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Case No: HP-2017-000053

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS
INTELLECTUAL PROPERTY LIST (CHANCERY DIVISION)
PATENTS COURT

Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 13 December 2018

Before :

MR JUSTICE ARNOLD

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Between :

(1) GLAXO GROUP LIMITED	**Claimants**
(2) GLAXO OPERATIONS LIMITED	
(3) GLAXOSMITHKLINE TRADING SERVICES LIMITED	
- and -	
VECTURA LIMITED	**Defendant**

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Justin Turner QC and **Geoffrey Pritchard** (instructed by **Gowling WLG (UK) LLP**) for the **Claimants**
Andrew Lykiardopoulos QC and **Anna Edwards-Stuart** (instructed by **Bristows LLP**) for the **Defendant**

Hearing dates: 21-22, 26-27, 30 November 2018

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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 ("Vectura") is the proprietor of European Patents (UK) Nos. 1 337 240 ("240"), 2 283 817 ("817"), 2 283 818 ("818"), 1 337 241 ("241") and 1 920 763 ("763") ("the Patents"). 240, 817 and 818 are all entitled "Method of making particles for use in a pharmaceutical composition", 241 is entitled "Method of preparing microparticles for use in pharmaceutical compositions for inhalation" and 763 is entitled "Pharmaceutical compositions for inhalation". The Patents all have the same earliest claimed priority date of 30 November 2000, which is not challenged. Vectura alleges that the Claimants ("GSK") have infringed the Patents by the manufacture and sale of dry powder inhalers ("DPIs") containing the active ingredients vilanterol trifenatate ("vilanterol") and/or umeclidinium bromide ("umeclidinium") which are used to treat asthma and chronic obstructive pulmonary disease ("COPD") and which GSK market under the trade mark Ellipta.

2. GSK deny infringement and claim revocation of the Patents on the grounds of obviousness over three items of prior art and insufficiency. The prior art relied upon by GSK is (i) International Patent Application No. WO 96/23485 "Carrier particles for use in dry powder inhalers" published on 8 August 1996 ("Staniforth"), (ii) International Patent Application No. WO 00/28979 "Dry powder for inhalation" published on 25 May 2000 ("Keller") and (iii) International Patent Application No. WO/53157 "Improved powdery pharmaceutical compositions for inhalation"

published on 14 September 2000 ("Musa"). In addition, GSK seek an *Arrow* declaration.

3. The Patents divide into two groups. The first group, consisting of 240, 817 and 818, claim methods of making "composite active particles" and composite active particles obtainable by those methods ("the WO701 Patents"). The specifications are very similar, and it is common ground that it is sufficient to refer to the specification of 240. The second group, consisting of 241 and 763, claim methods of making composite active particles (referred to as "microparticles") exhibiting delayed dissolution and microparticles suitable for delayed dissolution ("the WO702 Patents"). Again, the specifications are very similar, and it is common ground that it is sufficient to refer to the specification of 241. What all the Patents have in common is the use of magnesium stearate ("MgSt") to form the composite active particles.

4. The background to the dispute is as follows. On 5 August 2010 Vectura granted GSK a licence in respect of Staniforth and any patents deriving from it ("the Staniforth Patents"). GSK exploited the Staniforth Patents and paid Vectura substantial royalties pursuant to this agreement. The agreement identified an additional class of patent applications (referred to as "the Non-Assert Patents") in respect of which GSK had the option to take a licence. The Staniforth Patents expired on 31 January 2016. On 8 February 2016 GSK informed Vectura that it did not require a licence under of the Non-Assert Patents. GSK's position was and remains that it uses an obvious development of the process disclosed in Staniforth and not the processes claimed in the Patents. In July 2016 Vectura commenced proceedings against GSK in the USA for infringement of US Non-Assert Patents. In June 2017 GSK commenced these proceedings in respect of four of the Patents, with the fifth being added by agreement later.

5. In the European Patent Office, 240 was upheld by the Opposition Division following opposition by a third party; 817 and 818 have been opposed by GSK, but the proceedings are ongoing; 763 was upheld with amended claims following opposition by a third party, but the decision is under appeal; and 241 has not been opposed. Vectura has made an unconditional application to amend claim 1 of 763 to correspond with its main request in the appeal proceedings and has made a conditional application to amend claim 1 in accordance with one of its auxiliary requests. GSK opposes these applications, but only on the ground that they do not cure the invalidity of 763.

6. A complicating factor in the present case is that GSK contend that they have a *Gillette* defence because their process is objectively obvious in the light of the prior art (although GSK have not disclosed how the process was in fact developed). In a nutshell, GSK say that, although their process uses MgSt, this is disclosed by each of the three items of prior art. Although in theory this might make it unnecessary to decide whether the Patents were invalid or not infringed, in practice it is desirable to reach definite conclusions on both sets of issues for the reasons given by the Court of Appeal in *Fujifilm Kyowa Kirin Biologics Co Ltd v AbbVie Biotechnology Ltd* [2017] EWCA Civ 1, [2018] Bus LR 228 at [56]. The *Gillette* defence has led to experiments, expert evidence and argument as to the extent to which GSK's process produces different results to the prior art.

7. In most respects there was no dispute between the parties as to the applicable legal principles, which are well established, and so there is no need for me to set them out.

The witnesses

GSK's factual witnesses

8. GSK adduced evidence from three factual witnesses. Trevor Roche is a Scientific Leader for GSK who has worked for companies in what is now the GSK group since 1985 in various capacities. In his current role he has responsibilities relating to DPIs. He collated the information for and verified GSK's original and amended Product and Process Description ("PPD") and provided further details in a witness statement. Counsel for Vectura made no criticism of Mr Roche as a witness, but complained that his evidence showed that GSK had not disclosed all the relevant particle size data in their possession. As counsel for GSK pointed out, however, Vectura made no application for disclosure of such data.

9. Nigel Bowen is a manager at GSK who has worked for companies in what is now the GSK group since 1989 in various capacities including Senior Formulation Scientist. He was asked to prepare blends in accordance with Staniforth and Musa for GSK's experiments. He was not required to attend for cross-examination.

10. John Harrington is the Facility Manager and Senior Experimental Officer at the Leeds Electron Microscopy and Spectroscopy Unit at the University of Leeds. He undertook GSK's experiments and repeats, and attended the repeats of Vectura's experiments. Counsel for Vectura made no criticism of his evidence.

Vectura's expert witnesses

11. Both parties called experts in formulation science and experts in scanning electronic microscopy ("SEM") and electron dispersive X-ray spectroscopy ("EDX").

12. Vectura's formulation expert was Professor James Birchall. He obtained a Bachelor of Pharmacy degree from Bath University in 1993. He became a registered pharmacist (MRPharmS) in 1994 following a year as a pre-registration pharmacist at Abbott Laboratories UK and St George's Hospital in London. In 1998 he was awarded a PhD in pulmonary gene delivery by Cardiff University. He then became successively a Research Associate, Teaching Fellow (in 2000), Lecturer in Drug Delivery (in 2001), Senior Lecturer in Drug Delivery (in 2007) and Reader in Pharmaceutics (in 2007) at the Welsh School of Pharmacy at Cardiff University. In 2013 he was appointed to his current position as Professor of Pharmaceutical Sciences at what was by then the School of Pharmacy and Pharmaceutical Sciences at Cardiff University. Since January 2015 he has been a member of the Advisory Board at Qualicaps LLC, a manufacturer of pharmaceutical capsules for oral and inhalation delivery. He has published around 140 peer-reviewed publications on a range of topics including microneedle skin delivery, particulate formulation, dry powder inhaler formulation development and dry powder inhaler capsule testing, metered-dose inhaler formulation and nebulised lung delivery. Among other positions he is Associate Editor of *Critical Reviews in Therapeutic Drug Carrier Systems*.

13. Counsel for GSK submitted that Prof Birchall had insufficient experience to assist the court. Although he had done some work on delivering DNA via DPI, he had never made a DPI formulation for use in humans. He had no experience in commercial production of pharmaceuticals and had never scaled up a process. He has not used a high-speed blender and did not know that high-speed blenders were used for DPI manufacture until preparing for this case. In my view it is overstating the position to say that Prof Birchall had insufficient experience to assist the court, but I consider that he had less relevant experience than Prof Buckton.

14. Counsel for GSK also submitted that Prof Birchall had unreasonably maintained that more information could be obtained from the SEMs in the Patents and the parties' experiments than was the case. I have to say that I did find Prof Birchall's evidence on these topics unconvincing.

15. Vectura's SEM/EDX expert was Dr Alan Reynolds. He graduated from Chelsea College, University of London with a Batchelor of Science degree in Zoology in 1977. In 1990 he was awarded a PhD from Brunel University for an investigation using SEM and EDX as well as transmission electron microscopy. He was an Experimental Officer between 1979 and 2003 before being given an academic post equivalent to a Lecturer and, later, to a Senior Lecturer at Brunel University. Since 2008 he has been Deputy Director of the Experimental Techniques Centre at Brunel University and a Reader in Biological Electron Microscopy. In addition to his academic work and roles on various committees, he frequently prepares technical reports on sample analysis using SEM/EDX, amongst other techniques, for commercial clients. He has over 38 years' experience in trace element analysis including extensive experience of SEM and EDX.

16. Counsel for GSK rightly accepted that Dr Reynolds was a careful witness who did his best to assist the court. He nevertheless submitted that Prof Drummond-Brydson's evidence with respect to the EDX maps in the experiments was to be preferred to that of Dr Reynolds. I shall deal with this submission in context.

GSK's expert witnesses

17. GSK's formulation expert was Professor Graham Buckton. He graduated with a Bachelor of Pharmacy degree from Chelsea College, University of London in 1981, became a registered pharmacist in 1982 following a year as a pre-registration pharmacist at Charing Cross Hospital and obtained a PhD from King's College London in 1985. He was awarded a Doctor of Science degree by the University of London in 1997 for research in materials characterisation for drug delivery. From 1984 to 1988 he was a Lecturer in Pharmacy at King's College London. He was then successively Lecturer (in 1988), Senior Lecturer (in 1991), Reader (in 1995) and Professor (in 1998) at the School of Pharmacy, University of London in 1988 where he was Head of Department of Pharmaceutics from 2001 to 2015. Among other positions, he was Editor of the *International Journal of Pharmaceutics* from 1999 to 2009. He has published 186 full papers and contributed a chapter to *Pharmaceutics: The Science of Dosage Form Design* edited by Michael Aulton (1st edition 1988, 2nd edition 2002, "Aulton"). Since 2012 he has been a consultant.

18. Prof Buckton has collaborated with the pharmaceutical industry since 1984. The first such collaboration was with Eli Lilly on an inhalation project to explore how the

milling of an active ingredient caused changes to its surface properties. In 1987 he was seconded to Ciba-Geigy Pharmaceuticals for six months. In the late-1990s to early 2000s he supervised six PhD students in the inhalation field, in collaboration with AstraZeneca and Novartis. These included DPI projects in which the adaptation of carriers and active materials were researched. In 2000 he founded Pharmaterials Ltd, which provided pre-formulation testing, formulation development and (from 2008) GMP manufacture of clinical trial materials. In 2008 he sold the majority stake in Pharmaterials and in 2012 he sold his remaining stake and left the company.

19. Counsel for Vectura criticised Prof Buckton's evidence that the use of high-shear blenders for making DPI formulations was common general knowledge in November 2000, contending that Prof Buckton was at fault for failing to produce documentary evidence to support his position and for changing his position between his written evidence and his oral evidence. I shall consider the substance of Prof Buckton's evidence below. At this stage it suffices to say that I do not consider that Prof Buckton can be faulted for his approach to this issue in any event. I am satisfied that his discharged his duties as an expert witness entirely properly.

20. GSK's SEM/EDX expert was Professor Rik Drummond-Brydson. He graduated with a Bachelor of Science degree in Chemistry and Mathematics from the University of Leeds in 1985. He obtained a PhD in Physical Chemistry from the University of Cambridge in 1988 for work on electron energy loss spectroscopy. Between 1986 and 1994 he held a visiting position at MPI FHI Berlin and MPI Stuttgart. From 1988 to 1992 he was a Royal Society Research Fellow in the Physics department at Imperial College and in the Materials department at Oxford University. From 1992 to 1995 he was a Lecturer in Microstructural Science in the Materials department at Surrey University. Since 1996 he has been successively a Research Fellow in the Materials and Chemical Engineering department, Reader in Analytical Electron Microscopy (from 2000) and Professor of Nanomaterials Characterisation (from 2005) at Leeds University. Between 2010 and 2014 he was also a Co-Director at the Centre for Molecular Nanoscience in the School of Chemistry. He is currently Director of Research and Innovation in the School of Chemical Engineering. He has published over 400 academic papers, virtually all of which include electron microscopy data and its analysis. He also wrote an *RMS Handbook on Electron Energy Loss Spectroscopy* (Bios, 2001) recently contributed to chapter on Electron energy-loss spectroscopy and energy dispersive X-ray analysis to *RSC Nanoscience and Nanotechnology* (2015).

21. Counsel for Vectura made two main criticisms of Prof Drummond-Brydson's evidence. Due to scheduling difficulties, Prof Drummond-Brydson was unable to attend the repeats of Vectura's experiments and relied upon the written materials and what Mr Harrington told him. Counsel submitted that Prof Drummond-Brydson had not considered what Dr Reynolds had done with sufficient care and that Prof Drummond-Brydson had not approached the experiments with an open mind but concentrated on the theoretical limitations of EDX rather than analysing the actual data. I reject the latter criticism. As for the former, I think Prof Drummond-Brydson accepted that to begin with he had not fully appreciated precisely what Dr Reynolds had done, but any misunderstanding was cleared up in cross-examination.

Technical background

22. The parties did not prepare a technical primer in this case. Accordingly, the following account is based on the experts' reports. I shall generally express myself in the present tense, but unless otherwise stated I am referring to the position as at November 2000.

Pre-formulation

23. Pharmaceutical formulation starts with a process called pre-formulation, during which the physico-chemical properties (including, for example, solubility and stability) of the active pharmaceutical ingredient ("API") are determined, a salt form is selected (if required) and an understanding of different crystalline forms is developed. APIs can exist as crystalline forms or in an amorphous state. Due to their disordered molecular state, amorphous forms of API are generally less chemically stable, more hygroscopic and more variable in properties, than crystalline forms. Accordingly, it is generally preferable to develop inhalation formulations with crystalline forms of API.

Milling and micronisation

24. Milling and micronisation are processes of particle size reduction. Micronisation is a subset of milling usually regarded as being deployed to achieve a median particle size of between 1 and 10 μm. Crystalline APIs are usually prepared as reasonably large particles (at least 10s of μm in size). The formulation process for most APIs therefore generally starts with a milling (i.e. size reduction) step to produce particles with an appropriate median size for the intended formulation. Different formulation processes generally require a different median size of API particles. The most common form of mill for carrying out micronisation is an air jet mill (also known as a fluid energy mill).

Excipients

25. Pharmaceutical formulations rarely consist of API alone, rather they are usually a blend of API and one or more pharmacologically inactive ingredients called "excipients". Excipients are chosen and included in pharmaceutical formulations in order to (i) aid the formulation process by improving the handling and flow properties of the powder to allow large scale manufacture (including achieving uniformity of dose), and (ii) to achieve a product that will have a predictable therapeutic response and sufficient and reproducible quality, including features such as physical and chemical stability and suitable dissolution (as appropriate for the intended dosage form and route of administration). The excipients used and what roles they play will depend on the particular dosage form and route of administration (tablet, inhalation, etc.).

26. Tablets are the most frequently used dosage form. Common classes of excipients used in tablets include lubricants of various types. The most frequently used die-wall lubricant (an excipient that aids the removal of the formed tablet from the die of the tablet machine) is MgSt.

Homogeneity

27. Many APIs, especially those delivered directly to the lung for a local action, are highly effective at a low delivered dose (tens to hundreds of μg). The challenge is therefore to obtain a dosage form using micronised API particles that delivers a sufficiently reproducible low dose to the intended site of action each time the patient takes a dose. This can be called dose uniformity. In order to obtain dose uniformity of any API, it is necessary to obtain a suitably homogeneous blend between the API and the excipients that are used.

28. Agglomerates of either API or excipient can present issues when trying to obtain homogeneity of a blend, so it is common practice first to "de-lump" both API and excipient powders prior to blending (or mixing – the terms are interchangeable) them together. De-lumping is typically performed by passing a powder through a relatively coarse screen, with holes substantially greater than the size of the particles involved, in order to ensure that large aggregates of any particular component are broken up. As powders often tend not to flow through such screens unaided, it is usual to assist the passage through the screen by agitation. Typically, this is achieved on a small scale with a brush on a sieve, and on a larger scale with equipment such as a vibratory sieve or a cone mill.

29. Once de-lumped, the various ingredients are then blended to achieve an homogenous blend. I shall return to the question of the equipment used for this purpose below.

30. Due to their large surface to volume ratio, micronised particles tend to be influenced to a greater extent than larger particles by electrostatic charge. The effect of this is that micronised particles are relatively cohesive, and therefore they tend to agglomerate together. This tendency of micronised particles to agglomerate can negate the benefits of micronisation, by resulting in agglomerates that can be as large (or larger) than the original particles. This is detrimental to homogeneity, and hence dose uniformity. By 2000 it was well known that one way to address it was by using an "ordered mix" at the blending step.

Ordered mix

31. An ordered mix is one in which small particles, such as micronised API, are mixed with larger particles such that the small particles become adhered to the surface of the large particles, instead of each other. The large particles are described as "carrier particles". Lactose is often used as the carrier. The advantages of an ordered mix are that the large carrier particles are much easier to handle during processing as they are significantly less cohesive than micronised API, and so enhance flow. Furthermore, once an ordered mix has been created, it is generally stable, meaning it does not tend to segregate during handling and product manufacturing processes.

Anatomy and physiology of the respiratory tract

32. An understanding of the anatomy and physiology of the respiratory tract is essential in order to appreciate the challenges faced by the formulation scientist in developing pharmaceutical formulations for pulmonary administration. The primary concern of the formulator of an inhaled drug is to formulate and deliver the drug in such a way as to ensure the medicine reproducibly reaches the right area of the lung.

33. The respiratory tract can be divided into three main sections:

    i) the nasopharyngeal region which consists of the nose, nasal passages, the pharynx and the larynx;

    ii) the tracheobronchial (or conducting) region which consists of the trachea, bronchi and conducting bronchioles; and

    iii) the alveolar (or respiratory) region which consist of the respiratory bronchioles, alveolar ducts and alveoli.

34. The diameter of the airways in the respiratory tract decreases in size the further one moves towards the alveoli. There is also a progressive increase in the total surface area. There are also changes to the thickness and composition of the fluid layers throughout the lung. The upper airways contain a thick layer of watery mucus, which becomes thinner lower down in the lungs. In the alveolar region cells produce pulmonary surfactant which is a mixture of lipids and proteins. This surfactant is important in reducing the surface tension at the air-liquid interface to prevent the alveoli air sacs from collapsing during breathing.

35. When administering pharmaceuticals, the area of the respiratory tract which is to be targeted varies depending on the type of disease to be treated, and subsequently, the type of drug to be administered. For example, in the case of β2-agonists and steroids which are used for the treatment of common respiratory diseases such as asthma and COPD, the aim is to deliver the API locally to the bronchioles. As a result of the drug being directly targeted to its site of action, a lower dose is typically required using the pulmonary route of administration (as compared with oral administration) such that it can therefore be associated with reduced side effects. In such cases systemic uptake is to be avoided as far as possible. (In other cases, it may be desired to deliver a drug by pulmonary administration for systemic action.)

36. The physiology of the lung is such that only small particles (or droplets) can be inhaled and reach the relevant airways. In general terms inhaled particles with an aerodynamic size of greater than 10 μm will impact on the mouth and back of the throat, and so will not reach the lung. For effective inhalation and deposition in the lungs, particles with a median aerodynamic size in the region of about 1-5 μm are generally required. There are two types of size that are relevant for inhalation products. The first is the geometric size, which is the actual size that is observed (and measured) as the diameter of individual particles. The other is the aerodynamic size, which relates to how particles move in air streams and is often expressed as the mass median aerodynamic diameter ("MMAD"). The aerodynamic size is related to the geometric size by the density of the particles.

37. The physico-chemical properties of drug molecules can affect their fate once delivered into the lung. For example, if a drug is very hydrophilic, it will rapidly dissolve into the fluid which coats the airways and be cleared by absorptive mechanisms. Subject to the drug's site of action, this may or may not be advantageous. In contrast, very hydrophobic drugs will have reduced solubility in airway surface liquid and, to the extent that they are not insoluble and/or cleared by cilia (hair-like projections on cell surfaces) in the meantime, may be absorbed over a

longer period of time. Again, this may or may not be advantageous. Drugs for pulmonary use tend to be neither very hydrophilic nor very hydrophobic.

Inhalation devices

38. There are three main types of device for delivering inhalable medicinal products, namely nebulisers, pressurised metered dose inhalers (pMDIs) and DPIs. Nebulisers use compressed gases or ultrasonic vibration to disperse API containing solutions into droplets of an inhalable aerosolised form. pMDIs are handheld devices which rely on a pressurised gas to act as a driving force to propel either a suspension of micronised API or a solution containing API.

DPIs

39. DPIs are used to deliver an API in micronised dry powder form, typically blended with an excipient, to the lung to treat diseases such as asthma and COPD. They are handheld devices, set up so that, prior to the patient's inhalation, the API/excipient blend is exposed (for example, by opening a blister of drug within the device). Typically, the patient's own intake of breath then extracts the dose of powder from the inhaler (referred to as "actuation") and delivers the API to the lungs.

40. DPIs can be categorised as single and multi-dose, each with slightly different modes of operation. Some DPIs assist the release of the powder from the capsule using devices such as impeller or by using vibration. DPIs differ in the degree of turbulence they produce.

DPI formulation

41. The goal in DPI formulation is to achieve dose uniformity, that is to say, to have an acceptably uniform amount of the API liberated from the inhaler and carrier on each inhalation by the patient, and subsequently, to have a sufficiently reproducible amount of API reach the relevant part of the lung. A suitable formulation is achieved by formulating the powder such that the adhesion between the API and carrier is sufficiently strong to have the benefits of the larger particle size (of the carrier) during processing and filling of the powder in to the DPI, but also weak enough to allow the API to detach from the carrier to a consistent extent when the patient inhales, both throughout the duration of a single prescribed course of treatment and between different batches of product (i.e. between a prescribed course of treatment and subsequent ones). As mentioned above, the most frequently used carrier for DPI formulations is lactose.

Dosing terminology

42. DPIs generally have a claim for the mass of API per dose (i.e. the amount of API that is in a single dose capsule/blister for inhalation) known as the metered dose. It is well known that not all of the metered dose will be liberated from the inhaler upon actuation, as some will be left behind (e.g. particles stuck to the surfaces of the blister, device, etc). The dose that actually reaches the patient is known as the emitted dose or delivered dose. The emitted dose is significant for therapeutic effect and for the incidence of side effects

43. The most critical aspect in terms of therapeutic effect is the part of the emitted dose that reaches the targeted regions of the lungs. This is known as the fine particle fraction ("FPF"). The FPF is the fine particle dose divided by the emitted dose. It is also referred to as the respirable fraction. The remainder of the emitted dose is lost in places such as the patient's throat.

In vitro *testing of inhalable products*

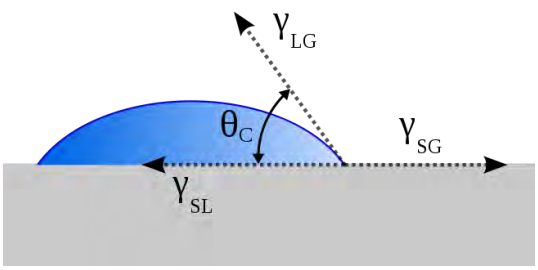
44. The degree to which API particles are expected to reach the lung can be tested using either a cascade impactor or impinger. Most commonly a twin-stage impinger ("TSI") is used. A TSI is a two-stage separation device made up of joined glass vessels. The upper stage is a simulation of the upper respiratory tract. The lower stage is a simulation of the lower respiratory tract (i.e. the lungs). The TSI collects the respirable dose in the lower impingement chamber of the device. A multi-stage impinger has more (often five) stages each with a different aerodynamic size cut off, allowing a more detailed understanding of the aerodynamic size distribution than a simple TSI. More recently, the next generation impactor ("NGI"), which also has multiple stages of different aerodynamic sizes and allows for collection of particles at each stage, has become available.

Dissolution and sustained release

45. Dissolution describes the process by which an API dissolves from a dosage form. The dissolution rate is directly proportional to the available surface area and solubility of the API in the solvent fluid.

46. There may be a desire to sustain the release of an API in order to reduce the frequency of dosing. One way of delaying dissolution is by the addition of hydrophobic materials. Such addition will slow dissolution, at least in part by covering surfaces and limiting fluid contact during dissolution.

47. It is possible to measure how hydrophilic or hydrophobic a particle is by measuring its contact angle. This can be done with both one- and multi-component systems. The measured contact angle is a composite of different contributing surfaces that the test liquid makes contact with. Thus, for example a heterogeneous surface made of two different particles will have a contribution from the extent of wetting of the test liquid on each material. It also follows that contact angle cannot be used to demonstrate that one material has coated another. The diagram below (from Wikipedia) shows the contact angle θ_c. In a spreading liquid, θ_c tends to zero. In a totally non-spreading drop, θ_c will approximate to 180^o.



The Patents

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48. The specification begins at [0002]-[0004] by explaining that it is known to treat patients with conditions such as asthma by pulmonary administration of "active particles" (i.e. particles comprising a pharmaceutically active material) using devices such as MDIs and DPIs. Particles with a mass mean aerodynamic diameter of greater than 10 μm generally do not reach the lung, but smaller particles are thermodynamically unstable and agglomerate. To improve the situation, powders for use in DPIs often include larger excipient particles referred to as carrier particles.

49. After acknowledging a number of items of prior art at [0006]-[0013], the specification states at [0014] that the first aspect of the invention is a method for producing "composite active particles" as claimed in claim 1. It continues:

> "[0015] The composite active particles are very fine particles of active material which have upon their surfaces an amount of the additive material. The additive material is preferably in the form of a coating on the surfaces of the particles of active material. The coating may be a discontinuous coating. The additive material may be in the form of particles adhering to the surfaces of the particles of active material. As explained below, at least some of the composite active particles may be in the form of agglomerates.
>
> [0016] When the composite active particles are included in a pharmaceutical composition the additive material promotes the dispersal of the composite active particles on administration of that composition to a patient via actuation of an inhaler. … The effectiveness of that promotion of dispersal has been found to be enhanced in comparison to a composition made by simple blending of similarly sized particles of active material with additive material."

50. At [0017] it is explained that the presence of the additive material on the surface of the active particles may confer controlled or delayed release properties and may provide a barrier to moisture.

51. The specification then states:

> "[0018] It has also been found that the milling of the particles of active material in the presence of an additive material produces significantly smaller particles and/or requires less time and less energy than the equivalent processes carried out in the absence of additive material. Using the method of the invention, it has been possible to produce composite active particles which have a mass median aerodynamic diameter (MMAD) or a volume median diameter (MD) of less than 1μm. It is often not possible to make such small particles by other milling methods.

> [0019] It is known that a milling process will tend to generate and increase the level of amorphous material on the surfaces of the milled particles thereby making them more cohesive. In contrast, the composite active particles of the invention will often be found to be less cohesive after the milling treatment."

52. At [0020] "milling" is defined as follows:

> "The word 'milling' as used herein refers to any mechanical process which applies sufficient force to the particles of active that it is capable of breaking coarse particles (for example, particles of mass medium aerodynamic diameter greater than 100μm) down to fine particles of mass median aerodynamic diameter not more than 50μm or which applies relatively controlled compressive force as described below in relation to the Mechano-Fusion or Cyclomix methods."

53. As is common ground, this definition encompasses two alternatives. The first involves reducing particle size diameter while the second involves applying "relatively controlled" compressive force.

54. The specification then explains why the application of a high degree of force is required:

> "It has been found that processes such as blending which do not apply a high degree of force are not effective in the method of the invention. It is believed that is because a high degree of force is required to separate the individual particles of active material and to break up tightly bound agglomerates of the active particles such that effective mixing and effective application of the additive material to the surface of those particles is achieved. It is believed that an especially desirable aspect of the milling process is that the additive material may become deformed in the milling and is smeared over or fused to the surface of the active particles. It should be understood, however, that in the case where the particles of active material are already fine, for example, having a mass median aerodynamic diameter below 20 μ[m] prior to the milling step, the size of those particles may not be significantly reduced. The important thing is that the milling process applies a sufficiently high degree of force or energy to the particles."

55. The specification goes on:

> "[0022] Where the additive particles are very small (typically < 1 micron), generally less work is required, firstly as it is not required to break or deform but only to deagglomerate, distribute and embed the additive particles onto the active particle and secondly because of the naturally high surface energies of such small additive particles. It is known that where two powder components are mixed and the two components

> differ in size there is a tendency for the small particles to adhere to the large particles (to form so called 'ordered mixes'). The short range Van der Waals interactions for such very fine components may be sufficient to ensure adhesion. However, where both the additive and active particles are very fine (for example less than 5 microns) a substantial degree of mixing will be required to ensure sufficient break-up of agglomerates of both constituents, dispersal and even distribution of additive particles over the active particles as noted above. In some cases a simple contact adhesion may be insufficient and a stronger embedding or fusion of additive particles onto active particles may be required to prevent segregation, or to enhance the structure and functionality of the coating.
>
> [0023] Where the additive particles are not so small as to be sufficiently adhered by Van der Waals forces alone, or where there are advantages to distorting and/or embedding the additive particles substantially onto the host active particles, a greater degree of energy is required from the milling. In this case the additive particles should experience sufficient force to soften and/or break, to distort and to flatten them. These processes are enhanced by the presence of the relatively harder active particles which acts as a milling media as well as a de-agglomerating media for such processes. As a consequence of this process the additive particles may become wrapped around the core active particle to form a coating. These processes are also enhanced by the application of a compressive force as mentioned above."

56. In [0025] the specification says that a wide range of milling devices and conditions are suitable for use in the method of the invention and that the milling conditions should be selected to provide the required degree of force. Ball milling is preferred, but a high pressure homogeniser may be more suitable for larger scale preparations. At [0026] especially preferred methods of milling are stated to be those involving the Mechano-Fusion, Hybridiser and Cyclomix instruments. At [0027] it is said that preferably the milling step involves the "compression of the mixture of active and additive particles in a gap (or nip) of fixed, predetermined width (for example, as in the Mechano-Fusion and Cyclomix methods described below) where the gap is not more than 10mm wide".

57. This is followed by a detailed description of milling with the Mechano-Fusion, Cyclomix and Hybridiser instruments. At [0029] it is explained that the Mechano-Fusion process is "designed to mechanically fuse a first material onto a second material". It is also said that the Mechano-Fusion and Cyclomix are "distinct from alternative milling techniques" and provide energy by "a controlled and substantial compressive force". It is said at [0030] that in the Mechano-Fusion the particles experience "very high shear forces and very strong compressive stresses" and "violently collide against each other with enough energy to locally heat and soften, break, distort, flatten and wrap the additive particles around the core particle to form a

coating." The Cyclomix is said in [0031] to produce "very high shear forces and compressive stresses" with effects similar to that of the Mechano-Fusion.

58. The Hybridiser is described at [0032] as follows:

> "This is a dry process which can be described as a product embedding or filming of one powder onto another. The fine active particles are fine or ultra fine additive particles are fed into a conventional high shear mixer pre-mix system to form an ordered mix. This powder is then fed into the Hybridiser. The powder is subjected to ultra-high speed impact, compression and share as it is impacted by blades on a high speed rotor inside a stator vessel, and is recirculated within the vessel. …. Typical speeds of rotation are in the range of 5,000 to 20,000rpm. The relatively soft fine additive particles experience sufficient impact force to soften, break, distort, flatten and wrap around the active particle to form a coating. There may also be a degree of embedding into the surface of the active particles."

It can be seen that this passage draws a distinction between the formation of an ordered mixture of active and additive particles using a "conventional high shear mixer" and the production of composite active particles using the Hybridiser.

59. At [0033] reference is made to "other preferred methods including ball and high energy media mills which are also capable of providing the desired high shear force and compressive stresses between surfaces".

60. At [0038] reference is made to the reduction of particle size of the API which may be of at least 10%, 50% or 70% during the milling step depending on the milling conditions used. At [0039] it is said that, advantageously, after the milling step the MMAD of the active particles is less than 9 μm. At [0040] reference is made to the additive particles being similarly reduced during milling and that "the size of the additive particles after the milling step is preferably significantly less than the size of the active particles, to enable the additive materials to more effectively coat the surfaces of the active particles". The coating is said preferably to be on average less than 1 μm thick and more preferably less than 0.5 μm thick and most preferably less than 200 nm thick.

61. At [0047] the specification contemplates, after milling, a de-agglomeration step involving mechanical breaking up of the unwanted agglomerates by (amongst other things) forcing them through a sieve.

62. From [0055] onwards, the nature of the additive material is described. Examples given include the amino acids leucine, isoleucine, lysine, valine, methionine and phenylalanine and salts of amino acids ([0061]); lecithin ([0063]); metal stearates including MgSt ([0064]); surface active materials including fatty acids ([0065]); sodium benzoate, hydrogenated oils, talc, certain metal dioxides and starch ([0066]).

63. The active particles are described from [0068] in broad terms as "comprising one or more pharmacologically active agents" and examples are given. Both dry form

preparations are contemplated and formulations which are milled in the presence of a liquid ([0074]-[0077]).

64. At [0084] it is explained that the pharmaceutical compositions for use in a DPI "may comprise essentially only the composite active particles or they may comprise additional ingredients such as carrier particles and flavouring agents". At the end of the paragraph it is said that preferably the carrier particles are of lactose.

65. At [0085] the size of the carrier particles is given in various ranges with a preference for 90% to be between 60 μm and 180 μm. It is explained that the inclusion of carrier particles can provide good flow and entrainment characteristics and improved release of the active particles in the airways.

66. At [0086] the specification states:

> "The ratio in which the carrier particles (if present) and composite active particles are mixed will, of course, depend on the type of inhaler device used, the type of active particles used and the required dose. The carrier particles may be present in an amount of at least 50% … based on the combined weight of the composite active particles and the carrier particles"

67. At [0087] the inclusion of fines with a particle size between 5 and 20 μm is contemplated.

68. At [0090] the specification states:

> "The invention also provides the use of an additive material as a milling aid in the milling of particles of active material. The term milling aid should be understood to refer to a substance which reduces the amount of energy required to mill the particles of active material and/or excipient material."

69. The specification describes six examples at [0093]-[0111]. In Example 1 micronized salbutamol sulphate with a particle size distribution of 1 to 5 μm and MgSt were milled in a stainless steel milling vessel with stainless steel balls for five hours at 550 rpm. An electron micrograph of the resulting powder is reproduced in Figure 1, but (like all the micrographs reproduced in the Figures) the quality of the reproduction is poor. The method was repeated using leucine and another electron micrograph is reproduced in Figure 2. The specification states at [0094] that the powders shown in the Figures "appear to have particles in the size range of 0.1 to 0.5μm". No other analysis is performed. Although the specification states when describing the Figures at [0091] that Figures 1 and 2 are SEMs "of the composite active particles of Example 1" the Example does not explain how it has been concluded that the particles shown are composite active particles.

70. Prof Birchall exhibited, and commented on, better copies of the SEMs reproduced in Figures 1 and 2 which had been provided to him by Vectura. I do not see the point of this evidence, since the better copies would not have been available to a skilled reader of 240. (Moreover, Figures 1 and 2 are not included in 241 or 763.) In any event, although Prof Birchall suggested that a discontinuous coating could be seen, his

evidence on this point was deeply unconvincing, focussing as it did on a 25 μm diameter particle which was not a composite active particle as contemplated by the specification because it would not reach the lungs. Furthermore, Prof Buckton and Prof Drummond-Brydson both gave unchallenged evidence that no surface coating could be seen.

71. In Example 1a micronised salbutamol sulphate and magnesium stearate were combined in a suspension of propanol and then processed in a high pressure homogeniser. The resulting particles are shown in Figure 3.

72. In Example 2 it is said that it was found that on drying the powder prepared in Example 1 using MgSt formed assemblies of particles which were hard to de-agglomerate. A sample of the powder was re-dispersed by ball milling for 90 minutes at 550 rpm in a mixture of ethanol, polyvinylpyridone (PVP) and HFA227 to produce a suspension suitable for use in a MDI. The composition was sprayed from a pressured can to produce dried composite active particles of salbutamol and MgSt with PVP. The particles, which are shown in Figures 4 and 5, were collected and found to be in the size range 0.1 to 4 μm.

73. In Example 4 MgSt was processed using a Silverson high shear mixer followed by a high pressure homogeniser to produce a particle size of less than 2 μm. This was blended with salbutamol sulphate using a spatula. The blend was then processed in a Mechano-Fusion mill, first at 1000 rpm for five minutes, followed by 5050 rpm for 30 minutes. Various ratios of salbutamol sulphate to magnesium stearate were used: 19:1, 9:1, 3:1 and 1:1.

74. The resulting particles were studied in two ways. First, electron micrographs of the 19:1 material were taken (Figures 9 and 10). The specification states at [0105] that these indicate that "the material was mostly in the form of simple small particles of diameter less than 5μm or in very loose agglomerates of such particles with only one agglomerate of the original type being visible". Nothing is said about a coating being visible.

75. Secondly, the 3:1 and 19:1 blends were then fired from a TSI and compared to a control of salbutamol only. The FPF obtained was calculated as a % of the total composition and the results set out in Table 1. More material was delivered as a FPF when MgSt was present (66% in both cases compared to 28%). There is no control consisting of either salbutamol in an ordered mix with lactose or salbutamol simply blended (rather than mechano-fused) with MgSt.

76. Although Prof Birchall suggested in his first report that a coating could be observed in Figures 9 and 10, he accepted in cross-examination that the skilled person would not be able to tell whether there was a coating from the images. Furthermore, Prof Buckton gave unchallenged evidence that Figures 9 and 10 did not enable the skilled reader to identify the nature of the association between the MgSt and active and that the FPF data in Example 4 did not inform the skilled reader as to the structure of the particles in the blend.

77. Example 5 describes a similar process to Example 4 using micronized glycopyrrolate and sodium salicylate, but no results are provided.

241

78. 241 uses the term "microparticles" rather than "composite active particles". The specification states:

> "[0012] The term 'microparticles' as used herein refers to particles of a size suitable for pulmonary administration or smaller, for example, having an MMAD of 10μm or less.
>
> [0013] The microparticles prepared using the method of the invention are able to release the active substance over a longer period than similarly-sized particles of the active substance alone and therefore a reduced frequency of administration, preferably only once a day or less, is possible. Furthermore, that delayed release of the active substance provides a lower initial peak of concentration of the active substance which may result in reduced side effects associated with the active substance.
>
> [0014] The hydrophobic material will be suitable for delaying the dissolution of the active substance in an aqueous medium. A test method for determining whether a particular hydrophobic substance is suitable for delaying that dissolution is given below. The test may also be used for determining the extent of the reduction in the rate of dissolution and references herein to a reduction in that rate are to be understood as referring to the test given below. An alternative measure of hydrophobicity is the contact angle. The contact angle of a material is the angle between a liquid droplet and the surface of the material over which it spreads. The hydrophobic material preferably has a contact angle of more than 90°, more preferably more than 95° and most preferably more than 100°. The skilled person will be aware of suitable methods of measuring the contact angle for a particular substance."

79. From [0020] lists of suitable hydrophobic materials are set out including magnesium stearate.

80. At [0038] the specification states:

> "The invention will be of particular value where the active substance is one which exerts its pharmacological effect over a limited period and where, for therapeutic reasons, it is desired to extend that period. Preferably, the microparticles comprise an active substance that, when inhaled; exerts its pharmacological effect over a period of less than 12 hours, the microparticles being such that the active substance exerts its pharmacological effect over a period greater than 12 hours. The duration of the pharmacological effect for any particular active substance can be measured by methods known to the skilled person and will be based on the administration of the dose of

> that, substance that is recognised as being optimal for that active substance in the circumstances."

81. The specification then largely mirrors the specification of 240. At [0048] it is explained that the microparticles according to the invention may be formulated on their own or used in formulations comprising additional ingredients such as carrier particles. The teaching of the need for milling and the requirement of more than mere contact adhesion is at [0055]-[0058] and mirrors [0020]-[0023] of 240.

82. The examples are based upon the same formulations. Examples 1a and 1b are essentially the same as Example 1 and 1a in 240. Example 1c is the same as Example 2 in 240, and Example 2 is the same as Example 3 in 240.

83. Example 3 is new and comprises milling micronised glycopyrrolate and magnesium stearate in a ratio of 75:25 in cyclohexane. Samples were taken after 60 minutes and subject to a dissolution test. Data is produced at Figure 2. It shows delayed dissolution over a control of pure drug without magnesium stearate.

84. Example 4 is the same as Example 4 in the 240 Patent except there is additional text at [0101] and [0102] describing a process for spray drying at 3:1 blend of salbutamol/magnesium stearate which is subject to a dissolution test and the results compared to a 3:1 blend (not spray dried).

The claims

85. Vectura only rely upon claims which require the MgSt to form a coating on the surface of the active. These claims are as follows.

240

86. Vectura relies upon claim 15 as dependent on claims 13, 12 and 1. Claim 1 is as follows:

> "A method for making composite active particles for use in a pharmaceutical composition for pulmonary administration,
>
> the method comprising a milling step in which particles of active material are milled in the presence of particles of an additive material
>
> so as to ensure a sufficient break-up of agglomerates of both active material and additive material, dispersal and even distribution of the additive material over the active material,
>
> and so that the particles of additive material become fused to the surface of the particles of active material,
>
> wherein the additive material is suitable for the promotion of the dispersal of the composite active particles upon actuation of an inhaler,
>
> wherein the milling step involves:

> (a) passing a mixture of particles of additive material and particles of active material, in a liquid, through a constriction under pressure;
>
> (b) use of a high pressure homogeniser in which a fluid containing the particles is forced through a valve at high pressure producing conditions of high shear and turbulence;
>
> (c) compressing a mixture of the active particles and additive particles in a gap of predetermined width;
>
> (d) ball milling; or
>
> (e) air jet milling particles of additive material with particles of active material,
>
> wherein the additive material includes a metal stearate or derivatives thereof
>
> and wherein the gap is not more than 10mm wide."

87. Claim 12 is as follows:

> "A method as claimed in any preceding claim wherein the metal stearate is zinc stearate, magnesium stearate, calcium stearate, sodium stearate or lithium stearate."

88. Claim 13 is as follows:

> "Composite active particles for use in a pharmaceutical composition obtainable by a method as claimed in any one of claims 1 to 12."

89. Claim 15 is as follows:

> "Composite active particles as claimed in claim 13 or claim 14, in which the additive particles form a coating on the surfaces of the particles of active material, preferably in which the coating is a discontinuous coating and/or in which the coating is not more than 1 μm thick."

817

90. Vectura relies upon claim 10 as dependent on claims 8 and 1. Claim 1 is as follows:

> "A method for making composite active particles for use in a pharmaceutical composition for pulmonary administration,
>
> the method comprising a milling step in which particles of active material are milled in the presence of particles of an additive material which is suitable for the promotion of the

> dispersal of the composite active particles upon actuation of an inhaler,
>
> wherein the composite active particles have, smeared over or fused on their surfaces an amount of additive material in the form of particles adhering to the surfaces of the particles of active material,
>
> wherein after the milling step the mass median aerodynamic diameter of the composite active particle is not more than 10 μm as determined using a multi stage liquid impinger,
>
> and wherein the additive material comprises magnesium stearate"

91. Claim 8 is as follows:

> "Composite active particles made according to claim 1-7 for use in a pharmaceutical composition for pulmonary administration,
>
> each composite active particle comprising a particle of active material and a particle of additive material smeared over or fused on the surface of that particle of active material,
>
> the composite active particles having a mass median aerodynamic diameter of not more than 10 μm as determined using a multi stage liquid impinger
>
> and the additive material being suitable for the promotion of the dispersal of the composite active particles upon actuation of a delivery device,
>
> and wherein the additive material comprises magnesium stearate"

92. Claim 10 is as follows:

> "Composite particles as claimed in claim 8 or 9, in which the additive particles form a coating on the surfaces of the particles of active material, preferably wherein the coating is a discontinuous coating."

818

93. Vectura relies upon claim 10 as dependent on claims 8, 3 and 1. It is common ground that this does not require separate consideration from 817.

241

94. Vectura relies upon claim 10 or 11 as dependent on claims 3 and 1. Claim 1 is as follows:

> "A method of preparing microparticles exhibiting delayed dissolution for use in a pharmaceutical composition for pulmonary administration, comprising
>
> the step of combining particles of an active substance with particles of a hydrophobic material by milling particles of the active substance in the presence of particles of the hydrophobic material
>
> so that the particles of hydrophobic material become fused to the surfaces of the particles of active substance."

95. Claim 3 is as follows:

> "A method as claimed in claim 2, wherein the hydrophobic material comprises magnesium stearate."

96. Claim 10 is as follows:

> "A method as claimed in any of claims 1 to 9, wherein the particles of hydrophobic material are present as a coating on the surface of the particles of active substance."

97. Claim 11 is as follows:

> "A method as claimed in claim 10, wherein the coating is a discontinuous coating."

763

98. Vectura primarily relies upon claim 1 as unconditionally proposed to be amended:

> "Microparticles for use in a pharmaceutical composition for pulmonary administration, comprising
>
> particles of an active substance having, on their surfaces, particles of a hydrophobic material present as a coating on the surface of the particles of active substance
>
> and suitable for promoting the dispersal of the active particles on actuation of an inhaler
>
> and suitable for delaying the dissolution of the active substance wherein the hydrophobic material comprises a metal stearate."

99. The conditional amendment adds "and wherein the coating covers at least 50% of the total surface area of the active particles".

100. To the extent necessary, Vectura also relies upon claims 2, 7 and 13 (claim 12 as proposed to be amended) which limit the claims to MgSt and to a discontinuous coating.

The skilled person

101. There is no dispute as to the identity of the skilled person to whom the Patents are addressed. The Patents are addressed to a formulation scientist with an interest in (and experience of) formulating pharmaceuticals for delivery by inhalation both at laboratory scale and on a larger scale for manufacture. In practice, the formulator would be part of a wider drug development team comprising specialists such as clinicians, toxicologists and regulatory personnel. The formulator would have access to appropriate analytical skills and be likely to have expertise in interpreting SEM images.

Common general knowledge

102. There is no dispute that all of these matters I have set out in the technical background section were common general knowledge.

MgSt

103. The use of MgSt as an excipient was well known in November 2000. If and to the extent that the skilled person was not familiar with (or could not remember) its properties, he or she could readily ascertain them by consulting either Aulton or Kibbe's *Handbook of Pharmaceutical Excipients* (3rd edition, 2000).

104. Accordingly, there is no dispute that the following properties of MgSt were common general knowledge:

i) it is hydrophobic;

ii) it was most frequently used as a die-wall lubricant in tabletting;

iii) when used in tabletting, MgSt may delay dissolution of the tablet. The degree to which this takes place can be decreased or increased by decreasing or increasing the mixing time of MgSt with the tablet powders:

iv) when blended with a powder, it covers the surfaces of the particles and results in changes in adhesion between the covered surfaces. This covering also causes the surfaces of the particles to be more hydrophobic (and therefore to delay dissolution);

v) the lowest amount of MgSt which achieved the required function should be used, but the amount to be used, and the degree of mixing to be used, would be determined empirically;

vi) there are a number of forms of MgSt. Furthermore, commercially available MgSt can vary in its properties from batch to batch; and

vii) MgSt, when blended with other powders, would spread over the surfaces of any other ingredients in the blender.

High-shear blenders

105. Somewhat surprisingly, the principal dispute with respect to common general concerns the use of high-shear (or high-speed) blenders (or mixers). There is no dispute that such blenders were commercially available in November 2000. Nor is there any dispute that the skilled person would be aware of high-speed blenders and their use for other purposes, such as making tablets. The issue is whether their use for making DPI formulations was common general knowledge, as GSK contend. Vectura disputes this.

106. It is common ground that DPI formulations were generally prepared on a laboratory scale using a tumbling mixer such as Turbula. GSK contend, however, that high-shear blenders were commonly used when making such formulations on a larger scale.

107. Prof Buckton's evidence in paragraph 5.31 of his first report was that by 2000 "a wide variety of mixers and mixer types were in common usage and well-known to the Formulator [including] tumbling mixers …, low shear mixers … and high shear mixers …". (He had previously defined "the Formulator" as a formulation scientist with a practical interest in and experience of developing inhalable pharmaceutical products.) In paragraph 9.4 he said that Fielder TRV blenders (a brand of high-shear blender) were commercially available in November 2000 and were "known as a preferred method for efficient blending of powder blends for inhalation". In paragraph 10.3 he said that the Formulator would "appreciate that [a tumbling blender] is not usually preferred when handling the larger quantities used in a production process", and would consider a TRV blender to be "standard" for inhalation formulations. In paragraph 10.8 he said that the Formulator would consider a TRV blender "an obvious choice for clinical trial and production scale processes of a DPI formulation".

108. In paragraph 2.4 of his third report, replying to Prof Birchall's first report, Prof Buckton said:

> "As I mentioned in paragraph 5.31 of my first report, high-shear mixers formed part of the common general knowledge of the Formulator and were typically used when transferring from development studies in the laboratory to production, where larger volumes of material were required to be blended. The purpose of using a high-shear blender in these circumstances (such as a TRV) is to achieve the same degree of homogeneity that was achieved in development scale using equipment such as a Turbula mixer. The use of a high-shear blender in these circumstances is not intended to change the character of the product that was developed at the laboratory scale, in fact the intent is to reproduce that product at the larger scale."

109. Prof Buckton went on in paragraph 2.6 to note that a brochure produced by GEA (which took over Fielder) in 2015 exhibited by Prof Birchall stated under the heading "TRV – High Shear Blending":

> "For more than 40 years, Turbo Rapid machines have delivered high intensity blending solutions for dry powders. The unique, high speed, TRV impeller blades provide the homogeneity and

> stability that are key factors in the production of inhalable drugs."

He added in paragraph 2.7 that high-shear blenders were not understood to effect a reduction in the size of carrier particles in a dry powder formulation.

110. Counsel for Vectura pointed out in cross-examination that Prof Buckton had not exhibited any documents to support his evidence concerning high-shear blenders. Prof Buckton's response was that he did not think that it was necessary to demonstrate "something which is so standard". In my view Prof Buckton can be forgiven for not appreciating that the point was as much of an issue as it turned out to be. Thus it was not even mentioned in Vectura's skeleton argument. Be that as it may, two documents were put in evidence by GSK which are relied upon as supporting Prof Buckton's evidence. I shall consider these below.

111. In his oral evidence Prof Buckton said that, when scaling up the manufacture of DPI formulations, it was normal to use a high-shear blender because it was difficult to achieve adequate homogeneity using a tumbling mixer at larger scales than laboratory scale. His recollection was that half a dozen major pharmaceutical companies had been using high-shear mixers for this purpose in 2000, and he was not aware of anyone who scaled up using a tumbling mixer. Counsel for Vectura submitted that Prof Buckton's position had become "far more extreme" than that he had taken in his written evidence. I do not agree with this: it was more firmly expressed and more fully explained, but the thrust of it was essentially the same. Counsel for Vectura also submitted Prof Buckton's recollection was mistaken. I accept that memory is fallible and that Prof Buckton could have been in error in thinking that the position was as he described it in November 2000. The reasons he gave for using a high-shear blender, however, were practical technical reasons. It was not suggested that he was wrong about those, and they are supported by the reference books referred to below. Moreover, there is no reason to suppose that anything material changed between November 2000 and, say, 2008 (which is when Pharmaterials acquired a high-shear blender according to Prof Buckton). Still further, Prof Buckton's recollection is supported so far as what GSK were doing by the evidence cited below. There is no reason to think that GSK's approach was unusual in this respect.

112. Turning to Prof Birchall, he said in paragraph 47 of his first report that, when developing a process on a larger scale than laboratory scale, "the skilled person would aim to optimise the mixing process using a tumbling mixer or a Turbula blender". In paragraph 20 of his third report he said that he was not aware of high-shear mixers being used for formulations for inhalation in 2000 and his view was that the same would be true for the skilled person. He also said that tumbling mixers were available in industrial scale sizes. In paragraph 21 he said that "the skilled person would not consider high shear mixers for inhalable formulations" because it would introduce a lot of static charge and heat and there would be an increased likelihood of particle size reduction.

113. In cross-examination, however, it became clear that Prof Birchall had had less experience of industrial processes in 2000 (or subsequently) than Prof Buckton. He first became aware of high-shear blending in the context of DPIs when preparing for this case. He accepted that tumbling mixers might not be suitable for fine particulate systems because there was not enough shear to reduce particle agglomeration,

although it was also necessary to avoid disadvantaging the interaction between the drug and the carrier.

114. As noted above, GSK rely upon two documents as supporting Prof Buckton's evidence. The first is an article by Anne Brindley *et al*, "Design, Manufacture and Dose Consistency of the Serevent Diskus Inhaler", *Pharmaceutical Technology Europe*, January 1995, 14-22. This article describes the design and manufacture of GSK's Serevent Diskus DPI. It states *en passant* at page 17 that "The micronized drug substance is blended with the lactose in a high-speed mixer". There is nothing to suggest that this method is regarded by the authors as unusual or worthy of comment; it is simply part of a flat description of the manufacturing process.

115. It is convenient to note at this point that Mr Roche gave evidence that GSK had used TRV25 blenders in the manufacture of their Flovent Diskus DPI which were submitted to the US Food and Drug Administration in 1988, approved in 2000 and launched in 2000 or 2001.

116. The second document relied upon by GSK is an extract from Herbert Lieberman *et al* (eds), *Pharmaceutical Dosage Forms Volume 2: Tablets* (2nd edition, 1990). This mentions high-speed mixers at page 41, says that tumbling-type blenders are not suitable for fine particulate systems because there may be not be enough shear to reduce particle agglomeration at page 44 and states in a summary of mixing problems and suggested approaches in Table 10 at page 63 that a solution to the problem of "poor-flowing cohesive powders in general" is to "use high-shear equipment". As counsel for Vectura pointed out, this book is not concerned with DPI formulations. The advice I have just quoted, however, is entirely general in nature. Moreover, Prof Birchall disclaimed any suggestion that the skilled person would be prejudiced against using a high-speed mixer.

117. Against this, Vectura relies upon a number of academic papers concerning DPI formulations exhibited by Prof Buckton and Prof Birchall which mention the use of tumbling mixers. The same is true of the examples in the prior art (with one exception discussed below). There are also a couple of papers that report the use of high-shear mixing for a drug that is said to be "not amenable to conventional methods" of DPI formulation using tumbling mixers. As Prof Buckton pointed out, however, all these authors were reporting laboratory scale preparations.

118. Vectura also relies upon two reference books which in my view lend more support to GSK's case than to Vectura's. The first is Aulton (2nd edition). In a section on "Mixing of powders" this states at page 191:

> "The mixer used should produce the mixing mechanisms appropriate for the formulation. For example, diffusive mixing is generally preferable for potent drugs, and high shear is needed to break up agglomerates of cohesive materials and ensure mixing at a particulate level. The impact or attrition forces generated if too-high shear forces are used may, however, damage fragile material and so produce fines."

119. At page 192 Aulton states:

> "Tumbling mixers are good for free-flowing powders/granules but poor for cohesive/poorly flowing powders, because the shear forces generated are usually insufficient to break up any aggregates. A common use of tumbling mixers is in the blending of lubricants … with granules prior to tableting.
>
> Tumbling mixes can also be used to produce ordered mixes, although the process is often slow because of the cohesiveness of the adsorbing particles."

120. Under the sub-heading "Scale-up of powder mixing" Aulton states at pages 193-194:

> "The extent of mixing achieved at a small laboratory scale during development work may not necessarily be mirrored when the same formulation is mixed at a full production scale, even if the same mixer design is used for both. Often, mixing efficiency and the extent of mixing is improved on scaleup owing to increased shear forces. This is likely to be beneficial in most cases, although when blending lubricants care is needed to avoid overlubrication …
>
> The optimum mixing time and conditions should therefore be established and validated at a production scale, so that the appropriate degree of mixing is obtained without segregation, overlubrication or damage to component particles … "

121. Vectura also relies upon Lloyd Allen and Howard Ansel, *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems* (10th edition, 2013), although this was published long after the priority date. Again, it seems to me that this is more supportive of GSK's case than Vectura's, The passage relied on at page 224 states:

> "Another method of mixing powders is tumbling the powder in a rotating mixer in a rotating chamber. Special small-scale large-scale motorized powder blenders mix powders by tumbling them … Mixing by this process is thorough but time-consuming. Such blenders are widely employed in industry, as are mixers that use motorized blades to blend powders in a large vessel."

My understanding is that "mixers that use motorized blades" are generally high-shear blenders.

122. Finally, GSK rely upon the reference in 240 at [0032] to making an ordered mixture of active and additive particles using "a conventional high shear mixer". On Vectura's case, the skilled person would be perplexed by this, as he would not be aware of the use of high-shear mixers for this purpose.

123. Overall, I find the evidence of Prof Buckton, supported as it is by the evidence concerning GSK's processes in 1995 and 1998-2000 as well the reference books and [240] at [0032], persuasive. Accordingly, I conclude that the use of high-shear

blenders to make DPI formulations on a larger scale was common practice, and in that sense common general knowledge, in November 2000.

Construction

124. Although it appeared at the beginning of the trial that there were a number of potential issues of interpretation of the claims, in the end there were only two. It is also important to note certain points on which there was agreement.

Composite active particles

125. It is common ground that this expression means that the additive particles have been structurally combined with the active particles to make composite particles so that they remain attached before, during and after actuation from the inhaler. It is also common that the expression "microparticles" in the WO072 Patents should be interpreted in the same manner.

Fused to the surface/smeared over or fused on the surface

126. Claim 1 of 240 requires that "the particles of additive material become fused to the surface of the particles of active material". Essentially the same language is to be found in claim 1 of 241 (save that "hydrophobic" is used rather than "additive"). Claim 1 of 817 requires that "the composite active particles have, smeared over or fused on, their surfaces an amount of additive material". It is common ground that these phrases are all ways of describing the same concept, namely that the structure of the additive particles is altered in the milling process so that they become structurally combined with the surface of the active particles. The additive particles no longer keep their original particulate shape and instead deform over the surface of the active particles (i.e. so as to form a coating, which may be discontinuous).

Form a coating

127. Claim 15 of 240 requires that the additive particles "form a coating on the surfaces of" the active particles. Essentially the same language is to be found in claim 10 of 817, claim 10 of 241 and claim 1 of 763 (as unconditionally proposed to be amended). It is common ground that the coating may be discontinuous. It is also common ground that this requirement adds little, if anything, to the requirement that the additive particles be fused to/smeared over the surfaces of the active particles.

Milling

128. There are two issues concerning the requirement in claim 1 of 240 and claim 1 of 1 of 817 for "a milling step in which particles of active material are milled in the presence of particles of an additive material" and the similarly worded requirement in claim 1 of 241 (but not 763).

129. The first issue is whether, as GSK contend, these claims, and those dependent on them, require the milling of the active and the additive particles to take place in the absence of any carrier, such as lactose. The second is whether, as GSK contend, these claims require particle size reduction (or whether the absence of size reduction of

lactose particles can be used to judge whether milling has taken place). Vectura disputes that the claims require either of these things.

130. *Milling in the absence of carrier?* It is common ground that Example 4 describes milling of the active and MgSt without the carrier present. On their face, however, the claims are indifferent as to whether or not carrier particles are also present when the milling step takes place.

131. In support of reading this limitation into the claims, GSK rely on [0086], which states that "the ratio in which the carrier particles (if present) and composite active particles are mixed [...]". They say that this indicates that the composite active particles must have been formed prior to mixing with the carrier particles.

132. Against this Vectura relies on [0090], which explains that milling aids can be used to reduce the amount of energy required to mill "the particles of active material and/or excipient material". Vectura contends that this makes it clear that an option is to mill particles of active material and excipient material together. Lactose is described as an excipient material in [0084]. In addition, Examples 2 and 3 contain excipients which are milled together with the active and the MgSt.

133. In my judgment Vectura's construction of the claims is the correct one. This is because the wording of the claims covers milling with carrier present. The fact that the carrier is absent in Example 4 does not justify reading such a limitation into the claims. Nor is this justified by [0086], which is concerned with the ratio between the carrier particles and the composite active particles rather than the order in which they are mixed.

134. In any event, as Vectura points out, GSK's reliance on [0086] cannot apply to the WO702 Patents, neither of which contains this teaching in their specifications (indeed 763 is not limited to any particular process steps). Save for teaching that lactose may be used in the formulation as a carrier (at [0048] in both) these two Patents say nothing about how it might be milled.

135. *What is milling?* It is common ground that the definition of "milling" in [0020] of 240 has two alternatives. On the face of it, only the first one involves particle size reduction of the active material, whereas the second merely involves the use of controlled compressive force. GSK nevertheless contend that the second alternative implicitly requires particle size reduction. In alternative GSK contend that the second alternative requires the use of either a Mechano-Fusion or Cyclomix instrument or a device which produces the essentially same compressive forces as those devices.

136. In my judgment Vectura's construction is again the correct one. The specification makes it clear at [0020] that "the particles size may not be significantly reduced" and that "the important thing is that the milling process applies a sufficiently high degree of force or energy to the particles". As Prof Buckton explained, the skilled person would understand that the technical purpose of the milling step was to exert a sufficient high degree of force to deform the additive material and not to achieve milling of the active material *per se*.

137. Counsel for Vectura submitted that the criterion for what constituted a sufficiently high degree of force was whether it achieved the required result, namely to fuse/smear

the additive particles onto the surfaces of the active particles to form a coating. I accept this submission, which accords with the technical purpose of the requirement for a milling step.

GSK's products and processes

138. Three GSK products are alleged to infringe the Patents. Relvar Ellipta comprises vilanterol as one of its two APIs. Incruse Ellipta comprises umeclidinium as the API. Anoro Ellipta comprises both vilanterol and umeclidinium. It contains two formulations: a formulation of vilanterol, MgSt and lactose monohydrate ("the Vilanterol Blend") and a formulation of umeclidinium, MgSt and lactose monohydrate ("the Umeclidinium Blend").

139. The process used by GSK to make the Vilanterol Blend and the Umeclidinium Blend is set out in GSK's PPD. In summary, GSK first pre-blend lactose and MgSt in a high-speed blender, namely a TRV25 or TRV65 blender. These differ in size and are used for different batch sizes. They then de-lump the active by mixing the active with a portion of the lactose/MgSt mix in a Quadro Comil U5 at 1500 rpm for about 1 min. A Comil is a device with an impeller which forces the mixture against a conically-shaped screen with holes. Following this de-lumping step, the rest of the lactose/MgSt is added to the active and the entire mix is again placed in the TRV for further blending using cooling jackets. The vilanterol blend is subjected either to 550 rpm or 480 rpm (depending on the TRV used) for 8.5 minutes. The umeclidinium blend is subjected either to 590 rpm or 460 rpm for 10 minutes.

Infringement

140. GSK dispute infringement for five main reasons. First, GSK deny that their process includes a milling step where this is required. Secondly, GSK rely on the fact that, if they mill, they do so in the absence of the lactose. Thirdly, GSK dispute that the MgSt particles become structurally combined with the active particles to form composite active particles. Fourthly, GSK dispute that the MgSt is fused to/smeared over the surfaces of the active particles so as to form a coating. Fifthly, GSK dispute that the MgSt is evenly distributed over the active material as required by claim 1 of 240. As I have construed the claims, however, the second reason falls away. The third, fourth and fifth reasons can be considered together. There is no dispute as to the remaining requirements of the relevant claims, such as delayed dissolution.

Milling

141. There is no dispute that there is no substantive reduction in particle size in the GSK process overall. Accordingly, if particle size reduction is required for milling, then GSK do not mill. As I have construed the claims, however, this is not a requirement. Accordingly, the question is whether the TRV blenders employed by GSK exert a sufficiently high degree of force to deform the MgSt.

142. GSK contend that it has not been shown by Vectura that the TRV blenders exert the same degree of compressive force as a Mechano-Fusion or Cyclomix (or Hybridiser) instrument. When Prof Birchall was asked about this, he accepted that the degree of force exerted by the TRV would be different to that exerted by the Mechano-Fusion instrument. It was not put to Prof Buckton that the degree of force exerted by the TRV

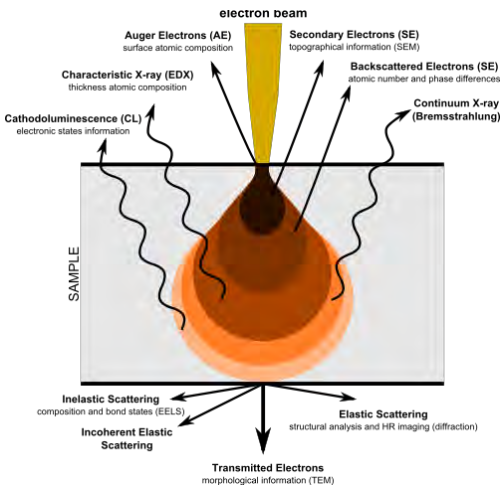
would be the same as that exerted by Mechano-Fusion, Cyclomix or Hybridiser instruments. Accordingly, I find that the TRV would exert a lesser degree of force than those instruments. That is not the end of the matter, however. As I have construed the claims, the remaining question is whether the force exerted by the TRV is sufficient to achieve the claimed result. That depends on what the result of GSK's process is.

Composite active particles, fused to/smeared over, to form a coating

143. Vectura relies upon the results of the SEM and EDX experiments carried out by the parties to establish that these integers of the claims are satisfied by GSK's process and products. GSK challenge the suitability of these techniques for this purpose. This gives to issues both on infringement and validity, and in particular insufficiency.

144. Before turning to the experiments, however, it should be noted that, as counsel for Vectura pointed out, there is no dispute that (as was common general knowledge in November 2000) MgSt covers the surfaces of particles when blended with a powder, and the more energetic and/or the longer the blending the more this will occur. Thus it is inherently likely that MgSt will coat the lactose particles in the first stage of GSK's process and it would not be surprising if some of the MgSt was transferred to the active particles in the second and third stages. It does not necessarily follow, however, that the MgSt will structurally combine with the active particles or become fused to/smeared over to the surfaces of the active particles.

145. *SEM*. SEM is a technique which enables high resolution images of a sample surface to be generated. A fine beam (about 10 nm in diameter) of electrons (referred to the incident electron beam) sweeps across the sample and travels into the sample in a region called the interaction volume. The interaction volume has a teardrop shape extending below the surface of the sample, as shown in the illustration below (I take this from the first report of Dr Reynolds, who took it from Wikimedia).



146. Secondary electrons are produced from the top 30 nm or so of the sample and are detected. A two-dimensional greyscale image of the sample surface can then be created. SEM on its own cannot be used to determine the chemical composition of the sample under examination. SEM can, however, be combined with EDX to obtain information about the elemental composition of the sample.

147. Counsel for Vectura did not suggest in closing submissions that it was possible to determine whether the active particles in GSK's products were coated with MgSt using SEM alone. Since this suggestion was advanced by Prof Birchall in his evidence, however, I shall deal with it. There are two problems with the suggestion. The first is that, as Prof Buckton pointed out, Prof Birchall compared post-processing images at high magnification with pre-processing images at low magnification. The second is that there was no control because no starting material was put through the blending processes in the absence of MgSt. When cross-examined on these points, Prof Birchall was uncomfortable and unconvincing, for example, resorting to his general experience when he had never seen vilanterol or umeclidinium particles prior to these proceedings.

148. *EDX*. The interaction of the incident electron beam with the sample also results in the emission of X-rays. These emanate from the entire interaction volume (and not just from the surface). Characteristic peaks present in the X-ray spectra can be used to identify the elements present in the interaction volume. The EDX machine will label significant peaks automatically, but it is good practice to check manually since peaks may be mislabelled or not labelled. A generally accepted rule of thumb is that a peak which is three times the level of the background radiation is a reliable indicator that the relevant element is present.

149. EDX also permits what is termed X-ray or EDX mapping. In contrast to point or small area X-ray spectra, which only provide information about the presence of elements within a point or small area of a sample, EDX maps provide information about both the presence and spatial distribution of elements within a larger area of a sample. The operator selects elements they wish to map and specifies a field of view. The machine then scans the incident electron beam across the field of view producing pixel spectra which are then used to build up a map.

150. It is common ground that EDX has certain limitations as a technique for present purposes. It will be convenient to consider these after describing Vectura's experiments.

151. *Vectura's experiments*. Each of the starting materials (being MgSt, vilanterol, umeclidinium and lactose monohydrate) were first subjected to analysis. The elemental signatures for MgSt, vilanterol and umeclidinium each contain a unique element and are therefore sufficiently different from each other to be identified and distinguished. The relevant peaks are those for magnesium (1.25 keV), chlorine (2.62 keV) and bromine (1.48 keV) respectively. The elemental signature for lactose monohydrate does not contain any unique elements, and is not therefore sufficiently different from those of MgSt, vilanterol and umeclidinium for lactose to be identified in these experiments.

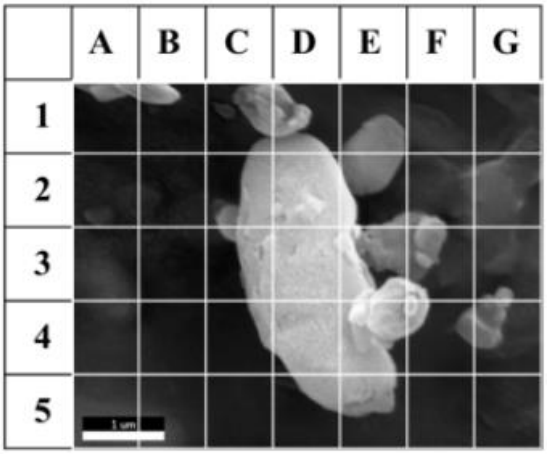
152. Samples of the pre-actuated Vilanterol and Umeclidinium Blends were analysed. Samples were also collected post-actuation by connecting the Anoro product to an NGI. Particles deposited on a carbon tab collected from stages 3 and 6 of the NGI should have a particle size of less than 5 μm (representing what would be present in the lung). The inhaler was actuated eight times to collect sufficient post-actuation particles for analysis. SEM/EDX analysis was then conducted at both lower and higher magnification for the post-actuation samples collected from stage 3 of the NGI and at lower magnification only for post-actuation samples collected from stage 6 of

the NGI. Vectura's experiments were carried out and repeated by Dr Reynolds for Vectura and were also repeated by Mr Harrington under Prof Drummond-Brydson's supervision for GSK.

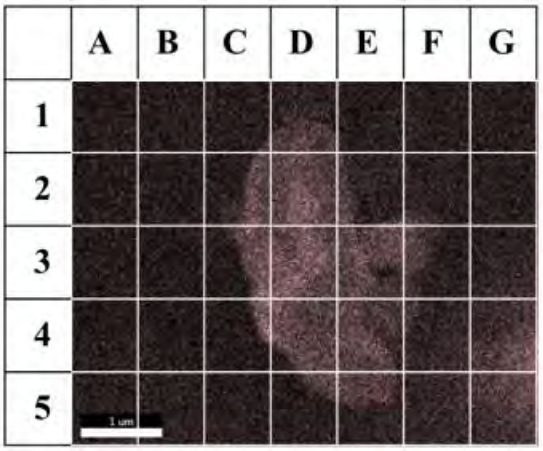
153. The most important analyses are those done at the higher magnification relating to particles collected from stage 3 of the NGI. These show the actuated particles as they are likely to be in the lung. Vectura contend that they show the presence of composite active particles of MgSt and active.

154. Dr Reynolds included in his first report as an example an SEM image and corresponding EDX maps for one of the vilanterol particles, overlaid with a grid to assist in identification of the components. These are reproduced below.

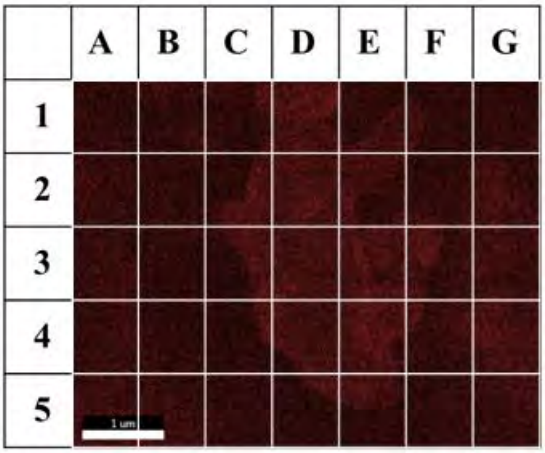
SEM image



EDX map for chlorine (pink)



EDX map for magnesium (red)

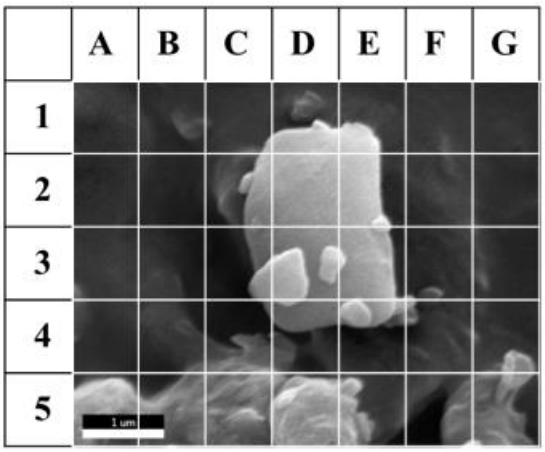


155. Vectura contend that, when the SEM image is compared with the two EDX maps, it can be seen that the largest particle in the SEM image is giving a chlorine signal (indicating that it is a vilanterol particle) in the first EDX map and a magnesium signal (indicating the presence of MgSt) in the second EDX map. Vectura say that the

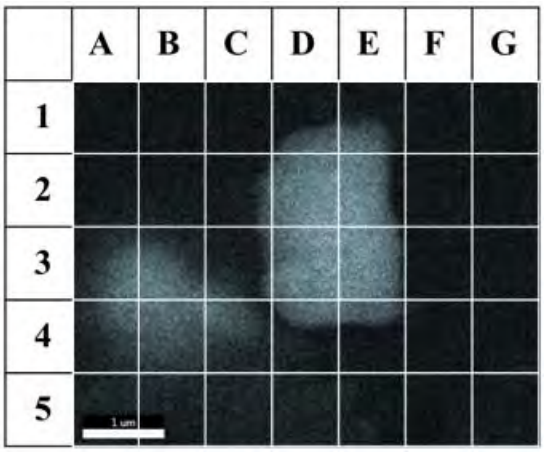
level of magnesium signal together with the fact that it corresponds well with the shape of the largest particle on the SEM image shows that the MgSt is present on the surface of the vilanterol particle.

156. A similar result can be seen for umeclidinium, except the relevant element indicating the presence of the active is bromine (blue). An example of this is reproduced below:

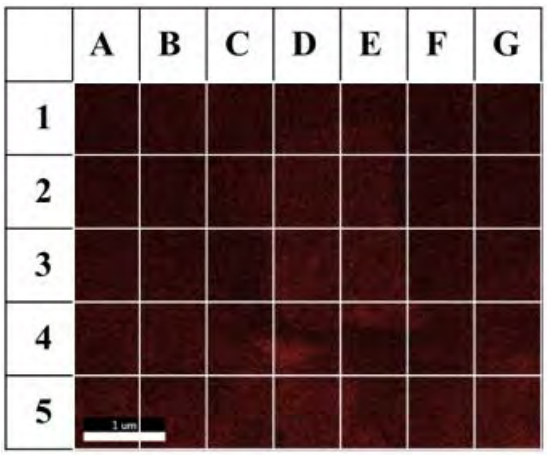
SEM image



EDX map for bromine (blue)



EDX map for magnesium (red)



157. Vectura contends that the same pattern can be seen for all six vilanterol particles and all six umeclidinium particles which were analysed in Vectura's Notice and repeats, and thus that these results are not anomalies. Vectura further contends that there is a striking contrast between the results of the experiments on GSK's products and the results of GSK's experiments following the teaching of Staniforth and Musa (as to which, see below).

158. GSK contend that all that the experiments show is that (as the skilled person would anticipate) MgSt gets everywhere and that it is possible to identify instances where

MgSt is closely associated with active particles. GSK dispute that the experiments demonstrate anything about the nature of that association, and in particular that MgSt particles are structurally combined with active particles with the MgSt fused to/smeared over the surfaces of the active particles to form a coating.

159. *The experimental techniques.* In considering the experiments, it is important to note the following points about the techniques which were employed. First, each carbon tab was used to collect particles delivered by eight actuations. As Dr Reynolds accepted, if particles were found together on the tab, this could be because they are arrived joined to each other or because they arrived separately and landed on top of each other.

160. Secondly, Dr Reynolds attempted to find, image and map individual particles. By contrast, when the experiments were repeated on behalf of GSK, Mr Harrington did not attempt to find, image and map individual particles, but samples of representative density. Vectura places considerable reliance upon Dr Reynolds' approach for reasons that will become apparent. As GSK point out, however, the SEM images show that in every case multiple particles were present (although it is frequently unclear whether the particles are wholly separate from one another).

161. Thirdly, during the Notice experiments no X-ray spectra were recorded by Dr Reynolds. During the Vectura repeats, point X-ray spectra were recorded at GSK's request. During the GSK repeats, small area spectra were recorded rather than point spectra. The difference between point and small area spectra is unimportant, but the X-ray spectra are important for the interpretation of the experiments as discussed below.

162. Fourthly, the experiments were qualitative in nature: only a very small number of particles were examined, and therefore it is not possible to draw any quantitative conclusions.

163. *Limitations of EDX.* Vectura's objective is to establish that a thin layer of MgSt has become structurally combined with, and coats the surface of, particles of vilanterol and umeclidinium. GSK contend that EDX is unsuitable for this purpose for four main reasons: first, the size of the interaction volume, and hence the poor spatial resolution of EDX; secondly, the poor signal-to-noise ratio of EDX maps; thirdly, the presence of relief effects in EDX maps; and fourthly, the low concentration of magnesium present. I will consider these in turn.

164. So far as the first point is concerned, it was common ground between Prof Drummond-Brydson and Dr Reynolds that the size (i.e. depth) of the interaction volume for a sample which was assumed to consist of a 100 nm layer of MgSt on top of vilanterol was about 1.5 μm; indeed, Dr Reynolds accepted that it could be as much as 1.8 μm. It follows that the theoretical maximum spatial resolution of the technique in the present case is around 1.5 μm. Dr Reynolds accepted that this meant that EDX was not an effective method for the analysis of the surface of the sample; rather, it could only provide information about the interaction volume as a whole.

165. GSK contend that this is significant because it means that the element whose presence has been detected may be anywhere within the interaction volume. If there is another particle within the interaction volume in addition to the particle of intertest, then the

other particle may be the source of the signal rather than the particle of interest. Dr Reynolds' view was that this risk was reduced by trying to focus on individual particles and using point spectra as a cross-check.

166. Turning to the second point, it was also common ground between Prof Drummond-Brydson and Dr Reynolds that each pixel spectrum in an X-ray map is collected over a much shorter period of time than a point or small area spectrum: of the order of a millisecond rather than of the order of 10 seconds. This results in point or small area spectra having a 100 times better signal-to-noise ratio than the pixel spectra in maps. It follows that point or small area spectra are more reliable than maps.

167. As to the third point, it was also common ground between Prof Drummond-Brydson and Dr Reynolds that a potential problem with interpreting EDX maps is the presence of relief effects caused by variations in the background radiation due to the different heights of the particles in the sample being different distances from the detector and the EDX software subtracting an average background level across the image when producing a map. The effect of this is produce a relief outline of the particles in a map. This effect is more pronounced where the signal-to-noise ratio is low.

168. The relief effect can be seen in a number of Vectura's bromine maps of vilanterol particles. Although umeclidinium cannot coat vilanterol, blue shadows of vilanterol particles can be seen in some of Vectura's high magnification images Prof Drummond-Brydson demonstrated these false positives further by manually adjusting the brightness and contrast of the maps (as opposed to leaving it to the software to decide on the brightness and contrast, which will be affected by the presence of "hotspots" of the elements in question in the image).

169. Vectura's answer to this is that the point and small area spectra show that the magnesium maps they rely upon are not artefacts: magnesium really is present. GSK contend that this is a logical fallacy: the fact that the point or small area spectrum recorded somewhere within the area covered by a map confirms the presence of magnesium in the interaction volume at that location does not show that the apparent distribution of magnesium shown by the map is real and not an artefact. On this question I found Prof Drummond-Brydson's evidence in favour of the latter contention more persuasive than Dr Reynolds' evidence in favour the former contention.

170. As for the fourth point, a standard text on EDX is Joseph Goldstein *et al*, *Scanning Electron Microscopy and X-ray Microanalysis* (4th edition, 2017). This states that, for elements that are present in the sample under analysis at less than 10 wt% (which Goldstein calls "minor constituents"), the atomic number dependence of the background "can lead to serious artefacts". Goldstein explains that, for elements which are present at 1 wt% or less ("trace constituents"), most maps are "nearly useless". When this was put to Dr Reynolds, he accepted that, at levels below 1 wt%, it would be foolhardy to rely upon an EDX map on its own; but said that, if the element in question was found in a point spectrum, then one could be satisfied that it was indeed present.

171. MgSt molecules are made up 111 atoms, only one of which is magnesium. Bearing in mind the atomic weights of magnesium and of the other atoms in the molecule, magnesium is present at only 4 wt% of magnesium stearate. (By contrast bromine and

chlorine are present in umeclidinium and vilanterol at about 15 wt%.) GSK accept that, if MgSt is present as a pure particle, it should be possible to detect it in the maps. GSK contend that, if MgSt is present in a thin layer on the surface of a drug particle, the concentration of magnesium would reduce below the level of detection in a map. Prof Drummond-Brydson gave unchallenged evidence that, due to the teardrop shape of the interaction volume, the layer of MgSt would need to be in the order of 500 nm (or half a micron) thick for it to reach the level of 4 wt% of the material in the interaction volume. It seems unlikely that the GSK process would produce a layer of that thickness.

172. For his part, Dr Reynolds accepted at one point in his cross-examination that EDX was not a good technique for picking up a thin coating of MgSt on particles of 3-4 μm because of the interaction volume. Counsel for Vectura submitted that this answer had to be taken in the context of Dr Reynolds' evidence as a whole, the overall tenor of which was that the EDX data could be relied upon.

173. *Absence of validation*. Given these limitations, GSK contend that it is important that Dr Reynolds made no attempt to validate the technique as an appropriate method for detecting composite active particles with MgSt fused to/smeared over the surface of active particles so as to form a coating. Thus he did not, for example, make SEM/EDX images of particles produced by following the teaching of Example 4 of the Patents, which would be expected to produce composite active particles in accordance with the claimed inventions. In my view this is a significant flaw in Vectura's experiments, particularly given the limitations of EDX discussed above.

174. *Conclusion*. As noted above, GSK do not dispute that the experiments show the presence of magnesium, and hence MgSt, in the samples examined. Nor do GSK dispute that it may be concluded that MgSt was closely associated with particles of the active ingredients. But the crucial question is whether Vectura's experiments demonstrate the presence of composite active particles with MgSt structurally combined with and fused to/smeared over the surfaces of active particles so as to form a coating. On this question there was little disagreement between the experts. Prof Drummond-Brydson's evidence, which was barely challenged, was that it was not possible to say whether the MgSt was in contact with the active (as opposed to adjacent to it) or, if it was, the nature of the association. Dr Reynolds accepted that the technique did not give any information as to the nature of the association and did not show that the MgSt was fused to the active. He also accepted that the MgSt could be adjacent to the active particles, although his view was that the maps suggested that the MgSt was on the surface. Having considered the evidence as a whole, I conclude that the limitations of EDX discussed above, together with the absence of validation, mean that one can have no confidence that the MgSt is on the surface of the active particles, let alone structurally combined with and fused to/smeared over them. It may be, but equally it may not.

175. It follows that Vectura has not established that GSK have infringed the Patents.

Insufficiency

176. GSK contend that the specifications of the Patents do not disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. Although a variety of insufficiency attacks were pleaded and opened in GSK's

skeleton argument, in closing submissions GSK confined their case to one of ambiguity. In short, GSK contend that the Patents are insufficient because they do not enable the skilled person to determine whether a process or product falls within the claims since they do not enable the skilled person to determine whether or not there are composite active particles with additive particles fused to/smeared over active particles so as to form a coating, and certainly do not enable the skilled person to do so without undue burden. There is no dispute that, if factually well-founded, this allegation is capable as a matter of law of amounting to insufficiency: see *Unwired Planet International Ltd v Huawei Technologies Co Ltd* [2016] EWHC 576 (Pat) at [149]-[163] (Birss J) in which the relevant legislative provisions and authorities are reviewed.

177. The starting point is that the Patents contain very little guidance indeed as to how the skilled person is supposed to determine whether a process has produced composite active particles in which the additive particles are fused to/smeared over the active particles so as to form a coating.

178. GSK accept that the skilled person would consider it plausible that, if the process described in Example 4 is followed, the MgSt would deform and spread over the surfaces of the active particles, but point out that the Example does not demonstrate that the MgSt particles are structurally combined with the active particles or fused to/smeared over them to form a coating. Even assuming that the skilled person took on trust the assertion that Example 4 did produce composite active particles as claimed, GSK contend that the skilled person would not know how to determine whether any other process did so.

179. In answer to a Request for Further Information from GSK, Vectura pleaded that the skilled person could use one or more of the following techniques: (i) SEM, (ii) time-of-flight secondary ion mass spectrometry ("ToF-SIMS") and (iii) X-ray photoelectron spectroscopy ("XPS"). Vectura did not rely upon ToF-SIMS or XPS, however. Furthermore, Prof Drummond-Brydson gave unchallenged evidence that they were unsuitable. Prof Birchall's evidence in his first report was that the skilled person could use SEM, dispersal and dissolution testing. Vectura did not rely upon dispersal or dissolution testing, however. Furthermore, as Prof Buckton explained, dispersal testing (i.e. determining the FPF) cannot show whether an increase in FPF is simply due to the presence of MgSt or due to the structural combination of MgSt and active particles required by the claims. Prof Birchall had no satisfactory answer to this point when it was put to him. Nor would dissolution testing assist.

180. Finally, Prof Birchall said that "as a further cross-check" the skilled person could carry out SEM/EDX on pre- and post-actuated samples. As Prof Birchall acknowledged, however, EDX was proposed by Dr Reynolds when asked by Vectura's solicitors what would be a suitable technique to determine the association (if any) between MgSt and the active ingredients in the GSK products. Neither Prof Birchall nor Prof Buckton had used EDX before, and Prof Buckton gave unchallenged evidence that it was not ordinarily used in pharmaceutical formulation. In short, although EDX existed in November 2000, it was not a technique that would have formed part of the common general knowledge of the skilled person. Vectura's answer to this is that the skilled person could have asked an analytical scientist like Dr Reynolds what technique to use. I find it difficult to understand, however, how a patent can be sufficient if it requires the use of an analytical technique which is not

mentioned in the specification and did not form part of the skilled person's common general knowledge.

181. In any event, in my judgment, the limitations of EDX mean that it is not a suitable technique for this purpose, at least in the absence of validation, as is demonstrated by Vectura's failure to establish infringement. That is not because I have concluded that GSK's products definitely do not have the characteristics called for by the claims. Rather, I have concluded that it is not possible to tell from the EDX data whether they do or not. This is not because of any peculiarity in GSK's process, but due to the nature of the technique and Vectura's failure to validate its use for this purpose. Accordingly, I conclude that the Patents are insufficient because they do not enable the skilled person to determine whether or not a process or product is within the claims. Certainly, the Patents do not enable the skilled person to do so across the breadth of the claims without undue effort.

The prior art

Staniforth

182. Staniforth discloses the use of an additive material such as MgSt in combination with lactose carrier particles for improving the respirable fraction of the active material in a DPI.

183. It begins by describing the background to the invention, including the known use of carrier particles (page 3 line 20 - page 4 line 8). At page 4 lines 18 - page 5 line 3 it notes that it has been proposed to add a ternary component such as MgSt or a colloidal silicon dioxide in an amount of 1.5% by weight based on the weight of carrier particles. It reports that the conclusion of that proposal was that the addition of the additive particles was undesirable. At page 5 lines 8-16 it explains that, contrary to the teaching in this prior art, the inventors have found that the presence of additive particles which are attached to the surfaces of the carrier particles to promote the release of the active particles from the carrier particles is advantageous "provided that the additive particles are not added in such a quantity that the active particles segregate from the surfaces of the carrier particles during fabrication of the dry powder and in the delivery device before use."

184. It continues at page 5 lines 17 - page 6 line 1:

> "Furthermore, we have found that the required amount of the additive particles is surprisingly small and that, if a greater amount is added, there will be no additional benefit in terms of inhalation performance but it will adversely affect the ability to process the mix. The required amount of additive particles varies according to the composition of the particles - in the case where the additive particles are of magnesium stearate (that being a material that may be used but is not preferred), we have found that an amount of 1.5 per cent by weight based on the total weight of the powder is too great and causes premature segregation of active particles from the carrier particles."

185. It goes on at page 6 lines 3-11:

> "The present invention provides a powder for use in a dry powder inhaler, the powder including active particles and carrier particles for carrying the active particles, the powder further including additive material on the surfaces of the carrier particles to promote the release of the active particles from the carrier particles on actuation of the inhaler, the powder being such that the active particles are not liable to be released from the carrier particles before actuation of the inhaler."

186. Staniforth explains, at page 7 lines 7-22, that the surface of a carrier particle is not usually smooth, but has asperities and clefts which are believed to be areas of high surface energy, and that it is advantageous to decrease the number of those high energy sites available to the active particles.

187. At page 8 lines 12-18 Staniforth states:

> "It is advantageous for as little as possible of the additive material to reach the lungs on inhalation of the powder. Although the additive material will most advantageously be one that is safe to inhale into the lungs, it is still preferred that only a very small proportion, if any, of the additive powder reaches the lung, in particular the lower lung."

188. At page 9 lines 9-15 it is stated that the additive is preferably an anti-adherent material or antifriction agent. Additive materials are identified at page 11 line 14 - page 13 line 13 and include amino acids, with leucine being preferred, phospholipid, lecithin, fatty acids, MgSt, sodium stearyl fumerate, lung surfactants and metal dioxides.

189. At page 16 line 13 - page 17 line 5 there is a discussion of the extent of surface coverage of carrier particles by additive materials. It is explained that the amount used in Example 1 is more than required to form a monolayer coating, but that there is in fact "no 'coating' of the carrier particles in the sense in which that word is normally used in the art, namely to refer to a continuous envelope around the carrier particle", Rather, the covering is discontinuous, which is considered to be an important and advantageous feature of the invention.

190. At page 17 lines 8-26 it is stated:

> "Preferably the additive material, whilst providing only a discontinuous covering for the carrier particles, does saturate the surface of the carrier particles in the sense that even if more additive material were provided substantially the same covering of the carrier particles would be achieved. When the additive material in the finished powder is particulate, some of the additive particles, either individually or as agglomerates, may act as carriers of active particles and may be separate from or may separate from the surfaces of carrier particles with active particles attached to their surfaces. The dimensions of the combined active particles and additive particle may still be within the optimum values for good deposition in the lower

> lung. It is believed that active particles which adhere to the additive particles on the carrier particles may in some cases be preferentially released from the surfaces of the carrier particles and thereafter be deposited in the lower lung without the additive particles."

191. At page 19 line 23 - page 20 line 14 it is explained that the invention also provides a method of producing particles for use in dry powder inhalers which is described in general terms. Staniforth goes on at page 20 lines 15-18 to say that the size of the carrier particles is an important factor in the efficiency of the inhaler and an optimum range is selected.

192. At page 21 lines 1-4 Staniforth says that the additive and the carrier particles may be mixed for between 0.1 hours and 0.5 hours using "a tumbling blender (for example a Turbula Mixer)". It adds at page 21 lines 5-10 that advantageously:

> "the method further includes the step of treating the carrier particles to dislodge small grains from the surfaces of the carrier particles without substantially changing the size of the carrier particles during treatment."

193. At page 21 lines 21-23 it states that advantageously the mixing step is prior to the treatment step.

194. Staniforth states at page 23 lines 8-13 that the treatment step is preferably a milling step which causes asperities on the surface of the carrier particles to be dislodged as small grains which become re-attached at areas of high energy.

195. The milling process is described at page 23 line 14 - page 24 line 2 as follows:

> "Preferably, the milling step is performed in a ball mill. The particles may be milled using plastics balls, or they may be milled using metal balls. Balls made of polypropylene material give less aggressive milling, whilst steel balls confer more aggressive action. The mill may be rotated at a speed of about 60 revolutions per minute. The mill may alternatively be rotated at a speed less than 60 revolutions per minute, for example at a speed less than 20 revolutions per minute, or for example a speed of about six revolutions per minute. That is a slow speed for ball milling and results in the gentle removal of grains from the surfaces of the particles and little fracture of the particles. Widespread fracture of the particles, which occurs with aggressive milling conditions, or at long milling times, may result in agglomerates of fractured particles of carrier material."

196. Staniforth explains at page 24 lines 25-27 that the gentle milling used in the treatment step is referred to as "corrasion".

197. It goes on at page 24 line 28 - page 25 line 27,

> "According to the invention, there is further provided a method of producing a powder for used in dry powder inhalers, the method including the steps of:
>
> (a) mixing carrier particles of a size suitable for use in dry powder inhalers with additive material such that the additive material becomes attached to the surfaces of the carrier particles.
>
> (b) treating the carrier particles to dislodge small grains from the surface of the carrier particles, without substantially changing the size of the carrier particles during treatment and
>
> (c) mixing the treated particles obtained in step (b) with active particles such that active particles adhere to the surfaces of the carrier particles and/or additive material
>
> A satisfactory dry powder may also be obtained by mixing the active particles, the additive material and the carrier particles in one step. Alternatively, the carrier particles may first be mixed with the active particles, followed by mixing with the additive material.
>
> Satisfactory dry powders may also be obtained by an alternative sequence of steps. For example, the carrier particles, additive material and active particles may be mixed together followed by a milling step. Alternatively, the carrier particles may first be milled before the addition of additive material and active particles.

198. The examples use various additive materials. Example 13 includes MgSt at a concentration of 1.5%. This consists of the following steps:

i) Sieved lactose with a range of diameters 90-125 μm is treated by milling (corrading) the lactose with additive particle of MgSt in a 2.5l porcelain pot with 200 ml of 3 mm steel balls which was placed on a ball mill at 60 rpm for 6 hours.

ii) The MgSt/lactose blend is then mixed with active particles of beclomethasone diproprionate (BDP) in a glass mortar.

199. Staniforth comments on the results at page 60 lines 1-14 as follows:

> "The poor initial homogeneity of the 1.5% magnesium stearate mix indicates the very strong tendency of the mix to segregate. The post-vibration results confirm the poor stability of the mix when subjected to conditions comparable to those that might occur during commercial processing. Thus, even though a 1.5% magnesium stearate mix may provide satisfactory results in terms of a respirable fraction, it does not meet the other

> important requirement of retaining homogeneity during conditions that are comparable to those that might occur during commercial processing. In contrast the powders containing leucin, as well as providing a satisfactory respirable fraction, had excellent initial homogeneities and the homogeneities remained satisfactory even after intense vibration."

Keller

200. Keller is in German and I shall refer to the agreed translation. It discloses the use of MgSt to improve the resistance to moisture and storage stability of dry powder formulations for inhalation.

201. It begins by noting that dry powder formulations for inhalation must fulfil a number of demands which are partially contradictory. At page 3 it discusses the use of carrier particles and ordered mixtures to improve the handling of microfine active compound particles. Such mixtures should be stable during processing, transportation and storage such that the active compound does not detach from the carrier, but the active compound particles must be detached as effectively as possible during dispersion in the inhaler in order to be inhaled.

202. On pages 4 and 5 there is a discussion of prior art including a discussion about the fact that crystalline lactose may contain a small amount of amorphous material which can preferentially absorb water in a humid environment and that storage stability of powder preparations is limited at high atmospheric humidity.

203. On page 6 reference is made to the fact that sensitivity to moisture is a problem with multidose DPIs which may be exposed to water vapour and that this may manifest as a decrease in the inhalable fraction resulting from stronger binding to the carrier particles.

204. Keller then states at page 6 lines 34-43:

> "The invention is therefore based on the object of lowering the sensitivity of the powder mixtures to moisture. This object is achieved according to the invention by the use of magnesium stearate. It has surprisingly been found that magnesium stearate is able to minimize the effect of penetrating moisture on the FPD and the FPF during storage of the inhalation powder, i.e to prevent or at least to considerably slow down a decline of the FPD and the FPF caused by moisture, and to stabilise the dry powder formulation."

205. It continues at page 7 lines 7-36:

> "Moreover, the use of magnesium stearate leads, as a rule, to a general improvement in the FPD and the FPF. It is conceivable that, in addition to providing general moisture protection, magnesium stearate also stabilises the carrier materials and active compounds by suppressing or slowing undesirable morphological phase transitions.

> The invention therefore relates to the use of magnesium stearate for improving the resistance to moisture, i.e. for lowering the sensitivity of dry powder formulations for inhalation to atmospheric humidity. The use of magnesium stearate accordingly brings about an improvement in storage stability and in particular a reduction of the influence of penetrating moisture on the FPF (and the FPD), which allows a high FPD and FPF to be maintained, even under comparatively extreme temperature and humidity conditions.
>
> The dry powder formulations obtainable according to the invention thus comprise a pharmaceutically inactive carrier of a noninhalable particle size, a finely divided pharmaceutically active compound of inhalable particle size (i.e. having a mean particle diameter of preferably at most 10 μm, in particular at most 5 μm) and - to improve the resistance to moisture - magnesium stearate, and they are preferably present in the form of so called interactive (or ordered or adhesive) mixtures. If desired, the dry powder formulations can also contain a fraction of carrier material having an inhalable particle size."

206. At page 8 lines 1-6 Keller states:

> "It has been found that magnesium stearate is suitable for improving the moisture resistance of fundamentally any desired dry powder formulations, regardless of the nature of the active compounds and carrier materials."

207. At page 13 lines 10-25 Keller says that the concentration of MgSt can vary within wide limits, with 0.1% to 2% by weight being preferred, although for toxicological reasons it will usually not be higher than approximately 1% by weight, and that the particle size is not particularly critical.

208. The method by which the dry powder formulations of the invention can be prepared is described at page 13 line 33 – page 14 line 7 as follows:

> "The dry powder formulations can be prepared according to the invention by mixing together a pharmaceutically inactive carrier having a non-inhalable particle size (which can, if desired, contain a fraction having an inhalable particle size), a finely distributed pharmaceutically active compound having an inhalable particle size, for example having a mean particle diameter of at most 10 μm (preferable at most 5 μm), and magnesium stearate. The constituents can in principle be mixed with one another in any desired sequence, but mixing should expediently be performed in such a way that – aside from adhesion to the carrier particles – the particles of the constituents are essentially retained as such, i.e. are not destroyed, for example, by granulation and the like. According to a preferred embodiment a preliminary mixture of magnesium stearate with the carrier can however be prepared first and the

> active compound particles can be admixed after that. According to another preferred embodiment, a preliminary mixture of the active compound with the carrier can be prepared first and the magnesium stearate can be admixed thereafter. The mixing can be performed in a manner known per se, for example in a tumbling mixer."

209. Example 1 describes the blending of lactose of < 200 μm with MgSt using a tumbling mixer following which formoterol fumarate dehydrate and the preliminary mixture of lactose and MgSt are screened and mixed by an unspecified method. This formulation is then compared to two control formulations which are set out in Table 1. The data show that the test sample (1-A) has a superior FPD and FPF after preparation and after 3-4 days storage. The control samples are a formulation comprising just lactose and the active (1-B) and a formulation comprising lactose, lactose fines and active (1-C).

210. In Example 2 an alternative mixing order is examined being the mixing of lactose and lactose fines, followed by the active. The preliminary mixture is then mixed with MgSt. Again, some improvement in FPD and FPF is observed after preparation.

211. Further examples use the mixing order of Example 1. Example 3 uses salbutamol sulphate as an active. Examples 4 and 5 look at varying the relative amounts of MgSt and active and an improvement from using MgSt is consistently observed.

212. Example 7 records longer term studies with Formulation 1-A of up to 12 months leading the inventors to conclude that the formulation according to the invention is "barely adversely affected over long periods of time, even under comparatively extreme temperature and humidity conditions".

Musa

213. Musa discloses the use of small percentage (less than 0.5% by weight) of lubricant in powdery pharmaceutical compositions for use in DPIs in order to increase the fine particle dose (i.e. the fine particle fraction).

214. It begins by describing the use of DPIs and the use of ordered mixes of micronized drug with coarse carrier particles, usually of lactose. At page 2 line 24 – page 3 line it says:

> "The redispersion of drug particles from the carrier surface is regard as the most critical factor which governs the availability of the medicament to the lungs. This will depend on the mechanical stability of the powder mix and the way this is influenced by the adhesion characteristics between the drug and the carrier and the external forces required to break up the noncovalent bonds formed between adhering particles. Too strong bonds between adhering particles may prevent indeed the separation of the micronised drug particles from the surface of carrier particles."

215. It then describes different approaches which have been taken to promote the release of drug particles in the prior art.

216. Reference is made at page 4 lines 3-12 to a thesis by Kassem which studied the effect of MgSt stearate on the de-aggregation of powders made of salbutamol sulphate and lactose. Although the respirable fraction increased when MgSt was added, the reported amount was too great and reduced mechanical stability of the mixture before use. At page 4 lines 12-22 Musa notes that Staniforth claims that the reported drawbacks can be solved by adding anti-adherent additives, preferably 1-2% leucine.

217. At page 4 line 23 – page 5 line 5 Musa states that it is an object of the invention that lubricants like MgSt can be advantageously and safely used as an excipient for powdery pharmaceutical composition based on a total weight of less than 0.5%. The optimum amount of MgSt depends on the active: for steroids it is 0.25% and for salbutamol base it is 0.1%.

218. At page 5 lines 6-12 Musa states:

> "The invention also provides a method for producing a homogenous carrier for powders for inhalation independently on the scale of mixing, the method including a step for coating the most as possible surface of the carrier particles with a little amount of lubricant. We have indeed found that it is advantageous to attain the highest as possible degree of coating of the carrier particles surface with the lubricant to increase the release of the active particles and, hence, the 'respirable' fraction."

219. It goes on at page 5 lines 16-23 that use of lubricants in such small amounts is sufficient to increase the flowability of the powder with causing stability problems before use and that the introduction of MgSt in those amounts is safe.

220. At page 5 line 25 – page 6 line 7 it is stated that:

> "Advantageously the carrier of the invention is prepared by mixing the carrier particles and the lubricant particles for at least 2 minutes in a mixer in such a way as that no significant change in the particle size of the carrier particles occurs. Preferably, the carrier is mixed for at least 30 min using a rotary body mixer with a rotating speed between 5 - 100 r.p.m. or a stationary body mixer with a rotating mixing blade or a high-speed mixer. More preferably, the carrier is mixed for at least two hours in a Turbula mixer at 16 r.p.m.
>
> Advantageously, the carrier particles and the lubricant particles are mixed until the degree of molecular surface coating is more than 10% as determined by water contact angle measurement".

221. Examples 1, 2 and 3 describe the preparation of ordered mixes of different micronized APIs (BDP in Example 1, salbutamol base in Example 2, budesonide in Example 3) at different concentrations. Examples 1 and 2 create a pre-blend by mixing lactose of 90-

150 μm with different amounts of MgSt for several hours in a Turbula mixer and then blending this pre-blend with the active ingredient for 30 minutes in a Turbula mixer at 32 rpm. The results are set out in Tables 1 to 4. Example 3 blends 0.25% MgSt with the lactose for two hours in a Turbula mixer at 16 rpm. The results are in Table 5. An increase in fine particle dose is observed in each example.

222. Example 4 examines the effect of mixing lactose and MgSt for different periods and uses measurement of contact angle to represent the degree of coating of MgSt over the lactose. The trend shown in Table 6 is that the degree of coating increases with mixing time up to about five hours.

223. Example 7 is a comparison between different mixers. A "sigma-blade mixer" (a high-shear mixer) is used to blend the lactose and the MgSt for 30 minutes. This is compared with a Turbula mixer at 16 rpm for two hours. In both cases the lactose/MgSt mixture is then mixed with BDP in a Turbula mixer at 32 rpm. The results are set out in Table 9. As Musa states at page 20, "No significant difference was observed in the fine particle dose".

224. Example 8 is a stability study. Example 9 generates further data similar to that in Example 1. From page 28 Musa goes on to discuss a small study in patients in which it found that MgSt did not accumulate in the bronchi or alveoli of patients.

Obviousness of the Patents

225. I shall consider the prior art in the order in which it was argued by counsel for GSK in his closing submissions (namely, in reverse chronological order). Having regard to my conclusions with regard to infringement and insufficiency, I will do so relatively briefly and will concentrate on Musa, which counsel for GSK evidently regarded as his best case.

Musa

226. Musa discloses the blending of MgSt with lactose so as to coat the lactose with the MgSt, followed by blending the mixture with API, to improve the FPF of a number of APIs. It is also expressly discloses the use of a "high-speed mixer" and of a "sigma-blade mixer" (i.e. a high-shear mixer) in the first stage, and teaches that the sigma-blade mixer achieves the same results as a Turbula mixer but more quickly.

227. In my judgment an obvious alternative would have been to use a high-shear blender in both stages of the process, particularly when scaling up from laboratory scale preparation to a larger scale such as manufacture for clinical trials. The purpose of using a high-shear mixer would not be to change the character of the powder. Thus the skilled person who used a high-shear blender following the teaching of Musa would not be aiming to reduce the particle size of the mixture. The use of a high-shear blender would be likely to spread the MgSt, however.

228. It would also have been obvious to apply Musa's process to a different API to those disclosed in Musa. Musa teaches that the amount of MgSt which should be used varies according to the API, and so the skilled person who was using the process for a new API would test a range of amounts of MgSt. Although Musa teaches that less than 0.5% MgSt should be used, it acknowledges prior art in which higher amounts

had been used. In my judgment it would be obvious to try a higher amount than 0.5% during the testing.

229. There is no evidence, however, that following the teaching of Musa using a high-shear blender for both stages and a greater quantity of MgSt would produce composite active particles with MgSt fused to/smeared over the active particles to form a coating as claimed in the Patents. GSK carried out experiments in which Example 1 of Musa was reproduced by Mr Bowen with BDP and vilanterol as the active ingredient and with 0.25% and 0.5% MgSt, and the resulting powders were examined by Mr Harrington using SEM/EDX. The BDP mixtures could not be successfully imaged using EDX. The vilanterol results show that MgSt lies close to vilanterol particles, but do not show that MgSt is attached to the surfaces of the vilanterol particles. GSK did not carry out an experiment in which using a high-shear blender was used or a greater quantity of MgSt (0.6% or 1%).

230. Vectura relies upon the fact that the results of the Musa experiments differ from the results of the Anoro experiments in that little correlation is apparent between the distribution of the magnesium and the distribution of the chorine in any of the EDX maps. (The same is true of the Staniforth experiments carried out by GSK.) Vectura contends that this demonstrates that there is a difference between the result of GSK's process and the results of the processes taught by Musa and Staniforth. I accept that there is an apparent difference, but for the reasons explained above this does not necessarily mean that the difference is a real one. In any event, even if there is a real difference, I am not persuaded that this shows that GSK's process infringes.

231. It follows that GSK have not established that any of the Patents are obvious over Musa.

Keller

232. Keller discloses the mixing of MgSt, lactose and API in any order to improve the FPF of the API, but one preferred sequence is for the MgSt and lactose to be mixed first followed by the API. Keller discloses the use of a range of quantities of MgSt, with 1% being preferred. Keller does not disclose the use of a high-shear blender at any stage. In my judgment it would nevertheless be an obvious alternative to use a high-shear blender when scaling-up. It would also have been obvious to apply Keller's process to a different API. There is no evidence, however, that following the teaching of Keller using a high-shear blender would produce composite active particles with MgSt fused to/smeared over the active particles to form a coating as claimed in the Patents. It follows that GSK have not established that any of the Patents are obvious over Keller.

Staniforth

233. Staniforth teaches the use of additive material together with lactose and active. Staniforth's preferred additive material is leucine, but nevertheless it expressly discloses the use of MgSt at less than 1.5% by weight. Vectura contend that it would not be obvious to follow the teaching of Staniforth using MgSt because Staniforth says that MgSt does not produce sufficient homogeneity. I disagree: it would not take invention for a skilled person to do what Staniforth expressly discloses, particularly given that the skilled reader is taught that MgSt gives good results in terms of the

respirable fraction. Thus an obvious step would be to try a lower amount of MgSt, say 1%. Staniforth does not disclose the use of a high-shear blender, but again that would be an obvious alternative when scaling up. There is no evidence, however, that following the teaching of Staniforth using a high-shear blender would produce composite active particles with MgSt fused to/smeared over the active particles to form a coating as claimed in the Patents. Although GSK repeated Example 13 of Staniforth (except that Mr Bowen used a stainless steel pot rather than a porcelain pot and a porcelain pestle and mortar rather than a glass one) with BDP and vilanterol as the active, the results were similar to those of the Musa experiments. It follows that GSK have not established that any of the Patents are obvious over Staniforth.

Obviousness of GSK's process and products

234. GSK contend that their process was obvious over each of Musa, Keller and Staniforth as at November 2000. GSK accept that it was not obvious to use vilanterol or umeclidinium as the active at that date, because those actives were not known then, but contend that that does not matter because it was obvious to apply the process to any active which was suitable for use in a DPI. I agree with this.

235. Again, I shall concentrate on Musa. Musa discloses everything in GSK's process except (i) the percentage of MgSt, (ii) a de-lumping step using a Comil, (iii) the use of a TRV blender and (iv) the speeds and quantities used. I will consider these in turn.

236. So far as the percentage of MgSt is concerned, GSK use 0.6% (umeclidinium) and 1% (vilanterol). Vectura contend that it would not be obvious to go above 0.5% MgSt in the light of Musa, but I disagree. In my judgment it would not take invention to use 0.6% or even 1% MgSt with a different active to those disclosed in Musa given that Musa acknowledges the use of higher percentages than 0.5% although it teaches that lower percentages are preferred.

237. Turning to de-lumping, it is common ground that it was standard practice to de-lump when blending cohesive powders. As discussed in paragraph 28 above, brushing through a sieve was a common way of doing this at laboratory scale, but that would be impractical on a larger scale and using a cone mill such as Comil was one way of doing it. Prof Buckton and Prof Birchall were agreed that a Comil can be used to de-lump in a non-aggressive, gentle manner. There is nothing to suggest that the conditions used by GSK were out of the ordinary. Vectura points out that GSK accept that the particular model of Comil (the Quadro U5) used by GSK was not available in November 2000; but there is no evidence that it differs in any material respect from models which were available then.

238. As for the use of a TRV, I have already concluded that the use of a high-shear blender was obvious in the light of Musa. Vectura questions whether GSK use standard models of TRV in view of the fact that, although GSK's PPD describes the TRV25 and TRV65 used as having "the standard impeller", Mr Roche said he did not know whether the impeller was standard. There is no evidence that the impeller used by GSK differs from the standard one, however. Vectura also points out that GSK have not established that the TRV25 and TRV65 models used by GSK are the same as the TRV25 and TRV65 models which were available in November 2000; but there is no evidence that they differ in any material respect.

239. As to the speeds and quantities used by GSK, the evidence is that such matters would be determined empirically by the skilled person. There is nothing to suggest that the speeds and quantities used by GSK would require invention to devise.

240. Accordingly, I conclude that GSK's process, and hence the products obtained as a direct result of that process, were obvious over Musa. For similar reasons I consider that they were also obvious over Keller and Staniforth.

GSK's claim for an *Arrow* declaration

The law

241. An *Arrow* declaration is, in effect, a declaration that, as of a particular date, a party has a *Gillette* defence against claims of infringement of later patents. The relevant legal principles have been recently considered in the *Fujifilm v AbbVie* litigation.

242. The jurisdictional position was summarised by Floyd LJ delivering the judgment of the Court of Appeal (cited above) at [98] as follows:

> "… we do not consider that there is any issue of principle which prevents the granting of *Arrow* declarations in appropriate cases. Drawing the threads together:
>
> (i) A declaration that a product, process or use was old or obvious at a particular date does not necessarily offend against s.74 of the Act.
>
> (ii) Such a declaration may offend against the Act where it is a disguised attack on the validity of a granted patent.
>
> (iii) Such declarations do not offend against the scheme of the EPC or the Act simply because the declaration is sought against the background of pending divisional applications by the counter-party.
>
> (iv) On the other hand the existence of pending applications cannot itself be a sufficient justification for granting a declaration.
>
> (v) Whether such a declaration is justified depends on whether a sufficient case can be made for the exercise of the court's discretion in accordance with established principles."

243. The principles upon which the Court will grant such discretionary relief were subsequently considered by Henry Carr J in *Fujifilm Kyowa Kirin Biologics Co Ltd v AbbVie Biotechnology Ltd* [2017] EWHC 395 (Pat), [2018] RPC 1 at [365]-[371]. In summary, he held that the Court must consider:

i) justice to the claimant;

ii) justice to the defendant;

iii) whether the declaration will serve a useful purpose. The attainment of commercial certainty in patent cases can constitute a useful purpose. The spin-off value of a judgment in other countries may be such a factor, but a declaration sought solely for the benefit of foreign courts will rarely be justified; and

iv) whether or not there are any other special reasons why the court should or should not grant the declaration.

244. At an earlier stage of this case Vectura applied to strike out GSK's claim for an *Arrow* declaration. The application was granted by HHJ Hacon sitting as a High Court Judge, but his decision was reversed by the Court of Appeal: *Vectura Ltd v Glaxo Group Ltd* [2018] EWCA Civ 196. Floyd LJ, with whom Birss J agreed, held:

> "25. The jurisdiction to grant an *Arrow* declaration is … discretionary. Identification of a relevant application is a necessary but not sufficient condition for an application for such relief. It is necessary to go further and examine whether it would serve a useful purpose. The point being made by paragraphs 98(iv) and 98(v) in *Fujifilm* is the contrast between a remedy which depends only on the existence of a patent (or application) and one whose availability turns on a critical examination of the purpose which its grant would serve.
>
> …
>
> 30. There is no dispute that the declaration must be formulated with clarity. The facts ultimately declared by the court must be clear, otherwise the declaration will simply give rise to further dispute and defeat the purpose for which it is granted. The declaration [i.e. the declaration sought] must also be clear so that the court can know what technical issues it has to decide. The declaration must therefore identify the combination of features of the products and processes in question on which the assessment of obviousness is to take place.
>
> …
>
> 34. … It is clear from *Arrow* and the subsequent cases that there is no requirement that the declaration should identify all the features of the product or process. …"

Assessment

245. *The declarations sought by GSK*. GSK seeks two declarations in the alternative, referred to as Declaration A and Declaration B. Declaration A is in the following terms:

> "A declaration that

(a) a process for formulating a pharmaceutical composition (to be administered by a DPI) in which (i) lactose monohydrate (with a median particle size of about 75µm with about 5% less than about 4.5 µm) and magnesium stearate (with a median particle size of about 8-11µm) are first blended together using a high speed blender (such as a Fielder TRV 25 or TRV 65) to produce a lactose/magnesium stearate pre-blend ('Pre-Blend'), (ii) micronized active ingredient combined with a portion of the Pre-Blend is then passed through a conical screen mill (such as a Comil) to de-lump the active ingredient, and (iii) the remaining Pre-Blend is added and the whole batch further blended using a high speed blender to produce an homogenous blend;

and wherein the blending steps in (i) and (iii) and the de-lumping step in (ii) do not materially reduce the size of the lactose monohydrate particles;

was obvious as of 30 November 2000 or at any date thereafter, and

(b) a pharmaceutical composition which is the direct product of the aforesaid process was obvious as of 30 November 2000 or at any date thereafter."

246. Declaration B is in the following terms:

> "A declaration that the Claimants' Processes described in the Annex A [which is the same as the PPD save for the fact that the particular Comil model (U5) is deleted] and the Claimants' Products which are direct products of those Processes (and save for the active ingredients therein) were obvious as of 30 November 2000 or at any date thereafter."

247. *Vectura's undertaking*. In response to GSK's application to strike out the claim for *Arrow* relief, Vectura gave an undertaking which was recorded in HHJ Hacon's order in the following terms:

> "… if this Court holds that none of the claims of the [Patents] are valid and infringed in a final decision in these proceedings that cannot be appealed, [Vectura] will not assert in the UK any patent applications from within the Non-Assert Patent families (as defined in the agreement between [GSK] and [Vectura] dated 5 August 2010) with a priority date on or after 30 November 2000 which subsequently proceed to grant against the processes described in the … PPD … and Products identified as being made directly therefrom …."

248. *GSK's submissions*. GSK contend that that the declarations would serve a useful purpose because neither success in defeating the infringement claims nor Vectura's undertaking give GSK the commercial certainty they require. GSK say that Vectura

has shown a propensity over many years to describe what is essentially a single inventive concept in a variety of ways. Vectura has the potential to continue to reformulate the inventive concept using applications which are still on file, even if GSK were successful in revoking each of the Patents.

249. In this regard GSK rely in particular on Vectura's International Patent Application No. WO 2014/1555134 entitled "Use of stearate in an inhalable formulation", which is pending in the European Patent Office as European Patent Application No. 2 978 415 ("415"), with a claimed priority date of 28 March 2013. 415 contains (among other things) claims covering the use of MgSt as a formulation density modifier with umeclidinium and vilanterol as pharmaceutically active material. 415 is not covered by Vectura's undertaking.

250. GSK also rely upon what Floyd LJ said at [34]:

> "The main relevance of 415, as it seems to me, is to show that Vectura continues to seek ways of protecting the use of magnesium stearate in these processes and products, and to that extent it supports the pleaded claim for *Arrow* relief."

251. *Vectura's submissions*. Vectura contends that its undertaking gives GSK all the protection they require assuming that Vectura is unsuccessful in its claim for infringement of the Patents, and according the declarations sought by GSK will not serve a useful purpose. In this regard, Vectura points out that GSK adduced no factual evidence in support of its claim for declaratory relief. Vectura also contends that the declarations are unclear, and therefore recipes for future disputes. In particular, Vectura contends that Declaration A is too unspecific and that Declaration B is meaningless because it does not specify the APIs, whereas the evidence is that formulations, and the processes for making them, are inevitably API-dependent at least to some extent.

252. *Discussion and conclusion*. I have already concluded that GSK's process, and the products obtained directly by means of that process, were obvious over Musa, Keller and Staniforth as at 30 November 2000. That is a necessary, but not a sufficient, foundation for the relief sought by GSK.

253. Counsel for Vectura pointed out that in *Generics (UK) Ltd v Yeda Research and Development Co Ltd* [2017] EWHC 2629 (Pat) at [205]-[212] I declined to grant an *Arrow* declaration because I was not satisfied that it would serve a useful purpose beyond my finding that the use of the claimant's product in a particular dosage regimen was obvious at a particular date.

254. The present case differs from that one in three respects, however. First, Vectura have failed to establish infringement of the Patents because they have not been able to identify a suitable analytical technique to demonstrate that certain requirements of the claims of the Patents are satisfied. Vectura would not necessarily face the same difficulty with differently formulated claims.

255. Secondly, I have not found that the Patents were obvious. It would be an open question as to whether patents with differently formulated claims were obvious or not.

256. Thirdly, and most significantly, Vectura has given an undertaking which is designed to give GSK comfort that, if they are successful in defeating Vectura's claims for infringement of the Patents, then they will not be vexed by further claims for infringement of other patents by the same process and products; yet Vectura's undertaking does not extend to patents deriving from (for example) 415. Counsel for Vectura was unable to give me any explanation for Vectura's unwillingness to extend its undertaking to (at least) 415. It follows that GSK are potentially at risk of a claim for infringement of a patent deriving from (at least) 415.

257. In this unusual combination of circumstances, I have come to the conclusion on balance that the grant of a declaration would serve a useful purpose, because it would formalise and emphasise the conclusion I have reached with respect to the obviousness of GSK's process and products. In particular, as counsel for GSK submitted, granting a declaration avoids the risk that my finding as to the obviousness of GSK's process and products might be interpreted as being obiter given my conclusions as to infringement and insufficiency.

258. I do not consider that Declaration A is appropriate, because it goes beyond what I have found and risks creating uncertainty. By contrast, Declaration B accurately reflects my conclusion as to the obviousness of GSK's process and products. I do not consider that there is any difficulty in the declaration not specifying the active ingredients, because the key features of the process do not depend on the identity of the API(s). It is true that the precise details of the equipment, quantities and speeds would be likely to vary according to the API(s) (which is why Declaration A is expressed at a more abstract level); but what I have concluded is that (viewed as at 30 November 2000) there was nothing inventive in the use of equipment of the kind, or in the quantities and speeds, that GSK use for formulating vilanterol and umeclidinium. By contrast, there might be something inventive in the use of, say, a novel form of high-shear blender invented in 2018.

Summary of principal conclusions

259. For the reasons given above I conclude that:

i) Vectura has not established that GSK's process or products infringe any of the Patents;

ii) all of the Patents are invalid on the ground of insufficiency;

iii) GSK have not established that any of the Patents were obvious over any of the cited prior art;

iv) GSK's process, and products obtained directly from it, were obvious over each of Musa, Keller and Staniforth; and

v) it is appropriate to grant GSK an *Arrow* declaration in the form of Declaration B, but not Declaration A.