CASE AUTH/3516/5/21

HEALTH PROFESSIONAL v CHIESI

Concerns about a webinar

A contactable complainant, who described him/herself as a health professional, complained about a webinar which he/she attended in May 2021. The webinar, organised by Chiesi Limited, was entitled 'Session 3: Evolving Developments in the Management of asthma'.

The detailed response from Chiesi is given below.

1 Prescribing information

The complainant alleged that prescribing information was not present in the invitation, at the beginning of the webinar, nor throughout the webinar. When presented at the end, the text of the Trimbow (beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium bromide) and Fostair (beclometasone dipropionate, formoterol fumarate dihydrate) prescribing information were illegible and shown for a short amount of time.

The Panel noted that the invitation to the webinar stated that the webinar for UK health professionals had been organised and funded by Chiesi and contained promotional content. There was no direct or implied mention of any Chiesi medicine in the invitation at issue. The Panel considered that whilst it might have been prudent to provide prescribing information, the invitation was not promotional in itself and therefore ruled no breach of the Code.

With regard to the complainant's concern that the prescribing information was not present at the beginning of the webinar, the Panel noted that this was not a requirement of the Code. The opening slide of the webinar recording provided by Chiesi, which was not included in the recording provided by the complainant, stated that the prescribing information was available at the end of the presentation in line with the Code's requirements.

The Panel viewed the recording provided by Chiesi and, in its view, the font of the prescribing information was difficult to read; the print was slightly blurred and enlarging it did not assist with its legibility. The Panel further considered that the length of time the prescribing information for Trimbow and Fostair was displayed was insufficient to allow attendees to read it and therefore ruled a breach of the Code.

2 Terminology

The complainant was very concerned at the use of the terms 'almost', 'pretty much', 'nearly', 'approx' etc throughout the webinar in relation to clinical data; there were

numerous examples where clinical impact was rounded up to 'almost' 60ml for example. The complainant alleged that such rounding up was potentially misleading.

The Panel noted that the complainant bore the burden of proof and did not consider that he/she had established that use of the terms 'almost', 'pretty much', 'nearly', 'approx' in relation to clinical data or referring to 'almost 60mls' when the actual value of the clinical data was 57mls which was included in the presentation slide was misleading as alleged and no breach of the Code was ruled.

3 Reference to fine particle formulation

The complainant statedthat data was used for Fostair with regard to lung deposition due to its 'fine particle formulation'. It was then implied that because Trimbow was also a 'fine particle' formulation, that one could expect lung deposition to the same degree as Fostair, however there was no evidence presented to demonstrate this. Additionally, the complainant alleged that the data presented on 'fine particles' was not balanced as it was implied that Fostair/Trimbow were able to reach further into the lungs than other competing molecules. To the complainant's knowledge, however, other competing molecules were of sufficiently small diameter to deliver sufficient lung deposition to be efficacious treatments; the complainant alleged this was not reflected in the evidence presented.

The Panel noted that the speaker presented a slide titled 'Extrafine formulation Fostair (beclomethosone formoterol) pMDI 100/6 can reach the large and small airways'. The presenter explained that it could be seen in a scintigraphy study (De Backer et al) that drug particles from the extrafine Fostair formulation were reaching small airways and noted that approximately 30% or more of the medicine was deposited in the lungs and of this around one third reached the small airways; the extrafine formulations were capable of reaching the distal lung. In summary, the presenter stated that as could be seen from the ATLANTIS study, the higher prevalence of small airway disease in asthma, particularly in GINA step four/five, and that using an extrafine formulation, such as Fostair, one could ensure that medicine reached large and small airways. The presenter then reminded viewers that Trimbow was also an extrafine formulation.

The Panel noted that Trimbow was described in its SPC as an aerosol with extrafine particles and that Chiesi provided evidence to substantiate the lung deposition associated with Fostair and Trimbow.

The Panel noted Chiesi's submission that it was clear that both Fostair and Trimbow were extrafine formulations which resulted in a higher proportion of lung deposition in the small airways than in the large airways.

The Panel noted that in referring to Trimbow as an extrafine formulation, following the details of how the extrafine Fostair formulation reached the small airways, there was the implication that Trimbow would similarly do so. Whilst the Panel noted that there was no evidence in this regard included in the webinar, it appeared from Chiesi's submission that it did have evidence of similar lung deposition between Fostair and Trimbow in COPD and lung deposition data for Trimbow in COPD. The Panel noted Chiesi's submission that the assumption would be that there would be similar deposition in asthma (given the same devices and similar lung deposition in COPD). On the evidence

provided, the Panel did not consider that it had been established that the statement itself nor its implication was misleading or could not be substantiated, as alleged, and the Panel ruled no breaches of the Code.

The Panel noted Chiesi's submission that the lung deposition data presented was purely a description of the data for Chiesi's products (Fostair and Trimbow) in isolation; it was not comparative to any specific comparator product and, therefore, could not be considered a comparison with competitor products. The Panel noted Chiesi's submission that at no point was reference made to Fostair or Trimbow being a more efficacious treatment than any competing molecules based on its lung deposition. The efficacy data for the majority of inhaled corticosteroid (ICS)/ long-acting bronchodilator inhalers (LABAs) and ICS/LABA/LAMAs was similar irrespective of the differences in particle size and/or lung deposition. In support of this, Chiesi submitted that it always briefed its speakers to ensure that lung deposition data was never linked to efficacy of maintenance treatments. The Panel did not consider that the complainant established that presenting data for Fostair and Trimbow misleadingly implied that the medicines were able to reach further into the lungs than other competing molecules. No breach of the Code was ruled.

4 Approval code and date of preparation

The complainant alleged that there was no approval code or date of preparation.

The Panel noted that the 2019 Code stated that promotional material other than advertisements appearing in professional publications must include the date on which the promotional material was drawn up or last revised. Whilst not a Code requirement, the Guidelines on company procedures relating to the Code stated that each certificate should bear a reference number with that reference number appearing on the promotional material so that there could be no doubt as to what has been certified.

The Panel noted that the opening slide of the webinar recording provided by Chiesi included the job code and a date of preparation of April 2021. As the date of preparation was given, the Panel ruled no breaches of the Code.

5 SABA claims linked to patient safety

The complainant was highly concerned for patient safety when it was suggested that changing patients' Short-Acting Beta Agonists (SABA) devices (on which they relied to save their lives where needed) were the 'low hanging fruit' and 'easy' to change them from a metered dose inhaler (MDI) to a dry-powder inhaler (DPI). The complainant alleged that the flippant remarks made trivialised the potential risk to patients by prompting clinicians to address the 'low hanging fruit' and change devices on which patients relied in life-saving situations.

The Panel noted that reference to SABA devices as the 'low hanging fruit' and it being the inhaler devices that were the easiest to change rapidly was made in the context of reducing the carbon footprint. The presenter suggested that a priority would be to reduce prescriptions of SABA and instead put patients on an effective maintenance therapy so that they used their reliever (ie SABA) less. The presenter also referred to considering the carbon footprint of different types of SABAs. The presenter then

described the clinical impact associated with SABA overuse, including asthma deaths and exacerbations. The presenter finished by highlighting that the audience should also consider whether they were using devices with the lowest carbon footprint and also discussed the importance in ensuring that the right patient was on the right device, and that correct inhaler training was always provided if deciding to change patients from pMDIs to DPIs for reasons of lowering carbon footprint. In this regard, the presenter referred to pMDIs being the absolute right treatment in certain patients and DPIs in others. The Panel further noted that the overall summary slide of the entire webinar stated that it was important that both pMDIs and DPIs were available to ensure patients had access to the device that best met their clinical need.

The Panel did not consider that the presenter's comments by prompting clinicians to address the 'low hanging fruit' in relation to reducing the carbon footprint and changing devices trivialised the potential risk to patients or affected patient safety as alleged. The Panel ruled no breaches of the Code including Clause 2 in this regard.

6A Inhaler device types

The complainant raised concerns of scaremongering. In the discussion on inhaler device types, the term 'it's a recipe for disaster' was used in relation to mixing patient device types. The complainant alleged that this was rather extreme language given that the majority of patients today did have different device types and was suggesting potential patient safety considerations if device types were mixed – of which the complainant was not aware of any evidence.

The Panel noted Chiesi's acknowledgement that the webinar discussion encouraged health professionals to 'not mix device types', and that 'giving people different device types was a recipe for disaster'. The Panel noted that the presenter stated that mixing devices with different inhaler techniques would result in patients often getting one wrong and referred to BTS and GOLD advice to not mix inhalers. The Panel noted Chiesi's submission that the advice from both BTS and GOLD was that, wherever possible, mixing inhaler device types should be avoided based on studies that demonstrated that patients who were prescribed the same device were significantly more likely to achieve asthma control than those prescribed mixed devices, and that COPD patients prescribed similar devices had a lower rate of exacerbations compared with those on mixed devices.

The Panel did not consider that the complainant had established that the webinar was scaremongering in relation to mixing inhaler devices. Nor that the webinar was misleading or incapable of substantiation in this regard and the Panel ruled no breaches of the Code.

6B Place in therapy for Trimbow

The complainant alleged that a second instance of scaremongering occurred in the Q&A when participants were encouraged to approach their local consultants to ask them to put Trimbow on the local guidelines for asthma and if they did not the 'threat' was that all Global Initiative for Asthma (GINA) step 4 and 5 guidelines would be sent to them for review. This, to the complainant, felt like an aggressive tactic to accelerate listing of Trimbow on local guidelines using scaremongering as a tactic.

The Panel noted Chiesi's submission that the reference to encouraging participants to approach their local consultants to ask them to put Trimbow on the local guidelines for asthma was in response to a question on if LAMAs should be prescribed in primary care and when to refer a patient into specialist care.

The Panel noted that, in this regard, the presenter suggested that if LAMAs were not initiated in primary care, then every GINA Step 4 patient would need to be assessed in secondary care, which would be unexpected and would not be utilising the significant experience accumulated within primary care over the years. The presenter encouraged the audience to be proactive if they had strong local guidance not to initiate a LAMA in primary care, and to reach out to their consultant to ask specifically if they wanted all similar patients to be referred, or if their wish was to initiate in primary care. The presenter urged practices to allow health professionals to do what they were comfortable with. The Panel noted from the transcript that the presenter stated 'I cannot see a reason to stop primary care healthcare professionals who are very comfortable with using Trimbow from treating patients accordingly. Now I'll, if we don't do that, then the future will be that every GINA step four patient would need to be assessed in a hospital'.

The Panel noted Chiesi's submission that the discussion focussed on prescribing within the comfort zone of an individual prescriber and clarifying the local guidance with their local consultant if there was any doubt. This was especially important given the long waiting times for specialist referrals, which would negatively impact on patient safety if health professionals in primary care were not able to make certain interventions with which they already had significant experience.

The Panel did not consider that the presenter's advice constituted 'scaremongering' as alleged and no breaches of the Code including Clause 2 were ruled.

7 Reference to 'safe'

The complainant alleged Trimbow was called a 'safe' medicine by the presenter in the Q&A session. This was not addressed by the Chiesi employee who was facilitating the webinar and fell short of the complainant's expectations of pharmaceutical companies.

The Panel noted Chiesi's submission that this appeared to relate to the same question at point 6 with regards to when to initiate a LAMA. The Panel noted Chiesi's submission that the word 'safe' was specifically used in the context of the practical clinical experience of Trimbow, triple therapy and LAMAs in COPD in general, with particular reference to glycopyronium and the long history of its use in general anaesthesia systemically; when the presenter went on to describe Trimbow (and LAMAs as inhaled therapies), they were referred to as a 'well-tolerated medicine'.

The Panel, however, noted that in response to the question, the presenter stated:

> **'Trimbow. Triple therapy, LAMAs. We've all been prescribing it for COPD patients. We have no problem giving a LAMA to an older patient in the sixties, seventies, eighties, who've smoked, got COPD, got cardiac disease. Cause these are safe medicines. So what's the hesitation to prescribe. Is it because as a prescriber you're unsure about safety? Well, we're talking about a younger asthma population and remember the product I've described today Trimbow has glycopyrronium and**

glycopyrronium for decades has been used in general anaesthesia, given systemically, anaesthetists pre-op perioperatively will give glycopyrronium systemically to dry the secretions, a bit of pharmacology again. Muscarinic receptors, M1 is in the lungs and M1 is in the heart. glycopyrronium is a LAMA, that's optimized for high binding to the lungs m3 and relatively low binding to the cardiac receptor. That's why anaesthetists merrily give it. And it's a very well tolerated medicine. So by inhalation there's even less concern. And you, you, you look at the cardiac safety of glycopyrronium of triple therapy. Trimbow there, isn't an issue in COPD patients. We know we didn't see anything in the TRIMARAN study. So the hesitation to prescribe Trimbow for asthma patients in primary care, younger asthma patients cannot be based on a safety concern. So what's it based on must be the, the national guidance's. They must be worried that you cannot make a sensible, sorry, bit strong word. You cannot make the right decision for your patients regarding efficacy.'.

The Panel considered that the presenter's use of the word safe was in relation to Trimbow and not limited to the class of medicines. The Panel therefore ruled a breach of the Code.

The Panel did not consider that the particular circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and was reserved for such use. No breach of the Code was ruled.

A contactable complainant, who described him/herself as a health professional, complained about a webinar which he/she attended on 25 May 2021. The webinar was entitled 'Session 3: Evolving Developments in the Management of asthma' and was organised by Chiesi Limited.

COMPLAINT

The complainant was extremely concerned about the webinar on a number of points. The complainant recorded the webinar for his/her reference after the broadcast (a copy of the link was provided). The complainant's specific concerns were as follows:

1 The prescribing information for a promotional webinar was not present in the invitation, was not present at the beginning of the webinar, or throughout the webinar until the very end. When it was presented at the end, the text of the Trimbow (beclometasone dipropionate, formoterol fumarate dihydrate, glycopyrronium bromide) and Fostair (beclometasone dipropionate, formoterol fumarate dihydrate) prescribing information were illegible to the complainant as a webinar attendee and were both shown for a short amount of time that would not have allowed him/her to read the prescribing information even if it was legible.

2 The complainant was very concerned throughout at the use of the terms 'almost', 'pretty much', 'nearly', 'approx' etc in relation to clinical data – there were numerous examples where clinical impact was rounded up to 'almost' 60ml for example. The complainant alleged that such rounding up was potentially misleading.

3 At the ~23 minute mark, data was used for Fostair with regard to lung deposition due to its 'fine particle formulation'. It was then implied that because Trimbow was also considered by Chiesi to be a 'fine particle' formulation, that one could expect

lung deposition to the same degree as Fostair. However, there was no evidence presented to demonstrate lung deposition in Trimbow. Additionally, the complainant alleged that the data presented on 'fine particles' was not balanced as it was implied that Fostair/Trimbow were able to reach further into the lungs than other competing molecules. To the complainant's knowledge, however, other competing molecules were of sufficiently small diameter to deliver sufficient lung deposition to be efficacious treatments – again, something which was not reflected in the evidence presented.

4 The complainant did not, at any point, observe a unique approval code or date of preparation, as required by the Code he/she believed.

5 The complainant was highly concerned for patient safety when it was suggested (~27 minutes in) that changing patients' Short-Acting Beta Agonists (SABA) devices (on which they relied to save their lives where needed) were the 'low hanging fruit' and 'easy' to change them from a metered dose inhaler (MDI) to a dry-powder inhaler (DPI). The complainant alleged that the flippant remarks made trivialised the potential risk to patients by prompting clinicians to address the 'low hanging fruit' and change devices on which patients relied in life-saving situations.

6 Additional concerns were raised in two instances of what the complainant perceived to be scaremongering. In the discussion in inhaler device types, the term 'it's a recipe for disaster' was used in relation to mixing patient device types. The complainant alleged that this was rather extreme language given that the majority of patients today did have different device types and was suggesting potential patient safety considerations if device types were mixed – of which the complainant was not aware of any evidence. A second instance of scaremongering occurred in the Q&A when participants were encouraged to approach their local consultants to ask them to put Trimbow on the local guidelines for asthma – and if they did not the 'threat' was that all Global Initiative for Asthma (GINA) step 4 and 5 guidelines would be sent to them for review. This, to the complainant, felt like an aggressive tactic to accelerate listing of Trimbow on local guidelines using scaremongering as a tactic.

7 The final concern the complainant observed was, again, in the Q&A at the end of the session when Trimbow was called a 'safe' medicine by the presenter (around ~52 minutes in). This was not addressed by the Chiesi employee who was facilitating the webinar and clearly fell short of the complainant's expectations of pharmaceutical companies.

When writing to Chiesi, the Authority asked it to consider the requirements of the 2019 Code. The case preparation manager adopted the numbering in the complaint:

1 Clause 4.1.
2 Clauses 7.2.
3 Clauses 7.2 and 7.4.
4 Clause 4.8 and 9.1.
5 Clauses 2, 7.2 and 9.1.
6 Clauses 2, 7.2, 7.4 and 9.1.
7 Clauses 2 and 7.9.

RESPONSE

Chiesi submitted that it took alleged breaches of the Code very seriously and had investigated the allegations made. Chiesi's response to each of the allegations is set out below.

1 Prescribing Information

Chiesi noted that the complainant raised a number of concerns regarding the presence of prescribing information:

a '**Prescribing information for a promotional webinar was not present in the invitation**'

In order to address this concern, Chiesi submitted that it would like to highlight that although the webinar in question was promotional, it considered the invitation itself to be non-promotional(copy provided). In particular, there was no reference to product, either directly or indirectly, within the invitation, or in the title. Given that the material at issue was non-promotional, and prescribing information was only required on promotional materials, Chiesi intentionally did not include prescribing information within the invitation.

Also of relevance was the prominent mention within the invitation that the webinar would contain promotional content. Chiesi believed this was important to ensure the audience was not misled as to the promotional content of the actual webinar.

b '**Prescribing information was not present at the start of the webinar**'

Chiesi obtained from the agency managing the webinar the actual webinar recording from the 25 May 2021, which included both the pre-recorded, pre-approved content, and the live Q&A at the end of the pre-recorded content (copies provided). From this recording, Chiesi could confirm that the webinar started at the beginning of the pre-recorded, pre-approved content, and that there was a prominent declaration on the first slide as to where prescribing information could be found (ie at the end of the presentation).

On comparison of the recording, of the actual webinar against the recording taken by the complainant, it was clear that he/she had missed the first one minute six seconds of the webinar, and therefore missed the aforementioned declaration.

c '**Prescribing information was illegible at the end of the presentation**' **and 'shown for a short amount of time**'

To address this concern, Chiesi analysed the length of time that the prescribing information relating to the relevant products was shown at the end of the presentation. From this analysis, Chiesi could confirm that the Trimbow prescribing information was shown for 16 seconds, and the Fostair prescribing information was shown for 15 seconds. In Chiesi's view, this was a significant amount of time for digital material, and sufficient to meet the requirements of the Code.

Chiesi disputed the allegation that the prescribing information was illegible, as its recording showed it to be clearly legible (copy provided). The Chiesi personnel facilitating the webinar also considered the prescribing information to be clear and legible. The recording provided by

the complainant was not as clear as Chiesi's own recording and experience on the day; the recording provided by the complainant was of inferior quality and appeared to jump at various points. Perhaps this resulted from the complainant experiencing connection challenges during the webinar.

2 Terminology

Chiesi noted that the complainant was very concerned at the use of the terms 'almost', 'pretty much', 'nearly', 'approx' in relation to clinical data, and described one specific instance where the 'clinical impact was rounded up to almost 60mls' which the complainant felt was 'potentially misleading'.

In order to address this broad allegation, Chiesi reviewed the transcript of the webinar (copy provided) to identify all instances where these terms were used. Chiesi referred to the breakdown below of all instances where similar terms were used, the scenario in which they were used and the actual value of the clinical data.

Statement	Scenario	Fact
'*The exacerbation reduction is about 20% and lung function is improved by approximately 80 to 150mls in the different studies*'	Discussion on summary of Long-Acting Muscarinic-Antagonists (LAMA) in asthma evidence	Trial 1: 86 ± 34 mL Trial 2: 154 ± 32 mL
'Nearly 1150 patients in this study'	TRIMARAN study baseline characteristics	1155 randomly assigned 1050 in safety population 1081 completed treatment
'Only about 35 patients in each arm dropped out'	TRIMARAN study baseline characteristics	Beclomethasone dipropionate (BDP)/Fluticasone furoate (FF)/glycopyrronium bromide (GB) arm: 35 patients BDP/FF arm: 34 patients
'Mean was about 55% predicted'	TRIMARAN study baseline characteristics	BDP/FF/GB arm: 55.2% BDP/FF arm: 55.7%
'About 20% had two or more exacerbations in the last year'	TRIMARAN study baseline characteristics	18% in both arms

'Almost 60ml difference'	TRIMARAN Results	57ml difference
'More than 400mls improvement'	TRIMARAN Results	401ml difference
'About 26% treatment difference in favour of Trimbow'	TRIMARAN Results	26.3%
'When you look at the power group, it's even bigger, 37% approximately'	TRIMARAN Results	37.7%

Chiesi firmly believed that all statements above accurately reflected the actual clinical data and were not misleading as alleged, or at all.

Chiesi submitted that with particular reference to the instance highlighted by the complainant, where the 'clinical impact was rounded up to 60mls', the actual value of the clinical data was 57mls improvement: firstly, Chiesi contended that 'almost 60mls' accurately reflects a 57mls improvement; and secondly, immediately after this statement there was a discussion specifically related to the clinical relevance of a 57mls improvement. Accordingly, the audience would have been in no doubt as to the clinical relevance of this data.

3 <u>Reference to fine particle formulation</u>

a The complainant referred to the presentation of data on 'fine particle formulation', and suggested that it was 'implied that because Trimbow was also considered by Chiesi to be a fine particle formulation, that one could expect lung deposition to the same degree as Fostair'. The complainant then went on to state that 'there was no evidence presented to demonstrate lung deposition in Trimbow'.

In response to this allegation, Chiesi referred to the summary of product characteristics (SPC) for both Fostair and Trimbow, both of which were specifically referred to as extrafine formulations. Chiesi believed it was important to educate health professionals and other relevant decision makers (ORDMs) on the extrafine formulation characteristics of both products as it was the primary reason for the increased potency of the corticosteroid component within both products thus a key consideration when prescribers were assessing an appropriate inhaled dose for their patients.

Chiesi had also summarised below the evidence to substantiate the lung deposition associated with Fostair and Trimbow:

- Higher proportion of lung deposition in the small airways compared to large airways for Fostair; similar lung deposition between healthy volunteers, asthma patients and chronic obstructive pulmonary disease (COPD) patients (DeBacker 2010 [pressurised metered-dose inhaler (pMDI); (copy provided)]; Virchow 2018 [DPI; (copy provided)]).
- Similar lung deposition between Fostair and Trimbow in COPD (Usmani 2018; (copy provided)).

Chiesi submitted that when taking all the above into consideration, it was clear that both Fostair and Trimbow were extrafine formulations which resulted in a higher proportion of lung

deposition in the small airways than in the large airways. Chiesi could also clearly demonstrate that it had lung deposition data for Trimbow in COPD, and the assumption would be that there would be similar deposition in asthma (given the same devices and similar lung deposition in COPD). Chiesi asserted that it was both reasonable and of interest to health professionals to include lung deposition characteristics for both products with the promotional material at issue as it was the primary reason for the increased potency of the corticosteroid component within both products which, as already mentioned, was a key consideration when prescribers were assessing an appropriate inhaled dose for their patients.

b The complainant also alleged that 'the data presented on fine particle fraction was not balanced, and implied that Fostair/Trimbow are able to reach further into the lungs than other competing molecules'. They then opined that 'other competing molecules are of sufficiently small diameter to deliver sufficient lung deposition to be efficacious treatments' and that 'this was not reflected in the evidence presented'.

Chiesi disputed the allegation that the lung deposition data was comparative to any specific comparator product, either directly or indirectly. Rather, Chiesi asserted that the lung deposition data presented was purely a description of the lung deposition data that existed for Chiesi's products (Fostair and Trimbow) in isolation and therefore, by definition, could not be considered a comparison with competitor products. The fact that the presenter did not mention other products did not render it unbalanced in any way.

Chiesi respectfully referred to previous PMCPA rulings where reference to one product in isolation did not infer a comparison where one did not exist (Cases AUTH/2834/4/16, AUTH/2822/2/16 and AUTH 3406/10/20).

Without prejudice to Chiesi's primary contention that the statement was not comparative, it was certainly capable of substantiation. Chiesi provided a publication which demonstrated that the proportion of peripheral lung deposition of Trimbow was higher than it was for Trelegy for all three of the components (0.48 ±0.13, 0.48±0.13 and 0.49±0.13 for beclometasone, formoterol and glycopyrronium, respectively; 1.96±0.84, 0.97±0.34 and 1.20±0.48 for fluticasone, vilanterol and umeclidinium, respectively).

At no point during the webinar, or Q&A, was reference made to Fostair or Trimbow being a more efficacious treatment than any competing molecules. In fact, the efficacy data for the majority of inhaled corticosteroid (ICS)/ Long-acting bronchodilator inhalers (LABAs) and ICS/LABA/LAMAs was similar irrespective of the differences in particle size and/or lung deposition. In support of this, Chiesi submitted that it always briefed its speakers to ensure that lung deposition data was never linked to efficacy of maintenance treatments.

4 Presence of Approval Code and Date of Preparation

Chiesi noted that the complainant alleged that there was a lack of 'unique approval code or date of preparation'.

The webinar recording taken by the agency managing the webinar, which included both the pre-recorded, pre-approved content, as well as the live Q&A at the end of the pre-recorded content (copy provided) confirmed that the webinar started at the beginning of the pre-recorded, pre-

approved content. It showed that on slide 1 there was a Veeva approval number as well as a date of preparation of the pre-recorded content (copy provided); UK-TRI-2100147; April 2021).

Chiesi submitted that given that the complainant missed the first 1 minutes 6 seconds of the webinar, it would appear that he/she also missed the Veeva approval number and date of preparation.

Chiesi provided the requested copy of the certificate for the pre-recorded webinar as well as the job number, job title and qualifications of the relevant signatories.

The signatories appeared on Chiesi's latest Nominated Signatories Form which was provided to the PMCPA on 17 February 2021.

5 SABA claims linked to patient safety

Chiesi noted that the complainant expressed his/her concern for patient safety with reference to a discussion within the webinar where 'it was suggested that changing patients SABA devices (on which they rely to save their lives where needed) were the 'low hanging fruit' and 'easy' to change them from an MDI to a DPI'.

It was important to consider the context in which this statement was made; namely the section of the webinar focused on the impact of inhalers on the environment, the relatively high clinical use of SABAs, and the importance of the right device for the right patient.

The commentary initially discussed the carbon footprint of inhalers, and then moved on to highlight the relatively high percentage of prescriptions for SABAs compared with maintenance treatments. At this point the presenter opined that if one wanted to do something about the carbon footprint of inhalers, then a priority would be to reduce prescriptions of SABA and instead put patients on an effective maintenance therapy so that they used their reliever (ie SABA) less. The presenter then moved on to describe the clinical impact associated with SABA overuse, including asthma deaths and exacerbations, Chiesi provided copies to substantiate this.

The presenter then recommended that patients were put on better maintenance treatments so that they could better manage their asthma, which would result in using their reliever medication less. The presenter then finished by highlighting that the audience should also consider whether they were using devices with the lowest carbon footprint. Importantly, the presenter also discussed the importance in ensuring that the right patient was on the right device, and that correct inhaler training was always provided.

Given the above commentary, Chiesi refuted the allegation that the webinar in any way posed a risk to patient safety. On the contrary, Chiesi firmly believed that patient safety was at the centre of its messaging, especially given the strong body of evidence supporting the view that SABA overuse was associated with significant morbidity and mortality, and therefore was an issue that needed to be addressed with a degree of urgency. Additionally, Chiesi also highlighted the importance that the right patient was on the right device, and of correct inhaler technique, again demonstrating the need to put the patient at the centre of its messaging.

6A Inhaler device types

Chiesi noted that the complainant raised concern over a discussion during the webinar on inhaler device types where 'the term 'it's a recipe for disaster' was used in relation to mixing patient device types'. The complainant considered that this was 'rather extreme language given that the majority of patients today do have different device types and was suggesting potential patient safety considerations if device types were mixed'.

Chiesi referred to the transcript of the pre-recorded webinar. Chiesi acknowledged that the discussion encouraged health professionals to 'not mix device types', and that 'giving people different device types is a recipe for disaster'. However, there was firm clinical rationale supported by institutions (described below) that supported this view.

1 Firstly, the advice from both BTS and GOLD (both of which were internationally renowned recommendations) was that, wherever possible, mixing inhaler device types should be avoided:

- '***Determinants of poor inhaler technique in asthma and COPD patients includes:… use of multiple devices…***' (Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report 2021; copy provided).

- '***Prescribing mixed inhaler types may cause confusion and lead to increased errors in use. Using the same type of device to deliver preventer and reliever treatments may improve outcomes***'. (BTS/ Scottish Intercollegiate Guidelines Network (SIGN) British Guideline on the Management of Asthma 2019; copy provided).

Both these guidelines recommended not mixing inhaler device types based on studies that demonstrated that patients who were prescribed the same device were significantly more likely to achieve asthma control than those prescribed mixed devices and that COPD patients prescribed similar devices had a lower rate of exacerbations compared with those on mixed devices.

2 Secondly, the actual wording in question suggested that mixing inhaler device types is a **recipe** for disaster, not that it **will** be a disaster. The discussion then described why this was the case: '***an MDI needs slow inhalation, and a dry powder needs a fast inhalation… If you mix up these different inhalation techniques, patients will often get one wrong***'.

Importantly, this section of the webinar finished by emphasising the importance of inhaler technique and bringing a patient with you.

Taking the above arguments together, it was clear, in Chiesi's opinion, that the discussion to avoid mixing device types was in line with current international recommendations and with patient safety in mind.

6B Place in therapy for Trimbow

Chiesi noted that the complainant considered a section of the Q&A to constitute 'scaremongering' when 'participants were encouraged to approach their local consultants to ask them to put Trimbow on the local guidelines for asthma - and if they didn't the "threat" was that all GINA step 4 and 5 guidelines would be sent to them for review'.

Transcript of the Q&A (copy provided) showed that this part of the discussion was in response to a question on when to refer a patient into specialist care.

The commentary suggested that if LAMAs were not initiated in primary care, then every GINA Step 4 patient would need to be assessed in secondary care. The presenter then went on to express their opinion that if this happened it would be unexpected and would not be utilising the significant experience accumulated within primary care over the years. The presenter then encouraged the audience to be proactive if they had strong local guidance not to initiate a LAMA in primary care, and to reach out to their consultant to ask specifically if they wanted all similar patients to be referred, or if their wish was to initiate in primary care. To finish, the presenter urged local practices to allow health professionals to do what they were comfortable with.

In light of the above, Chiesi vehemently denied the suggestion that there was scaremongering or a threat contained within the discussion, but instead contended that it focussed on prescribing within the comfort zone of an individual prescriber and clarifying the local guidance with their local consultant if there was any doubt. This was especially important given the long waiting times for specialist referrals (up to a year in some cases), which would negatively impact on patient safety if health professionals in primary care were not able to make certain interventions with which they already had significant experience.

7 Reference to 'safe'

Chiesi noted that the complainant stated that 'Trimbow was called a 'safe' medicine by the presenter', and that 'this was not addressed by the Chiesi employee who was facilitating the webinar and clearly fell short of our expectations of pharmaceutical companies'.

This aspect of the complaint appeared to relate to the discussion in response to a question on when to initiate a LAMA.

The word 'safe' was specifically used in the context of the practical clinical experience of LAMAs in general, with particular reference to glycopyronium and the long history of use in general anaesthesia. Importantly, when the presenter went on to describe Trimbow (and LAMAs as inhaled therapies), they were referred to as a 'well-tolerated medicine'.

Furthermore, within the body of the webinar, the presenter also referred to Trimbow as 'well tolerated' when discussing the adverse events within the clinical trials.

Taking the above points together, Chiesi refuted the allegation that Trimbow was referred to as 'safe' and it was Chiesi's view that any reference to actual products was sufficiently contextualised.

Details on the arrangements for the webinar

Chiesi submitted that the PMCPA had requested 'comprehensive details about the webinar', including 'Chiesi's role', 'copies of the presentation', the 'agenda', and 'all information sent to those who registered for the webinar'.

Health professionals were invited either via an email from a Chiesi sales representative, or from Guidelines in Practice (utilising a database of health professionals who had provided consent to

be contacted with pharmaceutical mailings). In both situations, the health professionals were directed to a registration website. Once a health professional was registered to attend the webinar, they would immediately receive a confirmatory email, and consequently two reminder emails (one email one day before the event, and then another one hour before the event).

In summary, Chiesi referred to the following documents (copies provided):

- Email invitation to webinar sent through third party
- Briefing to Chiesi commercial team to invite customers, with email template included
- Invitation to webinar, provided to healthcare professionals as an attachment to emails from the commercial team
- Registration page, and email reminders
- Pre-recorded, pre-approved, webinar content

Apart from the above documentation, there was no further information furnished, or correspondence entered into, with any webinar attendees, and no agenda provided other than that shown on the overview slide during the webinar itself.

In addition to the details of the webinar, the PMCPA had also requested 'comment on the role of the Chiesi employee facilitating the webinar', details on 'who was in charge of slide progression', and a 'copy of any briefings'.

The pre-recorded content for the webinar was developed remotely due to COVID-related restrictions, using a split screen with both the speaker and slides visible side-by-side. During the recording, the speaker presented each slide in turn, pausing after every slide to instruct the agency to move onto the next slide. Following the recording, the file was edited to remove the parts where the speaker instructed movement between slides. This pre-recording was then certified for use during the webinar on 25 May 2021 (copy provided).

On the day of the webinar, a senior member of the marketing team facilitated the Q&A session. This senior member of the marketing team had a strong knowledge of the Code, with significant experience within the pharmaceutical industry (ten years in marketing, and seven years as a sales representative). They were also very experienced managing speakers, webinars and facilitating Q&A sessions. Due to the significant experience of this individual, Chiesi did not provide a separate briefing.

With reference to the PMCPA's request for a speaker briefing, Chiesi submitted that it was worthy of note that the speaker was a very experienced speaker with the pharmaceutical agency and was fully aware of the requirements of the Code. This webinar was part of a series of webinars, and therefore was originally briefed at the start of the webinar series, before the pre-recording took place. Furthermore, any potential areas of concern were re-recorded to ensure compliance with the Code.

The speaker was additionally briefed verbally immediately before the webinar by the senior member of the marketing team facilitating the webinar. This verbal briefing included any potential areas of compliance concern, including reference to 'well tolerated' rather than 'safe' for Chiesi's products. As part of Chiesi's investigation into this complaint, it had spoken to the speaker who had confirmed that there was a clear briefing provided and he was fully aware of the Code requirements.

In reliance upon the facts and matters set out in this response, Chiesi strongly denied all of the allegations raised by the complainant and respectfully submitted that there had been no breach of any of Clauses 2, 4.1, 4.8, 7.2, 7.4, 7.9 and 9.1 of the Code.

PANEL RULING

1 Prescribing information

The Panel noted that the invitation to the webinar 'Evolving developments in the management of asthma' stated that the webinar, which was for UK health professionals only, had been organised and funded by Chiesi and contained promotional content. The Panel noted that there was no direct or implied mention of any Chiesi medicine in the invitation at issue. The Panel considered that whilst it might have been prudent to provide prescribing information, the invitation was not promotional in itself and therefore ruled no breach of Clause 4.1 in relation to the webinar invitation.

With regard to the complainant's concern that the prescribing information was not present at the beginning of the webinar, the Panel noted that this was not a requirement of the Code. The Panel noted, however, that the opening slide of the webinar recording provided by Chiesi, which was not included in the recording of the webinar provided by the complainant, stated that the prescribing information was available at the end of the presentation in line with the Code's requirements.

The Panel noted that in relation to presentations delivered at a meeting, it was an established principle that if prescribing information formed part of the presentation in the absence of alternative formats, it should be of sufficient clarity and duration so that it was easily readable. The Panel noted Chiesi's submission that the Trimbow and Fostair prescribing information was shown for 16 seconds and 15 seconds, respectively, which, in Chiesi's view, was a significant amount of time for digital material; further that its recording showed the prescribing information to be clearly legible. The Panel viewed the recording provided by Chiesi and, in its view, the font of the prescribing information was difficult to read; the Panel noted that the size of screen used by participants might be relevant to the legibility of the prescribing information but considered that the print was slightly blurred and enlarging it did not assist with its legibility. The Panel further considered that the length of time the prescribing information for Trimbow (33.39 – 33.54) and Fostair (33.54 - 34.09) was displayed was insufficient to allow attendees to read it. The Panel therefore ruled a breach of Clause 4.1 in relation to the webinar.

2 Terminology

The Panel noted that whilst the complainant raised concerns with regards to use of the terms 'almost', 'pretty much', 'nearly', 'approx' in relation to clinical data he/she only described one specific instance where the 'clinical impact was rounded up to almost 60mls', which in his/her view was 'potentially misleading'.

The Panel noted that Chiesi had reviewed the transcript of the webinar to identify all instances where the above terms were used and submitted the scenario in which they were used and the actual value of the clinical data. The Panel noted Chiesi's submission that with regard to where the 'clinical impact was rounded up to 60mls', the actual value of the clinical data was 57mls improvement; immediately after the statement, there was a discussion specifically related to the clinical relevance of a 57mls improvement so the audience would have been in no doubt as to

the clinical relevance of that data. The Panel noted that the presenter referred to 'almost 60mls' in relation to a slide which clearly stated 'adjusted mean difference 57ml'. A question was also asked in the Q&A section about the 57ml improvement in lung function shown and its clinical significance.

The Panel noted that the complainant bore the burden of proof and did not consider that he/she had established that use of the terms 'almost', 'pretty much', 'nearly', 'approx' in relation to clinical data or referring to 'almost 60mls' when the actual value of the clinical data was 57mls which was included in the presentation slide was misleading as alleged and no breach of Clause 7.2 was ruled.

3 Reference to fine particle formulation

The Panel noted that the speaker presented a slide titled 'Extrafine formulation Fostair (beclomethosone formoterol) pMDI 100/6 can reach the large and small airways'. The slide detailed a scintigraphy study (De Backer *et al*). The presenter explained that it could be seen in the study that drug particles from the extrafine Fostair formulation were reaching small airways and noted that approximately 30% or more of the medicine was deposited in the lungs and of this around one third reached the small airways; the extrafine formulations were capable of reaching the distal lung. In summary, the presenter stated that as could be seen from the ATLANTIS study, the higher prevalence of small airway disease in asthma, particularly in GINA step four/five, and that using an extrafine formulation, such as Fostair, one could ensure that medicine reached large and small airways. The presenter then reminded viewers that Trimbow was also an extrafine formulation.

The Panel noted the complainant's concern that the implication was that because Trimbow was also considered by Chiesi to be a 'fine particle' formulation, that one could expect lung deposition to the same degree as Fostair but there was no evidence presented to demonstrate lung deposition in Trimbow. The Panel noted that Trimbow was described in its SPC as an aerosol with extrafine particles. The Panel further noted the summarised evidence provided by Chiesi to substantiate the lung deposition associated with Fostair and Trimbow which included:

- Higher proportion of lung deposition in the small airways compared to large airways for Fostair; similar lung deposition between healthy volunteers, asthma patients and chronic obstructive pulmonary disease (COPD) patients (DeBacker 2010 [pressurised metered-dose inhaler (pMDI)]; Virchow 2018 [DPI]).

- Similar lung deposition between Fostair and Trimbow in COPD (Usmani 2018).

The Panel noted Chiesi's submission that it was clear that both Fostair and Trimbow were extrafine formulations which resulted in a higher proportion of lung deposition in the small airways than in the large airways.

The Panel noted that in referring to Trimbow as an extrafine formulation, following the details of how the extrafine Fostair formulation reached the small airways, there was the implication that Trimbow would similarly do so. Whilst the Panel noted that there was no evidence in this regard included in the webinar, it appeared from Chiesi's submission that it did have evidence of similar lung deposition between Fostair and Trimbow in COPD and lung deposition data for Trimbow in COPD. The Panel noted Chiesi's submission that the assumption would be that there would be similar deposition in asthma (given the same devices and similar lung deposition in COPD). On

the evidence provided, the Panel did not consider that it had been established that the statement itself nor its implication was misleading or could not be substantiated, as alleged, and the Panel ruled no breach of Clauses 7.2 and 7.4.

The complainant also alleged that 'the data presented on fine particle fraction was not balanced, and implied that Fostair/Trimbow were able to reach further into the lungs than other competing molecules' when in his/her view 'other competing molecules are of sufficiently small diameter to deliver sufficient lung deposition to be efficacious treatments'.

The Panel noted Chiesi's submission that the lung deposition data presented was purely a description of the data for Chiesi's products (Fostair and Trimbow) in isolation; it was not comparative to any specific comparator product, either directly or indirectly and, therefore, by definition, could not be considered a comparison with competitor products. The Panel noted Chiesi's submission that at no point during the webinar, or Q&A, was reference made to Fostair or Trimbow being a more efficacious treatment than any competing molecules based on its lung deposition. The efficacy data for the majority of inhaled corticosteroid (ICS)/ long-acting bronchodilator inhalers (LABAs) and ICS/LABA/LAMAs was similar irrespective of the differences in particle size and/or lung deposition. In support of this, Chiesi submitted that it always briefed its speakers to ensure that lung deposition data was never linked to efficacy of maintenance treatments. The Panel did not consider that the complainant established that presenting data for Fostair and Trimbow misleadingly implied that the medicines were able to reach further into the lungs than other competing molecules. No breach of Clause 7.2 was ruled.

4 Approval code and date of preparation

The Panel noted that Clause 4.8 of the 2019 Code stated that promotional material other than advertisements appearing in professional publications must include the date on which the promotional material was drawn up or last revised. Whilst not a Code requirement, the Guidelines on company procedures relating to the Code of Practice stated that each certificate should bear a reference number with the same reference number appearing on the promotional material in question so that there can be no doubt as to what has been certified. A particular reference number should relate to only one item of promotional material.

The Panel noted that the opening slide of the webinar recording provided by Chiesi included the Job Code UK-TRI-2100147 and a date of preparation of April 2021. As the date of preparation was given, the Panel ruled no breach of Clauses 4.8 and 9.1.

5 SABA claims linked to patient safety

The Panel noted that reference to SABA devices as the 'low hanging fruit' and it being the inhaler devices that were the easiest to change rapidly was made in the context of reducing the carbon footprint. The Panel noted that within this section of the webinar, the presenter initially discussed the carbon footprint of inhalers , and then moved on to highlight the relatively high percentage of prescriptions for SABAs compared with maintenance treatments. The presenter suggested that if one wanted to do something about the carbon footprint of inhalers, then a priority would be to reduce prescriptions of SABA and instead put patients on an effective maintenance therapy so that they used their reliever (ie SABA) less. The presenter also referred to considering the carbon footprint of different types of SABAs. The presenter then moved on to describe the clinical impact associated with SABA overuse, including asthma

deaths and exacerbations. The presenter finished by highlighting that the audience should also consider whether they were using devices with the lowest carbon footprint and also discussed the importance in ensuring that the right patient was on the right device, and that correct inhaler training was always provided if deciding to change patients from pMDIs to DPIs for reasons of lowering carbon footprint. In this regard, the presenter referred to pMDIs being the absolute right treatment in certain patients and DPIs in others. The Panel further noted that the overall summary slide of the entire webinar stated that it was important that both pMDIs and DPIs were available to ensure patients had access to the device that best met their clinical need.

The Panel did not consider that the presenter's comments by prompting clinicians to address the 'low hanging fruit' in relation to reducing the carbon footprint and changing devices trivialised the potential risk to patients or affected patient safety as alleged. The Panel ruled no breach of Clauses 7.2, 9.1 and 2 in this regard.

6A Inhaler device types

The Panel noted Chiesi's acknowledgement that the webinar discussion encouraged health professionals to 'not mix device types', and that 'giving people different device types was a recipe for disaster'. The Panel noted that the presenter stated that mixing devices with different inhaler techniques would result in patients often getting one wrong and referred to BTS and GOLD advice to not mix inhalers. The Panel noted Chiesi's submission that the advice from both BTS and GOLD was that, wherever possible, mixing inhaler device types should be avoided; the BTS/ Scottish Intercollegiate Guidelines Network (SIGN) British Guideline on the Management of Asthma 2019 stated '***Prescribing mixed inhaler types may cause confusion and lead to increased errors in use. Using the same type of device to deliver preventer and reliever treatments may improve outcomes***' and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report 2021 included that '***Determinants of poor inhaler technique in asthma and COPD patients includes:… use of multiple devices…***' (emphasis added by Chiesi).

The Panel noted Chiesi's submission that both guidelines recommended not mixing inhaler device types based on studies that demonstrated that patients who were prescribed the same device were significantly more likely to achieve asthma control than those prescribed mixed devices, and that COPD patients prescribed similar devices had a lower rate of exacerbations compared with those on mixed devices.

The Panel did not consider that the complainant had established that the webinar was scaremongering in relation to mixing inhaler devices. Nor that the webinar was misleading or incapable of substantiation in this regard and the Panel ruled no breach of Clauses 7.2 and 7.4.

6B Place in therapy for Trimbow

The Panel noted Chiesi's submission that the transcript of the Q&A showed that reference to encouraging participants to approach their local consultants to ask them to put Trimbow on the local guidelines for asthma was in response to a question on if LAMAs should be prescribed in primary care and when to refer a patient into specialist care.

The Panel noted that, in this regard, the presenter suggested that if LAMAs were not initiated in primary care, then every GINA Step 4 patient would need to be assessed in secondary care. The presenter then went on to express his/her opinion that if this happened it would be

unexpected and would not be utilising the significant experience accumulated within primary care over the years. The presenter encouraged the audience to be proactive if they had strong local guidance not to initiate a LAMA in primary care, and to reach out to their consultant to ask specifically if they wanted all similar patients to be referred, or if their wish was to initiate in primary care. To finish, the presenter urged local practices to allow health professionals to do what they were comfortable with. The Panel noted from the transcript that the presenter stated 'I cannot see a reason to stop primary care healthcare professionals who are very comfortable with using Trimbow from treating patients accordingly. Now I'll, if we don't do that, then the future will be that every GINA step four patient would need to be assessed in a hospital'.

The Panel noted Chiesi's submission that the discussion focussed on prescribing within the comfort zone of an individual prescriber and clarifying the local guidance with their local consultant if there was any doubt. This was especially important given the long waiting times for specialist referrals (up to a year in some cases), which would negatively impact on patient safety if health professionals in primary care were not able to make certain interventions with which they already had significant experience.

The Panel did not consider that the presenter's advice constituted 'scaremongering' as alleged and no breach of Clause 9.1 was ruled.

The Panel noted its comments and rulings above and consequently ruled no breach of Clause 2.

7 Reference to 'safe'

The Panel noted Chiesi's submission that this aspect of the complaint appeared to relate to the discussion in response to the same question at point 6 with regards to when to initiate a LAMA. The Panel noted Chiesi's submission that the word 'safe' was specifically used in the context of the practical clinical experience of Trimbow, triple therapy and LAMAs in COPD in general, with particular reference to glycopyronium and the long history of its use in general anaesthesia systemically; when the presenter went on to describe Trimbow (and LAMAs as inhaled therapies), they were referred to as a 'well-tolerated medicine'.

The Panel, however, noted that in response to the question, the presenter stated:

> 'Trimbow. Triple therapy, LAMAs. We've all been prescribing it for COPD patients. We have no problem giving a LAMA to an older patient in the sixties, seventies, eighties, who've smoked, got COPD, got cardiac disease. Cause these are **safe** medicines. So what's the hesitation to prescribe. Is it because as a prescriber you're unsure about safety? Well, we're talking about a younger asthma population and remember the product I've described today Trimbow has glycopyrronium and glycopyrronium for decades has been used in general anaesthesia, given systemically, anaesthetists pre-op perioperatively will give glycopyrronium systemically to dry the secretions, a bit of pharmacology again. Muscarinic receptors, M1 is in the lungs and M1 is in the heart. glycopyrronium is a LAMA, that's optimized for high binding to the lungs m3 and relatively low binding to the cardiac receptor. That's why anaesthetists merrily give it. And it's a very well tolerated medicine. So by inhalation there's even less concern. And you, you, you look at the cardiac safety of glycopyrronium of triple therapy. Trimbow there, isn't an issue in COPD patients. We know we didn't see anything in the TRIMARAN study. So the hesitation to prescribe Trimbow for asthma patients in primary

> care, younger asthma patients cannot be based on a safety concern. So what's it based on must be the, the national guidance's. They must be worried that you cannot make a sensible, sorry, bit strong word. You cannot make the right decision for your patients regarding efficacy.'.

The Panel considered that the presenter's use of the word safe was in relation to Trimbow and not limited to the class of medicines. The Panel therefore ruled a breach of Clause 7.9.

The Panel did not consider that the particular circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and was reserved for such use. No breach of Clause 2 was ruled.

Complaint received **26 May 2021**

Case completed **8 February 2022**