^2-Z^3-R^1$ (wherein $Z^1$ and $Z^3$ are each independently a bond, ~~optionally substituted~~ alkylene or ~~optionally substituted~~ alkenylene; $Z^2$ is a bond, ~~optionally substituted~~ alkylene, ~~optionally substituted~~ alkenylene, -CH(OH)-, -S- , -SO-,$-SO_2-$, $SO_2NR^2-$, $-NR^2SO_2-$, -O-, $-NR^2-$,$-NR^2CO-$, $-CONR^2-$, -C(=O)-O-, -O-C(=O) or -CO-; $R^2$ is hydrogen, ~~optionally substituted~~ alkyl, ~~optionally substituted~~ alkenyl, ~~optionally substituted~~ aryl or ~~optionally substituted~~ heteroaryl; $R^1$ is ~~optionally substituted~~ cycloalkyl, ~~optionally substituted~~ aryl, or ~~optionally substituted~~ heteroaryl, ~~optionally substituted cycloalkenyl or optionally substituted heterocycle~~, with $R^1$ being optionally substituted by one or two substituents selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, halogen or $C_1$-$C_6$ alkoxy; |
| the ring formed by $R^C$ and $R^D$~~, C ring or $R^B$~~ is optionally substituted with a non-interfering substituent selected from hydrogen, halogen, $C_1$-$C_6$ alkyl, $C_3$-$C_6$ cycloalkyl, phenyl or naphthyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy($C_1$-$C_6$)alkyl, amino, $C_1$-$C_6$ hydroxyalkyl, $C_2$-$C_8$ alkenyl, or hydroxyl, and the C ring or $R^B$ is optionally substituted with a non-interfering substituent selected from hydrogen, $C_1$-$C_6$ alkyl, amino, halogen and hydroxyl, at any position other than that where the group of $-Z^1-Z^2-Z^3-R^1$ (wherein, $Z^1$, $Z^2$, $Z^3$and $R^1$ are the same as defined above) locates; |
| ~~substitution group A: hydrogen, halogen, alkoxycarbonyl; carboxy, alkyl, alkoxy, alkoxyalkyl, nitro, hydroxy, alkenyl, alkynyl, alkylsulfonyl, optionally substituted amino, alkylthio, alkylthioalkyl, haloalkyl, haloalkoxy, haloalkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycle, nitroso, azide, amidino, guanidino, cyano, isocyano, mercapto, optionally substituted carbamoyl, sulfamoyl, sulfoamino, formyl, alkylcarbonyl, alkylcarbonyloxy, hydrazino, morpholino, optionally substituted aryl , optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heteroaryl alkyl, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted aryl thio, optionally substituted heteroarylthio, optionally substituted aralkyloxy, optionally substituted heteroarylalkyloxy, optionally substituted aralkylthio, optionally substituted heteroarylalkylthio, optionally substituted aryloxyalkyl, optionally substituted heteroaryloxyalkyl, optionally substituted arylthioalkyl, optionally substituted heteroarylthioalkyl, optionally substituted arylsulfonyl, optionally substituted heteroarylsulfonyl, optionally substituted aralkylsulfonyl and optionally substituted heteroarylalkylsulfonyl~~ |

296. There are certain other passages in the Application which are relevant to the arguments on added matter, but it is convenient to consider these in context.

*Assessment*

297. MSD advances a series of added matter objections which I will consider in turn. I will take them in the order in which counsel for MSD argued them in his oral closing submissions. Although a number of the objections include a complaint about

selections from multiple lists, it is convenient to consider those aspects of the objections together.

298. *The definition of X, Y and Z*. In the Application X can be O, S or NH, Y can be hydroxyl, mercapto or amino and Z can be O, S or NH. In the Patent X is limited to O, Y is limited to hydroxy and Z is limited to O.

299. Shionogi contends that these limitations find clear basis in the following passage in the Application:

> "[0034] X is O, S or NH and preferred is O.
>
> [0035] Y is hydroxyl, mercapto or amino and preferred is hydroxyl.
>
> [0036] Z is O, S or NH and preferred is O."

300. MSD contends that this passage must be read in context, and that the context is provided by the immediately preceding passage at [0032]-[0033]. Both these paragraphs identify various "further preferred" compounds and the latter ends with the words "The definition of each symbol is explained below". Accordingly, MSD argues that what is said at [0034]-[0036] relates, and relates only, to those further preferred compounds.

301. I do not accept this argument. In my judgment, it is premised on an over-literal reading of the Application. While as a matter of pure syntax MSD may be right to say that the definitions at [0034]-[0036] (and those which follow at [0038]-[0057]) are referable to the further preferred compounds, I am not persuaded that that is how the skilled team would understand them. In my view Shionogi is correct to say that the skilled team would interpret the teaching of this passage as generally applicable.

302. *The definition of $R^B$*. In the Application $R^B$ is defined as a substituent selected from substitution group A, which is quite a long list. In the Patent $R^B$ is defined as amino. Shionogi contends that this limitation finds basis in [0047] which states that among nine "more preferred" options for $R^B$ is "optionally substituted amino".

303. Counsel for MSD pointed out that "optionally substituted amino", and still less "amino" was not among the five "most preferred" options for $R^B$ listed in [0047]. This is beside the point. Limiting to a more preferred option rather than a most preferred option does not amount to added matter.

304. *The definition of the C ring*. The C ring is defined in the Application as an "N-containing aromatic heterocycle, wherein at least one atom neighboring to the atom at the bonding-position is N atom". The Application explains that:

> "[0023] C ring may contain a hetero atom(s) other than the N atom shown in the above formula. The atoms constituting C ring include C, O, N and S. The bonds constituting C ring include a single bond or double bond. C ring is a monocyclic ring or condensed ring (e.g., di- to penta-cyclic condensed ring) and preferred is a monocyclic ring or di-cyclic con- densed ring, and more preferred is a monocyclic ring.

> [0024] A monocyclic heteroaryl of C ring means 5- to 8-membered heteroaryl wherein one atom neighboring to the atom at the bonding-position is non-substituted N atom and which may contain further 1 to 4 of O, S and/or N atom, and preferably 5- or 6-membered heteroaryl …"

305. MSD contends that it is clear from the language of [0024] that the 1 to 4 of O, S, and/or N atoms are "further" to the non-substituent N atom i.e. the C ring may include up to *five* heteroatoms.

306. The Patent defines the C ring as:

> "a 5- to 6-membered N-containing aromatic heterocycle which may contain 1 to 4 of O, S, and/or N atom(s), wherein at least one atom neighboring to the atom at the bonding-position is non-substituted N atom".

307. Accordingly, MSD contends, what the skilled team learns from the Patent's disclosure is a different sort of C ring. It may comprise only up to *four* heteroatoms: the 1 to 4 of O, S and/or N are inclusive of the non-substituent N atom.

308. I do not accept this argument. In my judgment, it is premised on a misreading of [0024] of the Application. As Shionogi contends, the word "further" is to be read in the sense of "and further which may contain 1 to 4 of O, S and/or N atom". Thus the ring must have a non-substituted N atom neighbouring the bonding position, and further may have 1 to 4 heteroatoms. The Application is not saying that the total number of heteroatoms including the non-substituted N atom may be five.

309. *The definition of $R^1$*. $R^1$ is defined in the Application as follows:

> "$R^1$ is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl or optionally substituted heterocycle".

310. The Application explains at [0090] that:

> "In the definition of $R^1$, the substituent of 'optionally substituted aryl', 'optionally substituted heteroaryl', 'optionally substituted cycloalkyl', 'optionally substituted cycloalkenyl', and 'optionally substituted heterocycle' is preferably … More preferred is alkyl, haloalkyl, halogen (e.g., F, Cl, Br), alkoxy and further preferred is methoxy. Preferred is mono- or disubstituted one."

311. The terms "alkyl", "haloalkyl", and "alkoxy" are defined in the Application at as follows (emphasis added):

> "[0061] 'alkyl' means C1 to C10 straight or branched chain alkyl, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, isohexyl, n-heptyl, n-octyl, n-nonyl, n-decyl**.**

> Preferred is C1 to C6 alkyl, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, isohexyl.
>
> …
>
> [0071] The alkyl of 'alkoxy' is the same as above 'alkyl', and 'alkoxy' includes for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy. Preferred is methoxy, ethoxy.
>
> …
>
> [0081] 'haloalkyl' means the above 'alkyl' substituted with one or more of halogen. Preferred is halogenated C1 to C3 alkyl, for example, trifluoromethyl, chloromethyl, dichloromethyl, 1,1-dichloroethyl 2,2,2-tri chloro ethyl."

312. MSD contends that the Application thereby discloses that, whilst C1-C6 is preferred for alkyl, the preferred alkoxy and haloalkyl substituents are "methoxy, ethoxy" and "halogenated C1 to C3 alkyl" respectively.

313. In the Patent $R^1$ is defined as:

> "cycloalkyl, aryl, or heteroaryl, with $R^1$ being optionally substituted by one or two substituents selected from C1—C6 alkyl, C1—C6 haloalkyl, halogen or C1—C6 alkoxy."

314. Accordingly, MSD contends that the skilled team learns from the Patent that the alkyl, alkoxy and haloalkyl substituents on $R^1$ must all be C1-C6, which is different.

315. I do not accept this argument. In my judgment, it is again premised on a misreading of the Application. As Shionogi points out, the definitions of "alkoxy" and "haloalkyl" in [0071] and [0081] both begin by referring back to the definition of "alkyl" in [0061]. Accordingly, the limitation of the claim to optional substitutions with C1-C6 haloalkyl and C1-C6 alkoxy is a limitation to preferred embodiments of the alkyl portion of haloalkyl and alkoxy. It is immaterial that the Application also contained a disclosure of a narrower preferred range of each of these.

316. *The selection of non-interfering substituents*. The Application states that "the ring formed by $R^C$ and $R^D$, C ring and $R^B$ is optionally substituted with a non-interfering substituent". The Application explains that

> "[0054] Examples of non-interfering substituent [sic] on the ring formed by $R^C$ and $R^D$ (e.g., non-interfering substituent of $R^{19}$, $R^E$, $R^F$, $R^{11}$, $R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$ and $R^G$) are preferably hydrogen, halogen, alkyl, aralkyl, cycloalkyl, optionally substituted aryl, alkoxy, alkoxyalkyl, optionally substituted amino, hydroxy alkyl, alkenyl, alkoxycarbonylalkyl, heteroarylalkyl or hydroxy.
>
> …

> [0056] Examples of non-interfering substituent on C ring (e.g., non-interfering substituent of $R^3$, $R^4$, $R^8$, $R^9$ and $R^{10}$) are preferably halogen, alkyl, aralkyl, cycloalkyl optionally substituted aryl, alkoxy, alkoxyalkyl, optionally substituted amino, hydroxy alkyl, alkenyl, alkoxycarbonylalkyl, heteroarylalkyl or hydroxy, and more preferred is hydrogen, alkyl, amino, halogen or hydroxy.
>
> [0057] Examples of non-interfering substituent on $R^B$ (e.g., non-interfering substituent of $R^6$ and $R^7$) are preferably halogen, alkyl, aralkyl, cycloalkyl, optionally substituted aryl, alkoxy, alkoxyalkyl, optionally substituted amino, hydroxy alkyl, alkenyl, alkoxycarbonylalkyl, heteroarylalkyl or hydroxy, and more preferred is hydrogen, alkyl, amino, halogen, hydroxy."

317. The Patent provides that:

> "the ring formed by $R^C$ and $R^D$ is optionally substituted with a non-interfering substituent selected from hydrogen, halogen, C1-C6 alkyl, C3-C6 cycloalkyl, phenyl or naphtyl, C1-C6 alkoxy, C1-C6 alkoxy(C1-C6)alkyl, amino, C1-C6 hydroxyalkyl, C2-C8 alkenyl, or hydroxyl, and the C ring or $R^B$ is optionally substituted with a non-interfering substituent selected from hydrogen, C1-C6 alkyl, amino, halogen and hydroxyl".

318. MSD contends that the Patent combines the "more preferred" non-interfering substituents on the C ring and $R^B$ together with a selection from the list of "preferable" options on the $R^CR^D$ ring, some of which are further limited in a manner not previously disclosed, that is to say:

i) aralkyl, substituted aryl, substituted amino, alkoxycarbonylalkyl, and heteroarylalkyl groups are no longer suitable non-interfering substituents on the $R^CR^D$ ring;

ii) if an alkoxy group is chosen on the $R^CR^D$ ring, it should be limited to a C1-C6 alkoxy;

iii) if an alkoxyalkyl group is chosen on the $R^CR^D$ ring, it should be limited to a C1-C6 alkoxy on C1-C6 alkyl; and

iv) if a hydroxyalkyl group is chosen on the $R^CR^D$ ring, it should be limited to a C1-C6 hydroxyalkyl.

319. I do not accept this argument. The first point is simply a consequence of the limitation of the list of permissible substituents for the ring formed by $R^C$ and $R^D$. The second, third and fourth points concern the preferred chain length of alkyl groups which I have considered above.

320. *The combined selection*. MSD contends that that the combination of selections of permissible substituents for (i) X, Y and Z, (ii) $R^B$, (iii) the C ring, (iv) $R^1$, (v) non-

interfering substituents to the ring formed by $R^C$ and $R^D$ and (vi) non-interfering substituents to the C ring or $R^B$ amounts to a selection from multiple lists, and thus amounts to a new invention.

321. I do not accept this argument. In my judgment, applying the principles stated in the passage from the *Case Law of the Boards of Appeal* quoted above, the limitations to the scope of formula (I) amounted to a shrinking of the generic group of compounds. The only differences lay in the smaller size of the group. It is true that the shrinkage involved a degree of selection from multiple lists, but there was no singling out of specific compounds, or specific classes of compounds. Thus the skilled team is not taught anything different about the invention as a result of the limitations.

322. *The definition of "non-interfering substituent"*. The term "non-interfering substituent" was defined in the Application at [0050] as follows:

> "The non-interfering substituent means any substituent not interfering with the integrase inhibitory activity. The non-interfering substituent can be selected based on the determined integrase inhibitory activity and drug design using computer, as well as molecular weight, an [sic] der Waals' radius, electrostatic characteristic of the substituent. "

323. This definition of "non-interfering substituent" is missing from the Patent. MSD contends that the result of this is to broaden the disclosure; any type of "*non-interfering substituent*" will now do, where before they had to comply with the definition.

324. I do not accept this argument. The definition accords with the way in which I have construed the term "non-interfering substituent" in the context of the Patent. Accordingly, no matter has been added as result of the omission of the definition.

325. *Conclusion*. For the reasons given above, I conclude that the Patent as granted is not invalid on the ground of added matter.

Amendment

326. MSD contends that each of Shionogi's proposed amendments is impermissible since it would result in added matter. MSD also contends that the unconditional amendment lacks clarity, but I do not accept this.

327. *The unconditional amendment*. MSD contends that the limitation to "for use as an integrase inhibitor" amounts to added matter, particularly when viewed in combination with the requirement that "for preventing or treating a viral disease". I do not accept this. This is simply a restriction in the scope of the claim, in circumstances where the predominant focus of the Application was on integrase inhibitors for preventing or treating viral diseases. The skilled team is not taught anything new about the invention.

328. *The first conditional amendment*. MSD contends that the limitation to "HIV" rather than "a viral disease" amounts to added matter. Again, I do not accept this. This is simply a restriction in the scope of the claim, in circumstances where the predominant

focus of the Application was on HIV. The skilled team is not taught anything new about the invention. Accordingly, the first conditional amendment would be permissible were it not for the fact that it does not cure the invalidity of the Patent.

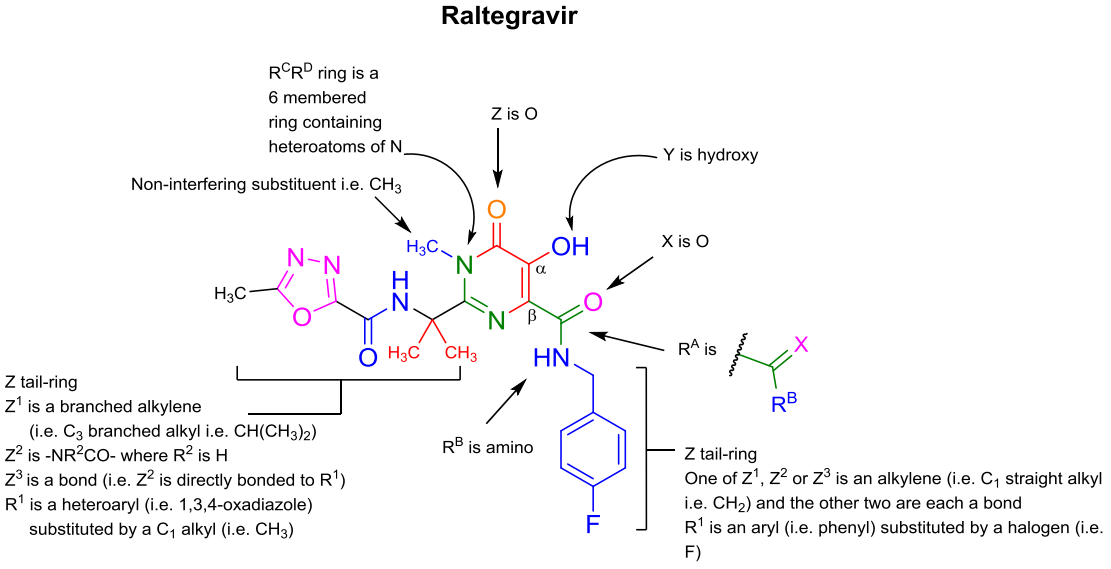
329. *The second conditional amendment*. Shionogi contends that basis for this amendment can be found in the Application at item (19) of [0020]. [0020] lists 21 "preferable examples" of - $Z^1$-$Z^2$-$Z^3$-$R^1$. Number (19) is "$Z^1$, $Z^2$ and $Z^3$ are not bonds at the same time".

330. As MSD points out, however, the claim has already been limited to item (12) in this list, "$R^1$ is optionally substituted cycloalkyl, optionally substituted aryl or optionally substituted heteroaryl". Accordingly, MSD contends that the second conditional amendment would add matter because it would teach that combination for the first time. In support of this contention, counsel for MSD relied upon the decisions of the Technical Boards of Appeal in T 1374/07 *Puratos NV/Bread improver* (unreported, 13 January 2009) at [2.2] and T 1506/13 *The Brigham and Women's Hospital Inc/Markers dermatomyositis polymyositis microarray* (unreported, 8 May 2015) at [4] that a selection of two components from one list is equivalent to a selection from two lists.

331. I accept this argument. The second conditional amendment does not merely amount to a shrinkage of the coverage of the claim as with the points discussed above. It singles out a specific combination of restrictions on $R^1$ and $Z^1$, $Z^2$ and $Z^3$ respectively which is not hinted at in the Application. It therefore does teach the skilled team something new about the invention. Moreover, as can be seen from the discussion in paragraph 256 above, this is not an accident: the purpose of the amendment is to exclude compounds which don't "work". Accordingly, the second conditional amendment is not permissible in any event.

Infringement

332. Shionogi contends that raltegravir satisfies the structural requirements of claims 1 and 6 in the manner summarised in the following helpful diagram.



333. MSD's only argument to the contrary is that the term "non-interfering substituent" is ambiguous. MSD does not dispute that, if that term is to be construed as I have construed it, then the structural requirements of claims 1 and 6 are satisfied. Nor does MSD dispute that the functional requirements of the claims are satisfied. Nor does MSD suggest that any of the proposed amendments would affect this conclusion.

334. Accordingly, I conclude that, if they were valid, claims 1, 6, 8 and 14 would be infringed both as granted and as proposed to be amended.

Summary of principal conclusions

335. For the reasons given above, I conclude that:

i) all the claims of the Patent, both as unconditionally proposed to be amended and as conditionally proposed to be amended, are invalid on the ground that the claimed inventions lack an inventive step;

ii) all the claims of the Patent, both as unconditionally proposed to be amended and as conditionally proposed to be amended, are invalid on the ground that the claimed inventions are insufficiently disclosed;

iii) the Patent as granted is not invalid on the grounds of added matter;

iv) Shionogi's unconditional and first conditional applications to amend the Patent would be permissible were it not for the fact that they do not cure the invalidity of the Patent, whereas the second conditional amendment is not permissible in any event since it would result in added matter; and

v) if they were valid, claims 1, 6, 8 and 14 would be infringed both as granted and as proposed to be amended.