NUMBER 87 February 2015

# CODE OF PRACTICE REVIEW

PMCPA | Prescription Medicines Code of Practice Authority

**The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.**

## CODE IN CONTEXT

The PMCPA has been developing and road testing the new 'Code in Context' module, which will be launched in March. We have been working closely with, and advised by, the Compliance Network of the PMCPA, whose members represent a range of pharmaceutical companies.

The aim of this toolkit is to enable in-house compliance specialists to run interactive workshops which will increase the value that staff attach to self-regulation and encourage positive engagement with the Code. The toolkit can be tailored to include in-house procedures and processes and includes a number of scenarios for discussion.

If you would like to know more about the toolkit please contact Elly Button (ebutton@pmcpa.org.uk, 020 7747 8884).

## GOODBYE AND WELCOME

Vicky Bewer who joined the Authority in May 2009, left in January 2015 to start a new job. The Authority thanks Vicky for all her hard work and wishes her every success in her now role. Elly Button has joined the PMCPA on a short term contract as Head of Communications. This is a busy time for us, as we continue to develop our website and other activities.

## PUBLIC REPRIMAND FOR CHIESI

In a case about the promotion Fostair, (Case AUTH/2618/7/13), Chiesi has been publicly reprimanded by the Code of Practice Appeal Board for providing inaccurate information to the PMCPA both during the consideration of the case and at a subsequent audit.

In Case AUTH/2618/7/13, the Panel ruled a claim in breach of the Code but additionally noted a discrepancy between the presentation of the claim at issue in the material provided by Chiesi and the citation of that claim by the parties. Following notification of the Panel's rulings, the complainant (AstraZeneca) provided a copy of the item at issue which showed the claim presented differently compared with the material provided by Chiesi. Before the PMCPA raised the matter with Chiesi, the company contacted the PMCPA and explained that an employee had changed the presentation of the claim after what should have been the final form, had been certified. This discrepancy had not been picked up by the company until it received the outcome of the Panel's consideration of the case. Following this admission by Chiesi, the Panel asked for further details and reconvened to consider the matter. Upon receipt of more information the Panel noted Chiesi's further admission that in its first undertaking, the date stated as being that on which the material was withdrawn was wrong; the material was actually withdrawn two weeks later.

The Panel reported Chiesi to the Appeal Board. On consideration of that report in October 2013, the Appeal Board noted Chiesi's submission that the failure to follow the correct approval process, and to recognise the difference between the approved leavepiece and the one that was distributed, and mistakes in its undertaking arose from human error and lack of attention to detail. In that regard the Appeal Board noted Chiesi had previously been censured for providing the PMCPA with inaccurate information (Case AUTH/2435/8/11) and it considered that Chiesi's repeated failure in this regard was completely unacceptable. Self-regulation relied upon the provision of complete and accurate information by pharmaceutical companies. The Appeal Board was extremely concerned about Chiesi's conduct and decided to require an audit of its procedures in relation to the Code and a subsequent re-audit.

The first audit was conducted in March 2014 and upon consideration of that audit report the Appeal Board noted that the company still had much work to do. In particular the Appeal Board was appalled that Chiesi had stated that a standard operating procedure had been updated when it had not. The Appeal Board considered that the further provision of false information to the PMCPA was completely unacceptable.

The second audit was conducted in October 2014 and upon its consideration of that report, the Appeal Board noted that progress had been made. The Appeal Board reminded the company that the provision of inaccurate information was completely unacceptable but on the basis that compliance plans were completed, progress continued to be made and the company's focus on compliance was maintained, the Appeal Board decided that, on balance, no further action was required.

Full details of Case AUTH/2618/7/13 can be found on page 3 of this issue of the Review.

## CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, run by the Prescription Medicines Code of Practice Authority and open to all comers, are held on a regular basis in central London.

These full day seminars offer lectures on the Code and the procedures under which complaints are considered, discussion of case studies in syndicate groups and the opportunity to put questions to the Code of Practice Authority.

The next Code of Practice seminar dates on which places remain available are:

Friday 27 March 2015
Friday 19 June 2015

Short training sessions on the Code or full day seminars can be arranged for individual companies, including advertising and public relations agencies and member and non member companies of the ABPI. Training sessions can be tailored to the requirements of the individual company.

*For further information regarding any of the above, please contact Nora Alexander for details (020 7747 1443 or nalexander@pmcpa.org.uk).*

## HOW TO CONTACT THE AUTHORITY

Our address is:
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7th Floor, Southside, 105 Victoria Street, London SW1E 6QT

www.pmcpa.org.uk

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| Telephone: | 020 7747 8880 |
| Facsimile: | 020 7747 8881 |

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or lmatthews@pmcpa.org.uk).

Direct lines can be used to contact members of the Authority.

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| Heather Simmonds: | 020 7747 1438 |
| Etta Logan: | 020 7747 1405 |
| Jane Landles: | 020 7747 1415 |

The above are available to give informal advice on the application of the Code of Practice.

The Authority rather than the ABPI is the contact point for information on the application of the Code.

**CASE AUTH/2618/7/13**

# ASTRAZENECA v CHIESI

## Promotion of Fostair

**AstraZeneca complained about a Fostair (formoterol/beclometasone pressurised inhalation solution) leavepiece issued by Chiesi. AstraZeneca marketed Symbicort (budesonide/formoterol turbohaler). Both medicines were indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid (ICS) and long-acting ß$_2$ adrenoceptor agonist (LABA)) was appropriate.**

**The detailed response from Chiesi is given below.**

**AstraZeneca alleged that 'for an extra fine day', immediately below 'New licence for Maintenance And Reliever Therapy' on page 1 of the leavepiece, was an unqualified and unsubstantiated claim for Fostair which suggested that patients returned to an improved pre-symptom state with Fostair; the illusion was compounded by the illustration.**

**The Panel noted that 'for an extra fine day' appeared within the headline 'New licence for Maintenance And Reliever Therapy for an extra fine day'. The Panel noted that 'extra fine' in the claim at issue had been written as two words. It appeared as one word 'extrafine' in the SPC when describing the formulation.**

**The Panel accepted that the use of 'for an extra fine day' was a play on words but considered that the heading to page 1 was not sufficiently clear about what 'extra fine' referred to, there was an implication that it referred to a clinical benefit and not just to the product's formulation as submitted by Chiesi and it was ambiguous in this regard. 'Extra' by implication rendered the claim 'for an extra fine day' comparative; use of the product for the new licence provided an extra clinical benefit over and above an appropriate comparator. This implication was misleading. Chiesi provided no data to support such an advantage. The Panel noted AstraZeneca's submission that there was no robust clinical evidence to show that Fostair's extrafine formulation translated into a clinical benefit compared with other licensed treatments.**

**The Panel did not consider that, within the context of the front page of the leavepiece, the heading and the image of a woman in a field with her arms outstretched implied that patients would return to a pre-symptom state with Fostair as alleged.**

**The Panel considered that the claim 'New licence for Maintenance And Reliever Therapy for an extra fine day' was ambiguous, misleading and could not be substantiated. Breaches of the Code were ruled. The Panel did not consider that in these circumstances Chiesi had failed to maintain high standards and no breach of the Code was ruled.**

**Following notification of the Panel ruling AstraZeneca wrote to the Authority, noting, *inter alia*, that it was surprised by the first paragraph of the Panel ruling which implied that during inter-company dialogue EXTRA FINE was put into upper case for emphasis as the leavepiece provided by Chiesi used lower case letters only within the claim at issue. This was at odds with the leavepiece upon which AstraZeneca had based its complaint, a copy of which it now provided.**

**Chiesi returned the signed undertaking on 4 September. On 11 September, before the Authority had contacted the company about this matter, Chiesi advised the Authority that a product manager had unilaterally altered the leavepiece after it had been electronically certified such that 'extra fine' read 'EXTRA FINE'. Chiesi was asked to explain the circumstances.**

**Following receipt of the additional information from both parties the original Panel reconvened to consider the matter in relation to Paragraph 8 of the Constitution and Procedure. Chiesi was so informed and asked to provide detailed comments which are summarized below.**

**The Panel considered the matter in relation to Paragraph 8.2 of the Constitution and Procedure which provided that the Panel might report a company to the Appeal Board. Such a report might be made notwithstanding the fact that a company had provided an undertaking requested by the Panel.**

**The Panel noted that it had considered the complaint in relation to the copy of the leavepiece provided by Chiesi in its response to the complaint, which bore the correct reference number and featured the claim 'extra fine' in lower case. The Panel noted that this version of the leavepiece had never been distributed. According to Chiesi, a product manager had unilaterally altered the leavepiece such that the claim in question was in upper case ('EXTRA FINE') and thus aligned with other Fostair materials. The signatories certified a printed version of a PDF file which had previously been electronically approved in Zinc. It was wrongly assumed that no changes had been made to the previously approved artwork. It appeared that it was this version that was provided to the Panel rather than the item in its final form as amended by the product manager. Chiesi stated that the employees in question had clearly acted outwith the company's standard operating procedure (SOP). It was not known why he/she had not followed the relevant SOP.**

**The Panel did not accept Chiesi's conclusion that this was evidence of a lone employee failing to**

**accord with approved SOPs. Firstly, the Panel noted that other Chiesi employees had been copied in on the relevant employee's emails to the agency. Secondly in the Panel's view, it should have been abundantly clear to each signatory that the version provided for certification was not in its final form as required by the Code and the relevant SOP. In the Panel's view, this raised concerns about the competence of each of the Code signatories given each had certified that they had examined the final form of the material.**

**The Panel considered that the failure of both the product manager and the signatories to adhere to the SOP was a matter of concern and raised questions about the importance of compliance within the company.**

**The Panel expressed concern about the certification arrangements.**

**The Panel was extremely concerned that Chiesi's response to the complaint quoted throughout the claim at issue in upper case whereas the leaflet supplied used lower case for 'extra fine'. The Panel was concerned that Chiesi had not noted the discrepancy on a number of occasions through from approval, inter-company dialogue and its response to the complaint. That the company only became aware of the matter when it was notified of the Panel's rulings was unacceptable. It further transpired that the company's original undertaking in this case incorrectly stated that the material was last used on 17 March 2013 and that was not so. A revised undertaking with a later date of final use had been provided. The Panel noted that an undertaking was an important document and the Authority must be able to rely on its accuracy.**

**The Panel was extremely disappointed by the conduct of Chiesi as outlined above. Self-regulation relied, *inter alia*, upon the provision of complete and accurate information to the Panel. Its previous conduct in this regard was not irrelevant. The Panel considered that the circumstances warranted reporting the company to the Appeal Board under Paragraph 8.2 for it to consider in relation to Paragraphs 11.3 and 11.4 of the Constitution and Procedure.**

**On considering the report the Appeal Board noted that as a result of staff failing to follow the relevant company SOP, the final printed version of the leavepiece at issue featured 'EXTRA FINE' in upper case whereas the Zinc copy approved by Chiesi's signatories featured 'extra fine' in lower case. Chiesi had provided the Zinc 'lower case' copy of the leavepiece in its response to the complaint without checking that that copy matched the final printed file 'upper case' copy; this despite the fact that in inter-company dialogue and throughout the complaints procedure, both parties had consistently referred to 'EXTRA FINE' in upper case. In the Appeal Board's view, the discrepancy between the two versions of the leavepiece should have been obvious to Chiesi from the outset. Chiesi had not certified the final form of the leavepiece. The PDF certified was not the final form as some of the pages were not the correct size and, in addition, the version certified used 'extra fine' in lower case and not 'EXTRA FINE' in upper case as on the final version. Neither the product manager nor the signatories had followed the company's SOP.**

**The Appeal Board also noted with concern that Chiesi's original undertaking and assurance in respect of the breaches ruled in this case was incorrect with regard to the final date on which the leavepiece was used.**

**The Appeal Board noted Chiesi's submission that the failure to follow the correct approval process, and to recognise the difference between the approved leavepiece and the one that was distributed, and the mistakes in the undertaking arose from human error and lack of attention to detail. In that regard the Appeal Board noted Chiesi had previously been censured for providing the PMCPA with inaccurate information (Case AUTH/2435/8/11). In that case the Appeal Board decided that Chiesi should be publicly reprimanded and it should undergo an audit of its procedures in relation to the Code to be carried out by the Authority. This was carried out in March 2012 and a second audit was required (carried out in October 2012). The report for the second audit included a recommendation that 'Chiesi needed to ensure…that all information provided to the PMCPA was accurate'. The Appeal Board considered that Chiesi's repeated failure to provide accurate information to the PMCPA was completely unacceptable.**

**Self regulation relied upon the provision of complete and accurate information by pharmaceutical companies. The Appeal Board was extremely concerned about Chiesi's conduct, and having considered all the sanctions available under Paragraph 11.3 of the Constitution and Procedure it decided that the company should be publicly reprimanded for providing inaccurate information to the Authority.**

**The Appeal Board also decided to require an audit of Chiesi's procedures in relation to the Code. Given the details of the company's ongoing and planned compliance activities, the Appeal Board decided that the audit should be conducted in five months' time (March 2014). On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.**

**Upon receipt of the March 2014 audit report, the Appeal Board considered that Chiesi's embarrassment at the errors which had led to the requirement for it to be audited were well founded.**

**The Appeal Board was extremely concerned that Chiesi had been audited twice in 2012 and that the current audit report highlighted a number of serious issues with Chiesi's compliance procedures and materials; it appeared that the company still had much work to do. The Appeal Board provided a number of detailed comments including its serious concerns that Chiesi had stated that a standard operating procedure had been updated when it had not. The Appeal Board was appalled that, in this regard, it appeared that Chiesi had yet again provided false information to the PMCPA; this**

**was completely unacceptable. The Appeal Board considered that its further concerns about the provision of false information should be added to the detail of that public reprimand. The Appeal Board was also concerned about the outcome of Chiesi's job bag audit (conducted by an external compliance consultant). A second job bag audit was due in April 2014 and the Appeal Board requested that the results, which needed to show a significant improvement, be provided at the next PMCPA audit.**

**The Appeal Board noted that the company had already been given a significant amount of time to ensure its procedures, policies and culture supported a robust compliance framework. The Appeal Board decided that Chiesi should be re-audited in October 2014 when the company must be able to demonstrate significant improvement. Upon receipt of the report for the re-audit, the Appeal Board would decide whether further sanctions were necessary.**

**Upon receipt of the October 2014 audit report, the Appeal Board noted that Chiesi had made progress since the audit in March 2014. The Appeal Board noted that this was not the first case in which Chiesi had been censured for failing to provide accurate information; such failings were completely unacceptable and must not happen again. The Appeal Board noted that Chiesi provided details of its plans to implement the audit report recommendations. On the basis that this work was completed, progress was continued and the company wide focus on compliance was maintained, the Appeal Board decided that, on balance, no further action was required.**

AstraZeneca UK Limited complained about the promotion of Fostair (formoterol/beclometasone pressurised inhalation solution). The material at issue was a leavepiece (ref CHFOS20130051). The front page read 'New licence for Maintenance and And Reliever Therapy for an extra fine day' above an image of a woman in a field with her arms outstretched. Beneath the illustration the claim 'Fostair is the first and only pMDI combination inhaler in the UK licensed for Maintenance and Reliever Therapy in asthma' was followed by the brand name in logo format and the strapline 'Extra-fine formulation. Adult asthma control'.

AstraZeneca marketed Symbicort (budesonide/formoterol turbohaler). Both Fostair and Symbicort were indicated in the regular treatment of asthma where use of a combination (inhaled corticosteroid (ICS) and long-acting $ß_2$ adrenoceptor agonist (LABA)) was appropriate. Inter-company dialogue had not resolved this matter.

**COMPLAINT**

AstraZeneca was concerned about the claim '… for an extra fine day' which appeared on the front cover of the leavepiece and was also used in other promotional material for Fostair. AstraZeneca noted that the wording '… for an extra fine day' appeared immediately below 'New licence for Maintenance And Reliever Therapy' which, in its view, therefore clearly represented a claim for Fostair that was unqualified and not substantiated. The claim suggested that the patient returned to an improved pre-symptom state with use of Fostair. This illusion was further compounded by the illustration.

AstraZeneca accepted that Fostair had an extra fine formulation and that reference to 'extra fine' within that context was acceptable. Furthermore, AstraZeneca accepted that Fostair was used on a [twice] daily basis. However, AstraZeneca alleged that linking aspects of the formulation to 'day' as in 'extra fine day' was a product claim which implied an efficacy suggestion that was at least ambiguous and not substantiated. In addition it was not clear about what this efficacy benefit was compared to. Further, linking of the statements 'New licence for Maintenance And Reliever Therapy' with 'extra fine day' by use of the word 'for' amounted to a promise as in 'New licence for Maintenance And Reliever Therapy **for** an extra fine day' (emphasis added).

AstraZeneca stated that there was no robust clinical evidence to show that Fostair's extra-fine formulation translated into a clinical benefit when compared with other licensed treatments. AstraZeneca had identified several studies that had evaluated the extra-fine formulation against other treatments and had yet to identify any that showed a clinical superiority in favour of the extra-fine formulation over clinically appropriate comparators. AstraZeneca noted that a number of review articles hypothesised on the potential benefits of extra-fine formulation but did not offer any substantive clinical evidence in support.

AstraZeneca alleged that the claim was misleading in breach of Clause 7.2 and incapable of substantiation in breach of Clause 7.4. AstraZeneca also alleged that the claim was in breach of Clause 9.1 as it failed to maintain high standards.

**RESPONSE**

Chiesi submitted that it took compliance with the Code very seriously and set out why the claim in question was not in breach of the Code as alleged by AstraZeneca.

A comparison of AstraZeneca's initial complaint sent to Chiesi and that submitted to the PMCPA demonstrated that the exact nature of the complaint was not entirely clear. Chiesi was unsure whether the use of the line 'an extra fine day', which had been used in isolation throughout the Fostair campaign for over twelve months since March 2012, or the use of the claim 'for an extra fine day', which had only been used in a campaign specifically relating to the launch of the new Fostair licence for maintenance and reliever therapy (MART) since February 2013, was what was at issue.

Chiesi noted that in April 2013 AstraZeneca raised the issue of 'an extra fine day' in the Fostair MART leavepiece (ref CHFOS20130051). The wording 'for an extra fine day' appeared at the end of the headline, 'New licence for Maintenance And Reliever Therapy', on the leavepiece at issue. Chiesi submitted that 'an extra fine day' was the focus of its response letter to AstraZeneca and discussions

during the subsequent telephone conference in June and it was used in isolation and without the word 'for' throughout the main Fostair campaign.

During inter-company dialogue Chiesi decided to continue using the line 'for an extra fine day' in the context outlined and which appeared in the Fostair MART leavepiece as it did not consider it to be in breach of the Code. Both parties were unable to reach a satisfactory resolution on this point and it was agreed that AstraZeneca would raise the issue with the PMCPA. Chiesi was now responding to a complaint about the use of the claim 'for an extra fine day' as contextualised in the Fostair MART leavepiece.

Chiesi submitted that 'for an extra fine day' was a reference to Fostair's extrafine formulation which was substantiated by Fostair's summary of product characteristics (SPC), Section 4.2 of which stated:

> 'Beclometasone dipropionate in Fostair is characterised by an extrafine particle size distribution which results in a more potent effect than formulations of beclometasone dipropionate with a non-extrafine particle size distribution (100 micrograms of beclometasone dipropionate extrafine in Fostair are equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation). Therefore the total daily dose of beclometasone dipropionate administered in Fostair should be lower than the total daily dose of beclometasone dipropionate administered in a non-extrafine beclometasone dipropionate formulation. This should be taken into consideration when a patient is transferred from a beclometasone dipropionate non-extrafine formulation to Fostair; the dose of beclometasone dipropionate should be lower and will need to be adjusted to the individual needs of the patients.'

Chiesi submitted that the wording 'Extra-fine formulation' used on the same page reinforced the link between the use of the headline 'for an extra fine day' and the formulation of the product. Similarly the use of capitals for 'extra fine' highlighted that message further. Due to the different potencies of the available beclometasone containing pressurised metered dose inhalers (pMDIs), Chiesi considered the extrafine formulation of Fostair to be an important safety message which had to be communicated to potential prescribers. Chiesi noted that in 2006 the Medicines and Healthcare products Regulatory Agency (MHRA) issued advice highlighting the potential safety issue concerning beclometasone pMDIs regarding extrafine formulations having a 2 to 2.5 fold greater potency than non-extrafine formulations. It was the potential safety issue that led to the Fostair campaign being based on 'an extra fine day'.

Chiesi submitted that the imagery served to further communicate and emphasise the extrafine formulation which was unique to Fostair in combination therapy. The illustration was constructed from small pink dots designed to represent extrafine particles. Chiesi had reviewed the imagery and confirmed it was appropriate and within the scope of suitability detailed in the supplementary information to Clauses 9.1 and 9.2. Chiesi disagreed with AstraZeneca's view that the imagery was misleading and considered that the imagery depicted a situation that was perfectly in line with the expectations of a patient with moderate asthma and strongly objected to it being considered an 'illusion'.

Chiesi submitted that the wording 'for an extra fine day' also reflected the posology of Fostair from the SPC which stated that it had to be taken on a daily basis. A patient who was prescribed Fostair would be taking an extrafine formulation daily and therefore each day would have an extrafine element to it because of Fostair's formulation.

Chiesi further submitted that the linking of the new MART licence to 'an extra fine day' on the leavepiece in the headline ''New licence for Maintenance And Reliever Therapy' for an extra fine day' was used to communicate that there was now another posology option available for treating patients with Fostair, with reinforcement of the above safety message relating to its extrafine formulation. Chiesi claimed that if a patient was treated with a maintenance and reliever therapy regimen they could potentially be using their inhaler at other times during the day as well as on a twice daily basis. That posology further supported the use of 'extra fine day'. Chiesi consequently refuted that the use of 'for an extra fine day' was a breach of Clause 7.4 as it was substantiated by the SPC.

Chiesi submitted that the Fostair MART campaign compared two different posology methods both from a clinical and patient perspective when treating asthma. There was no comparison of the efficacy of Fostair with any alternative inhaled corticosteroid/long acting beta agonist combination inhaler. The only efficacy comparisons made within the leavepiece were between Fostair MART and Fostair maintenance therapy. With there being no efficacy claims between Fostair and any other ICS/LABA combination inhalers available Chiesi disagreed that the piece inferred clinical superiority over any other product as alleged.

Chiesi noted that the only comparison made was a cost comparison between Fostair and Symbicort on page 5 and as part of the summary on page 6. A cost comparison between the only two ICS/LABA combination inhalers with a MART licence was relevant information to disseminate but it had agreed to cease doing so at AstraZeneca's request following inter-company dialogue. With cost being the only comparison made in the leavepiece Chiesi disagreed that the reader would interpret the piece as claiming clinical superiority of Fostair over the available alternative.

The leavepiece focussed on severe exacerbations, hospitalisations and systemic corticosteroid courses based on data from the MART-2 study. There was nothing in the leavepiece that suggested patients would be symptom free, in fact asthma symptoms were not referred to in any of the claims and were only mentioned with regard to how Fostair MART should be prescribed ie additional inhalations should be taken in response to symptoms. As there was

no focus on any reduction in asthma symptoms Chiesi disagreed that the claim 'for an extra fine day' suggested a patient returning to a pre-symptom state as alleged by AstraZeneca. Furthermore, the illustration represented the freedom and flexibility that a MART approach could offer a patient when managing their own asthma treatment and was not intended to be representative of a symptom free patient. Chiesi therefore did not consider that the illustration or the claim 'for an extra fine day' was in breach of Clauses 7.2 or 7.4.

Chiesi submitted that the claim 'New licence for Maintenance And Reliever Therapy for an extra fine day' was accurate, balanced, fair, objective and unambiguous and based on an up to date evaluation of all of the evidence and therefore denied any breach of Clause 7.2. The information was capable of substantiation as shown above and therefore Chiesi denied any breach of Clause 7.4 and thus denied a breach of Clause 9.1.

In summary, Chiesi submitted that it was unfortunate that inter-company dialogue had failed to reach a full resolution on the matters raised by AstraZeneca however this was in part due to a lack of clarity and the somewhat changing nature of the complaint. Chiesi submitted that as it had demonstrated that it was able to substantiate all wording and meet all of the necessary requirements of Clause 7.2, it denied a breach of Clauses 7.2, 7.4 and 9.1 as alleged by AstraZeneca.

**PANEL RULING**

The Panel noted that both AstraZeneca and Chiesi referred to 'extra fine' within the claim at issue in upper case both during inter-company dialogue and in their respective complaint and response to the PMCPA. However, the only promotional material was provided by Chiesi and this (the leavepiece in question) used lower case for 'extra fine' in the claim at issue. The Panel was unsure of the relevance of Chiesi's response with regard to the use of upper case for EXTRA FINE highlighting the link between 'for an extra fine day' and the formulation of the product.

The Panel noted the claim at issue 'for an extra fine day' appeared within the headline 'New licence for Maintenance And Reliever Therapy for an extra fine day'. 'Fostair is the first and only pMDI combination inhaler in the UK licensed for Maintenance And Reliever Therapy in asthma' appeared beneath the visual of a women with her arms stretched out in a field. 'Extra-fine formulation. Adult asthma control' appeared at the bottom in between the product logo and an image of an inhaler. The Panel noted Chiesi's submission that the use of the phrase 'for an extra fine day' was a reference to Fostair's extrafine formulation which was substantiated by the SPC. The Panel noted that Section 4.2 of the Fostair SPC, Posology and method of administration stated that 'Beclometasone dipropionate in Fostair is characterised by an extrafine particle size distribution which results in a more potent effect than formulations of beclometasone dipropionate with a non-extrafine particle size distribution …'.

The Panel noted Chiesi's submission that the use of the wording 'Extra-fine formulation' on the same page reinforced the link between the use of the headline 'for an extra fine day' and the product's formulation. The Panel noted that in this instance 'extra-fine' had been hyphenated when describing the formulation whilst 'extra fine' in the claim at issue had been written as two words. It appeared as one word 'extrafine' in Section 4.2 of the SPC.

The Panel accepted that the use of 'for an extra fine day' was a play on words but considered that the heading to page 1 was not sufficiently clear about what 'extra fine' was referring to, there was an implication that it referred to a clinical benefit and not just to the product's formulation as submitted by Chiesi and it was ambiguous in this regard. Use of the word 'extra' by implication rendered the claim 'for an extra fine day' comparative; use of the product for the new licence provided an extra clinical benefit over and above an appropriate comparator. This implication was misleading. Chiesi provided no data to support such an advantage. The Panel noted AstraZeneca's submission that there was no robust clinical evidence to show that Fostair's extrafine formulation translated into a clinical benefit compared with other licensed treatments. The Panel considered that the implied claim could not be substantiated. The Panel did not consider that, within the context of the front page of the leavepiece the heading and the image implied that patients would return to a pre-symptom state with the use of Fostair as alleged. The Panel noted that the leavepiece included various comparisons. Page 3 compared various clinical outcomes of Fostair MART vs Fostair plus salbutamol. Page 5 included a cost comparison between Fostair and Symbicort which Chiesi had agreed to discontinue using during inter-company dialogue. The Panel noted nonetheless that the front page of the leavepiece must be capable of standing alone as regards the requirements of the Code.

The Panel considered that the claim 'New licence for Maintenance And Reliever Therapy for an extra fine day' was ambiguous, misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled. The Panel did not consider that in these circumstances Chiesi had failed to maintain high standards and no breach of Clause 9.1 was ruled.

**FURTHER INFORMATION FROM THE COMPLAINANT FOLLOWING NOTIFICATION OF THE PANEL'S RULING**

Following notification of the Panel ruling AstraZeneca wrote to the Authority, noting, *inter alia*, that it was surprised by the first paragraph of the Panel ruling which implied that during inter-company dialogue EXTRA FINE was put into upper case for emphasis as the leavepiece provided by Chiesi used lower case letters only within the claim at issue. This was at odds with the leavepiece that AstraZeneca had based this complaint upon, a copy of which it now provided. AstraZeneca explained that the reason that it did not submit the item in question with its original letter was because it only had a poor quality copy.

**FURTHER INFORMATION FROM CHIESI FOLLOWING NOTIFICATION OF THE PANEL RULING**

Chiesi returned the signed undertaking on 4 September. On 11 September, before the Authority had contacted Chiesi about this matter, Chiesi initiated and held a teleconference with the Authority where it briefly advised that a product manager had unilaterally altered the leavepiece after it had been electronically certified such that 'extra fine' read 'EXTRA FINE'. Chiesi was asked to explain the circumstances briefly by email.

**FURTHER PMCPA CONSIDERATION**

Following receipt of the additional information from both parties the Authority decided that the original Panel should reconvene to consider this matter in relation to Paragraph 8 of the Constitution and Procedure. Chiesi was so informed and asked to provide detailed comments.

**COMMENTS FROM CHIESI**

Chiesi explained that following receipt of the PMCPA's letter advising it of the Panel's ruling it initiated an internal investigation to identify the cause of the discrepancy between the standard operating procedure (SOP) approved version and final printed version of the leavepiece. Chiesi stated that whilst not altering the intent of the message, the difference in type setting represented a breach of its SOP. An investigation found that the change to the final approved item was initiated by a product manager after certification and thus in breach of the relevant SOP. The change was made by a verbal order directly to the creative agency responsible for the production. The verbal order was confirmed in a series of emails which Chiesi submitted demonstrated that the change was made by the manager alone with no other member of Chiesi staff made aware of the specific change and as the resultant item matched other approved materials, there was no suspicion of this activity. The manager responsible was trained on the current SOP in March 2013 and its predecessor in March 2012. It appeared that the update was made in a moment of expediency prior to a key launch meeting, to align the leavepiece with other materials in which the term 'Extra Fine', appeared in upper case. The manager had left Chiesi.

In accordance with the current and previous SOP under which this leavepiece was approved, final signatories must provide wet ink signatures to confirm the final printed version was identical to the 'approved' electronic version. In this situation it appeared that the signatories were provided only with an office printed final version (with 'extra fine' in lower case) rather than a printer's proof, as such the version to be distributed was never checked. This represented a safety check which, in this isolated case, was bypassed by the individual involved. The approval of versions other than printer's proofs represented a breach of both SOPs and an audit by an external compliance company had thus been initiated.

The leavepiece was withdrawn from circulation on 30 March 2013; it was previously communicated to the PMCPA that this was 17 March 2013. During the company's investigation it transpired that not all field based staff had confirmed withdrawal by 17 March and thus 30 March represented the absolute final potential date of use. An updated acceptance of undertaking form was provided to supersede that previously sent.

Chiesi recognised that this additional information contained evidence of a lone employee failing to accord with approved SOPs and, as such, had facilitated the use of an uncertified item. It also apologised for the inaccurate date previously supplied.

Chiesi reassured the PMCPA that it had robust SOPs that were followed and regularly reviewed and trained upon in order to maintain high standards. In spite of this, it had undertaken a full audit of approved material carried out by an external company to assure Chiesi of compliance.

In response to a request for further information, Chiesi provided a copy of the email exchange between the relevant employee, the printing agency and the creative agency regarding approval of the leavepiece in question. Chiesi stated that clearly at numerous points throughout this interaction, the employee in question should have halted the print run and initiated a re-approval.

In response to a request for sight of the training provided to the manager about certification and the SOPs, Chiesi stated that both SOPs stated the originator had to ensure certain elements were complied with including ensuring that the final item was identical to the final artwork or proof approved electronically. Chiesi's manager was the originator of the leavepiece and had been documented as completing 'Read and Understand' SOP training in both cases. Coincidentally, Chiesi's manager was involved in the development of both SOPs, indicating more than a working knowledge of their contents.

Chiesi explained that as per its SOP, the material presented to the final signatories for certification was the item in its final form. The copy job bag submitted to the PMCPA with Chiesi's original response contained a copy of the certificate and a copy of the artwork that was electronically approved in January 2013. The electronic approval via Zinc was the authorisation for the material to go to print. The material was not considered certified at this point. There was no reason to believe any changes were implemented to the artwork approved on 29 January. Clean copies taken from these approved PDFs were provided to the certifiers for their final wet ink approval. Unfortunately, this assumption was incorrect.

Chiesi explained that a printer's proof came in two formats; either digital or hard copy. Essentially, the development of printing methods from litho press to digital press had led Chiesi to accept standard PDFs (digital proofs) as the *final form*. Once again, Chiesi hoped the answers provided reassured the Panel

that there was no malicious intent and, although representing a serious breach of a critical SOP, the situation was contained and not representative of the company's normal behaviours.

**FURTHER CONSIDERATION OF THE CODE OF PRACTICE PANEL**

The Panel noted that it was considering this matter in relation to Paragraph 8.2 of the Constitution and Procedure which provided that the Panel might report to the Appeal Board any company whose conduct in relation to the Code, or in relation to a particular case before it, or because it repeatedly breached the Code such that it raised concerns about the company's procedures, warranted consideration by the Appeal Board. Such a report to the Appeal Board may be made notwithstanding the fact that a company had provided an undertaking requested by the Panel.

The Panel noted that it had considered the complaint in relation to the copy of the leavepiece provided by Chiesi in its response to the complaint, which bore the correct reference number and featured the claim 'extra fine' in lower case. The Panel noted that this version of the leavepiece had never been distributed. According to Chiesi, a product manager had unilaterally altered the leavepiece such that the claim in question was in upper case ('EXTRA FINE') and thus aligned with other materials in anticipation of a key launch meeting. The signatories certified a printed version of a PDF file which had previously been electronically approved in Zinc. It was wrongly assumed that no changes had been made to the previously approved artwork. It appeared that it was this version that was provided to the Panel rather than the item in its final form as amended by the product manager.

The Panel considered that the relevant SOP made it abundantly clear that a print of a PDF document should not be used for final certification. The manager in question had clearly acted outwith the SOP. The Panel noted that the individual had received training on the relevant SOP and its successor UK-SOP-005. The training comprised a self-declaration that he/she had read the relevant SOP. It was not known why the manager had not followed the relevant SOP on such a vital matter.

The Panel did not accept Chiesi's conclusion that this was evidence of a lone employee failing to accord with approved SOPs. Firstly, the Panel noted that other Chiesi employees had been copied in on the manager's emails to the agency. Secondly in the Panel's view, it should have been abundantly clear to each signatory that the version provided for certification was not in its final form as required by the Code and the relevant SOP. In the Panel's view, this raised concerns about the competence of each of the Code signatories given each had certified that they had examined the final form of the material and that was not so.

The Panel considered that the failure of both the manager and the signatories to adhere to the SOP was a matter of concern and raised questions about the importance of compliance within the company.

The Panel noted that the relevant SOP had subsequently been updated (UK-SOP-005) and noted the differences between the two in relation to certification.

The Panel was concerned about the current certification arrangements as set out in Section M, Certification SOP 005 and Chiesi's explanation thereof and queried whether the final form of the materials was currently being certified by Chiesi. Final form did not just apply to the text/colour etc it also applied to the physical form of the material.

The Panel was extremely concerned that Chiesi's response to the complaint quoted throughout the claim at issue in upper case whereas the leaflet supplied used lower case for 'extra fine'. It was vital for effective self-regulation that the Panel and Code of Practice Appeal Board were able to rely on the accuracy of a company's response. The Panel was concerned that Chiesi had not noted the discrepancy on a number of occasions through form of approval, inter-company dialogue and its response to the complaint. That the company only became aware of the matter when it was notified of the Panel ruling was unacceptable. To compound these concerns it also transpired as a result of further questioning by the Panel regarding the claim and how long the material in question was in circulation that the company's original undertaking in this case incorrectly stated that the material was last used on 17 March 2013 and that was not so. A revised undertaking with a later date of final use had been provided. The Panel noted that an undertaking was an important document and the Authority must be able to rely on the accuracy of the information therein.

The Panel considered that the previous conduct of Chiesi was not irrelevant and noted that Chiesi had been the subject of previous audits.

The Panel was extremely disappointed by the conduct of Chiesi as outlined above. Self-regulation relied, *inter alia*, upon the provision of complete and accurate information to the Panel. It considered that the circumstances warranted reporting the company to the Appeal Board under Paragraph 8.2 for it to consider in relation to Paragraphs 11.3 and 11.4 of the Constitution and Procedure.

**COMMENTS FROM CHIESI ON THE REPORT**

At the consideration of the report Chiesi submitted that although errors had been made, it took the Code extremely seriously and was committed to making improvements; it had taken and had planned many actions to effect change. The company provided a detailed account of its 2013 compliance activities and a copy of its 2014 compliance programme. Chiesi submitted that it was committed to work with the PMCPA to improve its processes.

**APPEAL BOARD CONSIDERATION**

The Appeal Board noted that as a result of staff failing to follow the relevant company SOP, the final printed version of the leavepiece at issue featured 'EXTRA FINE' in upper case whereas the Zinc copy

approved by Chiesi's signatories featured 'extra fine' in lower case. Chiesi had provided the Zinc 'lower case' copy of the leavepiece in its response to the complaint without checking that that copy matched the final printed file 'upper case' copy; this despite the fact that in inter-company dialogue and throughout the complaints procedure, both parties had consistently referred to 'EXTRA FINE' in upper case. In the Appeal Board's view, the discrepancy between the two versions of the leavepiece should have been obvious to Chiesi from the outset. Chiesi had not certified the final form of the leavepiece. The PDF certified was not the final form as some of the pages were not the correct size and, in addition, the version certified used 'extra fine' in lower case and not 'EXTRA FINE' in upper case as on the final version. Neither the manager nor the signatories had followed the company's SOP.

The Appeal Board also noted with concern that Chiesi's original undertaking and assurance in respect of the breaches ruled in this case was incorrect with regard to the final date on which the leavepiece was used.

The Appeal Board noted Chiesi's submission that the failure to follow the correct approval process, and to recognise the difference between the approved leavepiece and the one that was distributed, and the mistakes in the undertaking arose from human error and lack of attention to detail. In that regard the Appeal Board noted Chiesi had previously been censured for providing the PMCPA with inaccurate information (Case AUTH/2435/8/11). In that case the Appeal Board decided that Chiesi should be publicly reprimanded and that, in accordance with Paragraph 11.3 of the Constitution and Procedure, it should undergo an audit of its procedures in relation to the Code to be carried out by the Authority. This was carried out in March 2012 and a second audit was required (carried out in October 2012). The report for the second audit had stated as a recommendation that 'Chiesi needed to ensure…that all information provided to the PMCPA was accurate'. The Appeal Board considered that Chiesi's repeated failure to provide accurate information to the PMCPA was completely unacceptable.

Self regulation relied upon the provision of complete and accurate information by pharmaceutical companies. The Appeal Board was extremely concerned about Chiesi's conduct, and having considered all the sanctions available under Paragraph 11.3 of the Constitution and Procedure it decided that the company should be publicly reprimanded for providing inaccurate information to the Authority.

The Appeal Board also decided to require an audit of Chiesi's procedures in relation to the Code. Given the details of the company's ongoing and planned compliance activities, the Appeal Board decided that the audit should be conducted in five months' time (March 2014). On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

**APPEAL BOARD FURTHER CONSIDERATION**

Upon receipt of the March 2014 audit report, the Appeal Board considered that Chiesi's embarrassment at the errors which had led to the requirement for it to be audited were well founded.

The Appeal Board was extremely concerned that Chiesi had been audited twice in 2012 and that the current audit report highlighted a number of serious issues with Chiesi's compliance procedures and materials; it appeared that the company still had much work to do. The Appeal Board provided a number of detailed comments including its serious concerns that Chiesi had stated that a standard operating procedure had been updated when it had not. The Appeal Board was appalled that, in this regard, it appeared that Chiesi had yet again provided false information to the PMCPA; this was completely unacceptable. The Appeal Board considered that its further concerns about the provision of false information should be added to the detail of that public reprimand. The Appeal Board was also concerned about the outcome of Chiesi's job bag audit (conducted by an external compliance consultant). A second job bag audit was due in April 2014 and the Appeal Board requested that the results, which needed to show a significant improvement, be provided at the next PMCPA audit.

The Appeal Board noted that the company had already been given a significant amount of time to ensure its procedures, policies and culture supported a robust compliance framework. The Appeal Board decided that Chiesi should be re-audited in October 2014 when the company must be able to demonstrate significant improvement. Upon receipt of the report for the re-audit, the Appeal Board would decide whether further sanctions were necessary.

Upon receipt of the October 2014 audit report, the Appeal Board noted that Chiesi had made progress since the audit in March 2014. The Appeal Board noted that this was not the first case in which Chiesi had been censured for failing to provide accurate information to the Panel; the Appeal Board reiterated that such failings were completely unacceptable and must not happen again. The Appeal Board noted that Chiesi provided details of its plans to implement the recommendations in the audit report. On the basis that this work was completed, progress was continued and a company wide focus on compliance was maintained, the Appeal Board decided that, on balance, no further action was required.

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| **Complaint received** | **22 July 2013** |
| **Undertaking received** | **4 September 2013** |
| **Appeal Board Consideration** | **15 October 2013, 9 April 2014, 10 December 2014** |
| **Interim Case Report first published** | **11 December 2013** |
| **Case completed** | **10 December 2014** |

**CASE AUTH/2726/8/14**

# ANONYMOUS, NON CONTACTABLE HEALTH PROFESSIONAL v GLAXOSMITHKLINE

## Promotion of Seretide

**An anonymous, non contactable health professional complained about the use of the TORCH (TOwards a Revolution in COPD (chronic obstructive pulmonary disease) Health) study (Calverley *et al* 2007) in the promotion of Seretide (salmeterol/fluticasone) by GlaxoSmithKline UK.**

**The complainant noted that an editorial (Gøtzsche 2014) published in the Journal of the Royal Society of Medicine, 'Questionable research and marketing of a combination drug for smoker's lung', challenged both the design and analysis of the TORCH study and questioned the quality of the data.**

**The complainant noted that data from the TORCH study had been used to promote Seretide over at least the last six years. TORCH was perceived as a 'landmark' trial involving over 6,000 patients that confirmed the efficacy of Seretide in COPD. It was probable that over a number of years this promotion also shaped, rightly or wrongly, the perception of health professionals and influenced key prescribing decisions.**

**The complainant stated that the central issue was that the TORCH study did not meet its primary endpoint. Despite this, both historical and current promotional claims for Seretide referred to favourable secondary endpoints. The complainant alleged it was misleading to make promotional claims based on secondary endpoints (and/or post-hoc analyses) from a study that did not meet its pre-defined primary endpoint. It might be that the primary and secondary endpoints were clearly and prominently stated in Seretide promotion. However, it was unrealistic to expect time-pressured health professionals to be able to correctly apportion appropriate weighting and context to this evidence when making key prescribing decisions. The complainant stated that the criticism by Gøtzsche further supported the view that the TORCH study results should never have been used in the promotion of Seretide.**

**The complainant noted that Seretide promotion was accessible to the public. A search using 'healthcare professional + Seretide + TORCH study' revealed the following link as the first hit which directly led to an unsecured area of the GlaxoSmithKline website in the UK where prior registration as a health professional was not necessary in order to gain access.**

**The detailed response from GlaxoSmithKline is given below.**

**The Panel noted that at its inception the TORCH study (Calverley *et al* 2007) was the largest ever multicentre, long-term chronic obstructive pulmonary disease study and the first to investigate the effect of the salmeterol/fluticasone propionate combination and its components on chronic obstructive pulmonary disease mortality. It was a prospective randomized double-blind trial comparing a combination regimen of salmeterol and fluticasone in a single inhaler with placebo, salmeterol alone or fluticasone propionate alone for three years. The primary endpoint was the time to death from any cause for the comparison between the combination regimen and placebo. Key secondary endpoints included the reduction in COPD morbidity and the difference in quality of life (QoL), each between the combination regimen and placebo. Other endpoints included difference in composite endpoint made up of overall mortality and COPD admissions, COPD-related mortality, clinic post-bronchodilator FEV1, other COPD exacerbation endpoints, health status and health utilisation. The reduction in death from all causes amongst COPD patients in the combination therapy group as compared to placebo did not reach the predetermined level of statistical significance. Treatment with the combination regimen resulted in significantly fewer exacerbations compared with placebo including those exacerbations requiring hospitalization. The combination regimen was also significantly better than each of its components alone in preventing exacerbations and these benefits were accompanied by sustained improvements in health status and FEV1. It was noted that the greater number of patients withdrawing from the placebo group was likely to have resulted in an underestimation of the effect of the combination regimen on all the secondary outcomes. The study authors also noted that the size of the TORCH study was modest compared with studies of mortality associated with other major chronic illnesses such as cardiovascular disease and thus the results of the mortality analysis should be viewed in this context.**

**The Panel noted that there was a post-hoc analysis of the TORCH study secondary endpoint data which was referred to in some of the materials provided by GlaxoSmithKline.**

**The Panel considered that, in principle, when a primary endpoint failed to achieve statistical significance it was not necessarily unreasonable to refer to secondary endpoint data so long as this was placed within the context of the overall study findings. The nature of the material might also be relevant.**

**The Panel examined the materials provided and only considered those items which referred to the secondary endpoint data from the TORCH study**

**including the post-hoc analysis as these were the only items covered by the complaint.**

**The Panel examined the material published at Seretide.co.uk. The Panel noted that the 'Efficacy and Clinical Evidence' page summarized clinical data from five studies including the TORCH study. Each reference to the TORCH secondary endpoint data was preceded by the statement 'The primary endpoint of the effect of Seretide 500 Accuhaler on all-adverse mortality did not meet statistical significance p=0.052'. The Panel considered that the secondary endpoint data was placed within the context of the study. No breach was ruled.**

**In relation to the Seretide campaign materials the Panel noted that the Seretide TR Campaign pilot appeared to be a 24-page slide deck. Slide 12 onwards referred to Seretide in COPD. Slides 14 and 15 each headed '… And benefit over the long term' discussed the clinical benefits of Seretide 500 Accuhaler over three years with reference to the secondary endpoints of the TORCH study. Slide 16 introduced the TORCH study and made it clear that the primary endpoint did not achieve statistical significance. More detailed information about the TORCH study appeared at Slide 17. The Panel was concerned that the information about the primary endpoint of the TORCH study appeared after the slides discussing the secondary endpoint data. The Panel considered that the secondary endpoint data on Slides 14 and 15 could not take the benefit of the subsequent qualification about the non-statistically significant primary endpoint on Slides 16 and 17 and thus had not been placed within the context of the TORCH study. The slide deck was misleading and the misleading impression was incapable of substantiation. Breaches were ruled.**

**The Panel noted that 'Seretide COPD slides for RVT' referred to Seretide in COPD in relation to NICE guidelines, clinical benefits and appropriate prescribing. The Panel noted that with the exception of Slide 4, none of the other slides which discussed clinical secondary endpoint data from the TORCH study had placed such data within the context of the non-statistically significant primary endpoint. The slide deck was misleading in this regard and the misleading impression was incapable of substantiation. Breaches were ruled.**

**The Panel noted that the COPD Cost-Effectiveness slides discussed a multinational economic analysis of the TORCH study, (Briggs *et al* 2010) based on health outcome data including cost and EQ-5D utility data. The presentation did not appear to have any mention of clinical data from TORCH. The TORCH study was referred to on Slide 13. The Panel considered that whilst it would have been helpful to provide additional relevant information about the TORCH study on Slide 13, the failure to do so did not render that slide misleading or incapable of substantiation. No breach was ruled.**

**The Secondary Care Campaign Detail Aid included the statement 'TORCH was a three-year study. The primary endpoint of the effect of Seretide on mortality did not meet statistical significance p=0.052' at the beginning of every page which discussed the secondary endpoint data. The data had been placed in the context of the non-statistically significant primary endpoint. No breach was ruled.**

**The Panel noted that two items were each designed to be made into cubes the sides of which discussed the TORCH study. It was made clear that the primary endpoint did not achieve statistical significance. No breach was ruled in relation to each item. This ruling also applied to another item described as 'Seretide COPD DXS click – through content'.**

**The Panel had no information about how the Primary Care Campaign iPad 2012 was used. It considered that overall the secondary endpoint data was not sufficiently qualified. There was no reference to the primary endpoint data. The material was misleading. The misleading impression was incapable of substantiation. Breaches were ruled.**

**The Panel noted the large number of pages of the Secondary Care Campaign iPad 2012 but had no information about how representatives were directed to use the material. The Panel noted that sometimes the material referred to the non-statistically significant primary endpoint when discussing secondary endpoint data and sometimes it did not. The material was inconsistent in this regard. The Panel considered that the failure to refer to the non statistically significant primary end point was such that certain pages were misleading and the misleading impression was incapable of substantiation in relation to secondary endpoint data. Breaches were ruled.**

**The Panel noted that site architecture was more difficult to decipher in the balance of the secondary care campaign ipad material which comprised the specialist modules. Most pages discussing TORCH secondary endpoint data featured the primary endpoint as a prominent and integral part of the page. In the absence of any detailed allegation from the complainant in relation to the secondary care campaign ipad 2012 detail and its layout and noting the complainant bore the burden of proof, the Panel considered the specialist modules provided were not misleading or incapable of substantiation in relation to secondary endpoint data and ruled no breach. With regard to the allegation that GlaxoSmithKline promotional material based on secondary endpoints from the TORCH study were accessible to the public as a search including the terms 'health professional, Seretide and TORCH study' identified a promotional site for Seretide did not, in the Panel's view, mean that the site was therefore promoting Seretide to the public. Access to such sites did not have to be restricted to health professionals so long as the requirements in the relevant supplementary information were met. No breach was ruled.**

**The Panel noted its rulings of breaches of the Code above. There did not appear to have been a consistent approach in relation to the certification of material which discussed secondary endpoint data from TORCH. Some material was qualified in relation to the non-statistically significant primary**

**endpoint and some was not. The Panel considered that high standards had not been maintained and a breach was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach was ruled accordingly.**

An anonymous, non contactable health professional complained about the use of the TORCH (TOwards a Revolution in COPD (chronic obstructive pulmonary disease) Health) study (Calverley *et al* 2007) in the promotion of Seretide (salmeterol/fluticasone) by GlaxoSmithKline UK Limited. Seretide's indications included the symptomatic treatment of patients with COPD, with an FEV1 (forced expiratory volume in one second) <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who had significant symptoms despite regular bronchodilator therapy.

**COMPLAINT**

The complainant noted that an editorial (Gøtzsche 2014) published in the Journal of the Royal Society of Medicine, 'Questionable research and marketing of a combination drug for smoker's lung', challenged both the design and analysis of the TORCH study and questioned the quality of the data derived. The complainant stated that Gøtzsche prompted a personal, deeper consideration of the use of data from the TORCH study in the promotion of Seretide.

The complainant noted that data from the TORCH study had been used to promote Seretide over at least the last six years such as in historical journal advertisements and in Seretide promotional literature used at booths/symposia at past respiratory conferences in the UK and in Europe. TORCH was perceived as a 'landmark' trial involving over 6,000 patients that confirmed the efficacy of Seretide in COPD. It was probable that over a number of years this promotion also shaped, rightly or wrongly, the perception of many UK health professionals and influenced key prescribing decisions directly or indirectly.

Putting aside the perceived 'landmark' status of the TORCH study, the complainant stated that the central issue was that the TORCH study did not meet its primary endpoint. Despite this, both historical and current promotional claims for Seretide referred to favourable secondary endpoints. The use of the TORCH study in promotion seemed to have missed closer scrutiny by responsible authorities for a very long time, in part possibly because of its perceived 'landmark' status although Case AUTH/2006/5/07 did perhaps provide an early opportunity to assess the wider consideration, beyond the issue raised by the complainant, of whether the TORCH study was actually suitable to support secondary endpoint claims in the promotion of Seretide given that the primary endpoint of the study was not met.

Raising awareness and encouraging debate about the TORCH study in a scientific non-promotional setting was understandable. However, in a promotional setting, the complainant alleged it was misleading to make promotional claims based on secondary endpoints (and or *post-hoc* analyses) from a study that did not meet its pre-defined primary endpoint. This fell well below expectations in relation to the promotion of prescription medicines.

It might be the case that the primary and secondary endpoints were clearly and prominently stated in Seretide promotion. However, in the UK time-pressured healthcare environment where health professionals were subject to Seretide promotion, it was unrealistic to expect them all to be able to correctly apportion appropriate weighting and context to this evidence when making key prescribing decisions based on favourable secondary endpoints when the associated primary endpoint was not met.

The complainant stated that the criticism by Gøtzsche about the TORCH study and marketing of Seretide further supported the view that the TORCH study results should never have been approved for use in the promotion of Seretide. Also, the title of Gøtzsche impacted on the wider pharmaceutical industry reputation and came when intense media spotlight on allegations related to sales practices in China and Poland had only just abated.

The complainant noted that GlaxoSmithKline continued to make claims based on secondary endpoints from the TORCH study in the promotion of Seretide. This was Seretide promotion that was accessible to the public. A Google search using 'healthcare professional + Seretide + TORCH study' revealed the following link as the first hit which directly led to an unsecured area of the GlaxoSmithKline website in the UK where prior registration as a health professional was not necessary in order to gain access to the information below: http://hcp.gsk.co.uk/products/seretide/prescribing-seretide/efficacy.html.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 2, 7.2, 7.4, 7.10, 9.1 and 23.1.

**RESPONSE**

GlaxoSmithKline noted that the anonymous complainant stated that his/her complaint related to the use of data from the TORCH study in the promotion of Seretide and was prompted after reading an article entitled 'Questionable research and marketing of a combination drug for smoker's lung' (Gøtzsche 20140).

GlaxoSmithKline noted that the complainant did not complain about any specific promotional materials for Seretide in particular, but referred to the promotion of Seretide over the last six years at the very least such as in historical journal advertisements and in Seretide promotional literature used at booths/symposia at past respiratory conferences in the UK and Europe'. The case preparation manager confirmed that it was unclear as to exactly which pieces of promotional material the complainant was complaining about.

GlaxoSmithKline submitted that the TORCH study was a three-year, randomised, double-blind, controlled study of 6,112 patients with moderate-to-severe COPD. The study commenced in

September 2000 and took place in 42 countries and 444 centres. Patients were randomised to three years of twice-daily treatment with either Seretide 50/500 Accuhaler, fluticasone propionate 500µg, salmeterol xinafoate 50µg, or placebo. The primary endpoint was all-cause mortality for the comparison of the Seretide 50/500 Accuhaler vs placebo. The key secondary endpoints were reduction in COPD morbidity between Seretide 50/500 Accuhaler and placebo (measured by rate of moderate and severe exacerbations) and difference in quality of life (QoL) between Seretide and placebo (measured by the St George's Respiratory Questionnaire (SGRQ)). Lung function and safety endpoints including adverse events and bone fracture information were also evaluated.

The results showed that for the primary endpoint, Seretide 50/500 Accuhaler did not meet statistical significance on all-cause mortality (p=0.052) and that for the two key secondary endpoints Seretide 50/500 Accuhaler reduced the rate of moderate/severe COPD exacerbations by 25% vs placebo (p<0.001) and produced a statistically significant (p<0.001) improvement in quality of life score as measured by the SGRQ vs placebo (-3.1 units).

The authors concluded that 'The reduction in death from all causes among patients with COPD in the combination therapy group did not reach the predetermined level of statistical significance. There were significant benefits in all other outcomes among these patients'.

GlaxoSmithKline submitted that the complainant inferred several criticisms and concerns. These were:

a) The perception that TORCH was a 'landmark' study.

b) The use of positive secondary endpoints in promotional materials when the primary endpoint for the study was not met.

c) That Seretide promotion was accessible to the public.

and in addition that

d) The responsible authorities seemed to have 'missed closer scrutiny' of the use of the TORCH study in promotion.

**a) The perception that TORCH was a 'landmark' study**

GlaxoSmithKline noted the complainant's submission that 'The TORCH study was perceived as a "landmark" trial .... that confirmed the efficacy of Seretide in COPD'. The complainant inferred that 'landmark' was an inappropriate descriptor for the study by placing it in inverted commas throughout his/her letter, but did not expressly state this was the case as such. Indeed the complainant hinted at slight ambivalence in this regard by stating that 'The TORCH study was perceived as a "landmark" trial ..... It is probable that this promotion [by GlaxoSmithKline] also shaped (**rightly** or wrongly) the perception of many UK health professionals' (emphasis added). GlaxoSmithKline noted that, nonetheless, it had been asked to consider whether 'landmark' might exaggerate the importance (of TORCH) and thus might not encourage the rationale use of Seretide.

GlaxoSmithKline noted that the Oxford Dictionary defined 'landmark' as 'An event or discovery marking an important stage or turning point in something'.

GlaxoSmithKline submitted that at the time of its inception and initiation the TORCH investigators stated that:

> 'The "TOwards a Revolution in COPD Health" survival study will be the largest ever, multicentre, long-term chronic obstructive pulmonary disease study, and the first to investigate the effect of salmeterol/fluticasone propionate combination and its components on chronic obstructive pulmonary disease mortality. A significant effect of salmeterol/ fluticasone propionate combination on chronic obstructive pulmonary disease morbidity and mortality would represent a real step forward in the pharmacological management of chronic obstructive pulmonary disease. Even if this does not prove to be the case, the data gathered will shed new light on the natural history of this disorder.'

GlaxoSmithKline submitted that two years later, when the TORCH results were first made available in November 2006, an article in the CHEST Physician (The Official News Publication of the American College of Chest Physicians) described TORCH as a 'landmark' study.

GlaxoSmithKline submitted that in February 2007 the TORCH study results were published in the New England Journal of Medicine (NEJM). The fact that they were published in such a prestigious international journal with an Impact Factor of 54.42, indicated that the results were considered to be of major importance to the scientific and medical community. The NEJM stated on its website that 'Of the thousands of research reports submitted each year, about five per cent are eventually published in NEJM .... And that they employ a highly rigorous peer-review and editing process to evaluate manuscripts for scientific accuracy, **novelty, and importance**' (emphasis added).

Furthermore, a Google search on 20 August 2014 showed that that there had been 1,460 citations of the TORCH study, further emphasising the impact that it had had on the medical and scientific community worldwide since its publication in 2007.

TORCH had been the subject of four complaints to the PMCPA - two, 'no breaches', one breach of Clause 4.1 and the one breach of Clauses 7.2 and 7.4. In two of the cases, the case report showed that TORCH was referred to as a 'landmark' study at the time of the evaluation of the case; a descriptor which was never questioned by the complainant nor the PMCPA at the time.

GlaxoSmithKline submitted that the original

promotional material for TORCH referred to it as a 'landmark' study, which again was never questioned by the Medicines and Healthcare Products Regulatory Agency (MHRA) when it pre-vetted material between May and September 2007 and again between July and November 2012.

In summary, TORCH was perceived as a 'landmark' study by health professionals within the UK and elsewhere and had held this status without question for the last ten years. GlaxoSmithKline therefore refuted that by describing TORCH as a 'landmark' study it might have exaggerated its importance and thus might not have encouraged the rational use of Seretide. Breaches of Clauses 7.2, 7.4 and 7.10 were denied.

**b) The use of positive secondary endpoints in promotional materials when the primary endpoint for the study was not met**

GlaxoSmithKline submitted that TORCH was a highly ambitious study not least as its primary endpoint was all-cause mortality at the end of a three-year treatment period. Prior to TORCH, no trials had assessed the effect of inhaled corticosteroids and long-acting bronchodilators, alone or in combination, on mortality in COPD patients, despite their known benefit in reducing symptoms and exacerbations. Since TORCH, the Cochrane review showed that there had been four trials where all-cause mortality had been the primary outcome for combination therapies in COPD. However, the overall conclusion of the Cochrane review was that for 'ICS/LABA [inhaled corticosteroid/long acting beta agonist] combination therapies compared to placebo, an overall reduction in mortality was seen, but this outcome was dominated by the results of one study (TORCH) of fluticasone/salmeterol ... and that generally, deaths in the smaller, shorter studies were too few to contribute to the overall estimate'.

Thus, even though a statistical difference was not seen between the Seretide and the placebo treatment arms in TORCH, the level of statistical significance was close to being significant, with a P value of 0.052, which was acknowledged as such in the Cochrane review as well as in the Seretide summary of product characteristics (SPC). Section 5.1 of the SPC stated that 'There was a trend towards improved survival in subjects treated with Seretide compared with placebo over 3 years however this did not achieve the statistical significance level $p \leq 0.05$'.

GlaxoSmithKline submitted two documents from the Medicines Healthcare Regulatory Agency (MHRA) which gave guidance on the use of secondary endpoints from clinical trials in promotional materials. The first related to the pre-vetting of promotional materials and stated that for 'Clinical Studies – Findings from secondary endpoints of clinical studies should be set within the context of the primary endpoint and companies should not 'cherry-pick' favourable findings'. The second in a general communication in MAIL related to advertising and the presentation of clinical data and stated that 'If the main study endpoint showed no differences in efficacy between two products, it would usually be misleading to highlight data from one of the other efficacy parameters measured which showed a difference unless this information is placed in context of the overall study findings'.

GlaxoSmithKline maintained that Seretide had been promoted in accordance with the above guidances, a practice which had been confirmed by the MHRA which reviewed all promotional material related to Seretide in the immediate pre-vetting period (May-September 2007) and then again in an audit (July-November 2012). At no point did the MHRA raise any concerns in the way in which the secondary endpoints had been portrayed nor that TORCH was described as a 'landmark' study.

GlaxoSmithKline submitted that as stated above, TORCH had been the subject of four complaints with the PMCPA and none of these related to the inappropriate use of secondary endpoints in promotional material.

GlaxoSmithKline noted in particular that in Case AUTH/2006/5/07 breaches of Clauses 7.2 and 7.4 were ruled as 'The Panel considered that overall the exhibition panel detailing the mortality data did not make it sufficiently clear that the data was not statistically significant particularly given the description of TORCH as a landmark study'. What was important to mention in this case was that at no time was the use of secondary outcome questioned by either the complainant or the PMCPA and even in this case the non-significance of the primary endpoint was mentioned albeit not sufficiently clear enough.

Secondary endpoints were routinely included in promotional material in the UK as they provided information which might be of particular interest to the health professional, allowing them to make informed decisions as to which treatment might be appropriate for individual patients. Information about the secondary endpoints in the TORCH study was of particular interest to health professionals in the therapeutic area of COPD as no currently available combination products had had a statistically significant impact on all-cause mortality and the secondary endpoints used in the TORCH study were frequently used as primary endpoints in other studies.

**c) That Seretide promotion was accessible to the public**

GlaxoSmithKline noted that the complainant had deliberately used the term healthcare professional in his/her search to access the site, as well as the acronym for the study TORCH, which had never been used in any non-promotional materials/websites for patients and which it would be reasonable to assume, that the general public did not know about.

The PMCPA guidance on Digital Communications stated that 'Generally speaking it would not be unreasonable for a company to try to ensure that its sites are ranked high on lists when the search is for that company or one of its medicines (brand or generic)'. The guidance also allowed for the use of search engine optimisation and meta data.

GlaxoSmithKline submitted that as the complainant had used the brand name Seretide and the acronym TORCH for the pivotal study relating to a GlaxoSmithKline product, it was not surprising that this was the first 'hit'.

When the search terms referred to above were entered into Google the following was displayed:

Seretide | Prescribing Seretide - Efficacy | Respiratory | GSK ...
hcp.gsk.co.uk/**pro**ducts/**seretide**/prescribing-**seretide**/efficacy.html
Seretide (salmeterol xinafoate/fluticasone propionate) efficacy information to support UK healthcare professionals in their daily practice. ... placebo (in a *post-hoc* analysis) (p<0.001). Read the TORCH study summary or the TORCH study in full ...

GlaxoSmithKline submitted that it was clear from the text highlighted in bold that this site was for health professionals who sought information about prescribing Seretide and was not one for the general public.

On opening up the website, the first page was displayed as follows:

> 'health.gsk. For UK Health Professionals.
>
> Not a Healthcare Professional? Visit our Public Site.'

GlaxoSmithKline submitted that once again it was made quite clear that the website was for UK health professional and that if the reader was not one, then they should visit the public site with the relevant URL provided.

Conversely, if the search terms Seretide and patients were entered into Google, the following was revealed https://www.google.co.uk/#q=patient+seretide. Here the first two entries were from the Medicines Compendium.com and related to the product information leaflet for the accuhaler and evohaler, the third entry from patientuk.com and the fourth from GlaxoSmithKline which stated the following:

> 'Seretide - | GSK Pharma UK | Public Site | (salmeterol ...
> public.gsk.co.uk/products/**seretide**.html.'

This website did not mention the TORCH data. GlaxoSmithKline therefore refuted a breach of Clause 23.1.

**The content of the website**

GlaxoSmithKline submitted that the complainant made no direct comment about the information contained on the Health.gsk website for health professionals but had drawn several yellow lines against those sections which he/she no doubt wished to bring to the PMCPA's attention.

These were the prescribing information for Seretide (which the Code required to be present for a health professional website), and brief information relating to TORCH, with the first statement being:

> 'TORCH was a 3 year study. The primary endpoint of the effect of Seretide 500 Accuhaler on all-cause mortality did not meet statistical significance; P=0.052'. This was then followed by the results of the two key secondary endpoints and a post hoc analysis and 'Read the TORCH study summary or the TORCH study in full.'

**d) The responsible authorities seemed to have 'missed closer scrutiny' of the use of the TORCH study in promotion**

GlaxoSmithKline was unclear what the complainant meant by 'responsible authorities'. Within the UK, however, the MHRA reviewed the TORCH study results in great detail as part of a regulatory submission. Following this review, the licence was broadened to allow for patients with an FEV1 <60% to be included and Section 5.1 of the Seretide SPC was updated with a new section relating to TORCH (both the design and the study results), which amounted to 30 lines of new text, as well as the inclusion of a tabulated summary of the results. Additionally, Seretide promotional materials were prevetted between 21 May and 3 September 2007 and all Seretide materials were submitted for an audit between July and November 2012. The MHRA's comments with respect to the TORCH data could be provided if required, but it did not criticise the use of secondary endpoints within the material.

GlaxoSmithKline therefore refuted the statement that the MHRA or indeed the PMCPA had not given close enough scrutiny to the TORCH data and its use in a promotional setting within the UK.

**Overview and context of the publication**

GlaxoSmithKline noted that the complainant stated that Gøtzsche 'Challenged both the design and analysis for the TORCH study and questioned the quality of the data derived'. GlaxoSmithKline noted that a similar publication by Gøtzsche appeared in the Journal of the Danish Medical Association in February 2014, where *inter alia*, he questioned whether Seretide should have been licensed for COPD. This article prompted a number of Danish health professionals to publish several articles refuting statements made by Gøtzsche; one of those health professionals was Professor Jørgen Vestbo, a member of the steering committee for the TORCH study at the time of its conduct and analysis and for which the original Danish version with accompanying English translation were provided.

GlaxoSmithKline noted that no complaint was ever made against GlaxoSmithKline Denmark about TORCH and the use of its secondary endpoints to the Ethical Board for the Danish Pharmaceutical Industry.

**Summary**

GlaxoSmithKline submitted that the complainant referred to the promotion of Seretide over the last six years in the UK and Europe but did not comment on any specific examples of promotional material which

he/she considered to be in breach of the Code. The complaint was based on an editorial by Gøtzsche which was very similar to the article published in a Danish journal earlier this year and for which the Danish affiliate was not found to be in breach of its local regulations.

GlaxoSmithKline therefore denied breaches of Clauses 2, 7.2, 7.4, 7.10, 9.1 and 23.1.

GlaxoSmithKline provided all Seretide materials that were in current use at the time of receipt of the letter on 8 August 2014. In addition, it had provided historical material relating to Seretide and the promotion of the TORCH clinical study which included the following 3 items:

COPD Secondary Care Campaign
Date of preparation November 2011

COPD Advertisement
Date of preparation February 2012

TORCH Leave piece
Date of preparation May 2011

GlaxoSmithKline explained that the TORCH study results first became available seven and a half years ago on 21 February 2007, so at this time, the results of this study would have been included in many promotional materials. However, the Code only required a pharmaceutical company to archive materials for three years after date of last use. In June 2010 GlaxoSmithKline introduced the electronic approval system called Zinc Maps, and a search of this database was undertaken on 18 August 2014. Several searches had been undertaken. Using the search term 'TORCH' in the section entitled 'Short description text' yielded five results – three of which related to clinical papers concerning the study and the other two, a leavepiece for general practitioners that was certified in both May and December 2011. As the complainant referred to 'Historical Journal Advertisements and promotional literature at booths and symposia', a search of all these items was undertaken. For advertisements 43 items were shown. Some referred to Avamys (fluticasone), others to the asthma indication and only one advertisement in February 2012 referred to TORCH. For exhibition panels, there were 12 items, most of which were very general in nature and none of them referred to TORCH.

The company trusted that the above material satisfied the need of the PMCPA to review all current Seretide promotional materials as well those that mentioned the TORCH study in the past.

**PANEL RULING**

The Panel noted that the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure such complaints were accepted and like all complaints, judged on the evidence provided by both parties. Complainants had the burden of proving their complaint on the balance of probabilities; as the complainant was anonymous and non-contactable it was not possible to ask the complainant for further information.

The Panel noted that GlaxoSmithKline had been asked to respond to Clause 7.10 in relation to an allegation that describing TORCH as a landmark study might have exaggerated its importance and thus not have encouraged the rational use of Seretide. The Panel noted GlaxoSmithKline's comments about this matter. The Panel did not consider that the complainant had made an allegation about the use of the term 'landmark' *per se*. The complainant referred to the perception that TORCH was a landmark study and then stated that 'it is probable that this promotion also shaped (rightly or wrongly) the perception of many UK HCPs and influenced key prescribing decisions ...'. In the Panel's view the complainant had not stated or inferred that the word 'landmark' contravened the Code. Indeed the complainant appeared to accept that the term may have 'rightly' influenced the perception of UK health professionals. The complainant bore the burden of proof. It was not possible to contact the complainant to clarify matters. The Panel therefore considered that there was no complaint in relation to the very narrow point about the principle of using the term 'landmark' to describe the TORCH study and thus it could not make a ruling about the use of the term landmark and Clause 7.10. The Panel noted that consideration of the term 'landmark' might nonetheless, be relevant when considering allegations about claims based on the secondary endpoints in materials within the scope of the complaint.

The Panel noted the complainant had not identified any specific materials other than pages from a website in relation to the allegation that the material therein was accessible to the general public. GlaxoSmithKline had been asked to provide all current Seretide material (including electronic material) and, if that did not encompass every secondary endpoint from the TORCH study which had been the subject of a promotional claim, it should also provide historical materials such that all such endpoints/claims were covered. GlaxoSmithKline explained that the TORCH study results first became available seven and a half years ago (21 February 2007) and its results would have been included in many promotional materials. The Code only required these to be archived for three years after the date of last use. The Panel noted that there was no such time limitation in relation to requests from the MHRA. In response to this complaint, GlaxoSmithKline provided *inter alia* all current Seretide materials. The company introduced an electronic approval system in June 2010. Relevant search terms had been used and according to GlaxoSmithKline all relevant materials were submitted.

The Panel noted that the complainant referred to Case AUTH/2006/5/07 and noted GlaxoSmithKline's submission on this point. The Panel noted that Case AUTH/2006/5/07 concerned the graphical depiction of the non-statistically significant 16% reduction in mortality on an exhibition stand. The Panel in Case AUTH/2006/5/07 had considered that overall the

exhibition panel did not make it sufficiently clear that the mortality data depicted was not statistically significant, particularly given the description of TORCH as a landmark study. The Panel considered that on glancing at the exhibition panel delegates would be struck by the prominent subheading 'Primary outcome - Seretide 500 Accuhaler survival result'. The results were then depicted in the graph which showed a visual difference between Seretide and the control group alongside an emboldened arrow and '16.5%' which was in a larger, bolder typeface than the explanatory text immediately beneath. A delegate who did not take the time to read the entire exhibition panel would be left with the impression that the 16.5% risk reduction was statistically significant. The Panel considered that graph was misleading and that its content could not be qualified by the text below. Breaches of the Code were ruled. The Panel noted that the issue in Case AUTH/2006/5/07 was different to that presently before the Panel, Case AUTH/2726/8/14.

The Panel noted that at its inception the TORCH study (Calverley *et al* 2007) was the largest ever multicentre, long-term chronic obstructive pulmonary disease study and the first to investigate the effect of the salmeterol/fluticasone propionate combination and its components on chronic obstructive pulmonary disease mortality. It was a prospective randomized double-blind trial comparing a combination regimen of salmeterol and fluticasone in a single inhaler with placebo, salmeterol alone or fluticasone propionate alone for three years. The primary endpoint was the time to death from any cause for the comparison between the combination regimen and placebo. Key secondary endpoints included the reduction in COPD morbidity and the difference in QoL, each between the combination regimen and placebo. Other endpoints included the difference in composite endpoint made up of overall mortality and COPD admissions, COPD-related mortality, clinic post-bronchodilator FEV1, other COPD exacerbation endpoints, health status and health utilisation. The reduction in death from all causes amongst COPD patients in the combination therapy group as compared to placebo did not reach the predetermined level of statistical significance. Treatment with the combination regimen resulted in significantly fewer exacerbations compared with placebo including those exacerbations requiring hospitalization. The combination regimen was also significantly better than each of its components alone in preventing exacerbations and these benefits were accompanied by sustained improvements in health status and FEV1. The study authors noted that the greater number of patients withdrawing from the placebo group was likely to have resulted in an underestimation of the effect of the combination regimen on all the secondary outcomes. The study authors also noted that the size of the TORCH study was modest compared with studies of mortality associated with other major chronic illnesses such as cardiovascular disease and thus the results of the mortality analysis should be viewed in this context.

The Panel noted that there was a *post-hoc* analysis of the TORCH study secondary endpoint data which was referred to in some of the materials provided by GlaxoSmithKline.

The Panel noted the allegation that in a promotional setting, it was misleading to make claims based on secondary endpoints from a study that did not meet its pre-defined primary endpoint. The Panel considered that, in principle, when a primary endpoint failed to achieve statistical significance it was not necessarily unreasonable to refer to secondary endpoint data so long as this was placed within the context of the overall study findings. The nature of the material might also be relevant.

The Panel examined the materials provided and only considered those items which referred to the secondary endpoint data from the TORCH study including the *post-hoc* analysis as these were the only items covered by the complaint.

The Panel examined the material published at Seretide.co.uk. The Panel noted that the 'Efficacy and Clinical Evidence' page (UK/SFC/005c/13) summarized clinical data from five studies including the TORCH study. Each reference to the TORCH secondary endpoint data was preceded by the statement 'The primary endpoint of the effect of Seretide 500 Accuhaler on all-adverse mortality did not meet statistical significance p=0.052'. The Panel considered that the secondary endpoint data was placed within the context of the study. No breach of Clauses 7.2 and 7.4 were ruled.

In relation to the 'Seretide campaign' materials the Panel noted that the Seretide TR Campaign pilot (UK/SFC/0025/14(1)) appeared to be a 24-page slide deck. Slide 12 onwards referred to Seretide in COPD. Slides 14 and 15 each headed '... And benefit over the long term' discussed the clinical benefits of Seretide 500 Accuhaler over three years with reference to the secondary endpoints of the TORCH study. Slide 16 introduced the TORCH study and made it clear that the primary endpoint did not achieve statistical significance. More detailed information about the TORCH study appeared at Slide 17. The Panel was concerned that the information about the primary endpoint of the TORCH study appeared after the slides discussing the secondary endpoint data. The Panel considered that the secondary endpoint data on Slides 14 and 15 could not take the benefit of the subsequent qualification about the non-statistically significant primary endpoint on Slides 16 and 17 and thus had not been placed within the context of the TORCH study. The slide deck was misleading. The misleading impression was incapable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that 'Seretide COPD slides for RVT' (UK/SFC/0389h/13) referred to Seretide in COPD in relation to NICE guidelines, clinical benefits and appropriate prescribing. Slide 4 'Seretide in COPD: Clinical benefits' included 'TORCH was a 3-year study. The primary endpoint of effect of Seretide 500 Accuhaler on all cause mortality did not meet statistical significance (p=0.052)' and discussed secondary endpoint data. Subsequent slides referenced the TORCH study in relation to health related quality of life score, three-year outcome data, and long-term benefits. It appeared that a reference to the TORCH study on the summary

Slide 13 in relation to rate of exacerbations was incorrectly referenced to Vestbo *et al* 2003. In addition, it appeared that a claim about the *post-hoc* analysis and lung function decline had been incorrectly referenced to Briggs *et al* 2010, a health economic analysis. The Panel noted that with the exception of Slide 4, none of the other slides which discussed clinical secondary endpoint data from the TORCH study had placed such data within the context of the non-statistically significant primary endpoint. The slide deck was misleading in this regard. The misleading impression was incapable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled. The Panel considered that the referencing of this slide deck was confusing. Each slide had details of the referencing but the same number did not link to the same study consistently. For example, reference 1 was sometimes a reference to TORCH and in other slides was a reference to Vestbo.

The Panel noted that the COPD Cost-Effectiveness Slides (UK/SFC/0229/11(2)) was a presentation which discussed a multinational economic analysis of the TORCH study, (Briggs *et al* 2010) based on health outcome data including cost and EQ-5D utility data. The presentation did not appear to have any mention of clinical data from TORCH. The TORCH study was referred to on Slide 13. The Panel considered that whilst it would have been helpful to provide additional relevant information about the TORCH study on Slide 13, the failure to do so did not render that slide misleading or incapable of substantiation. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel then examined the historical material. The Panel noted that the historical material was certified between November 2011 and August 2013. It noted that the applicable Code would be the 2011 Code, or either of the 2012 Codes (first and second editions). The requirements of Clauses 7.2 and 7.4 were the same in all three Codes and the same in the 2014 Code.

The Secondary Care Campaign Detail Aid (ref UK/SFC/0207/11) included the statement 'TORCH was a three-year study. The primary endpoint of the effect of Seretide on mortality did not meet statistical significance p=0.052' at the beginning of every page which discussed the secondary endpoint data. The data had been placed in the context of the non-statistically significant primary endpoint. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that items UK/SFC/0150a/11 and UK/SFC/0150/11 were each designed to be made into cubes the sides of which discussed the TORCH study. The Panel did not have the final items. It was made clear on the Results 'All-cause Mortality' sections and Conclusion sections that the primary endpoint did not achieve statistical significance. No breach of Clauses 7.2 and 7.4 was ruled in relation to each item. This ruling also applied to the one page item, item UK/SFC/0040a/12, which was described as 'Seretide COPD DXS click – through content'. Again, the Panel did not have the final item or information about its use. In the absence of detailed allegations, the Panel made its ruling on the single page which discussed the non-statistical primary endpoint finding at the outset before the reference to secondary endpoint data. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel then examined the Primary Care Campaign iPad 2012 UK/SFC/0129/12(1). The Panel had no information about how it was used. The Panel accepted it was unlikely that all 77 pages would be displayed during a representative detail. Three pages headed '… and benefit over the long-term' discussed secondary endpoint data from the TORCH study in relation to lung function, rate of exacerbations and improvements in qualify of life. A highlighted box on the right of the first two of the three pages read 'TORCH study'. This appeared to be the first mention of the TORCH study. It was unclear whether this was a link to the TORCH study or information about it. No print out of any link had been provided with these 2 pages. In any event, in the Panel's view, any qualification necessary to ensure that a claim complied with the Code should be an integral part of the claim or within the visual field of the claim in question and not relegated to a link or footnote etc. A fourth page headed 'Seretide 500 Accuhaler improves QoL [quality of life] total score over 3 years' featured a graph showing the change from baseline in SGRQ total score over three years referenced to Calvery *et al*, 2007 (TORCH). There was no highlighted box referring to the TORCH study. The Panel considered that overall the secondary endpoint data was not sufficiently qualified by a reference to the primary endpoint. There was no reference to the primary endpoint data. The material was misleading. The misleading impression was incapable of substantiation. A breach of Clauses 7.2 and 7.4 was ruled.

The Panel examined the Secondary Care Campaign iPad 2012 (UK/SFC/0131/12(1)). The Panel noted the large number of pages but had no information about how representatives were directed to use the material. This was especially important given that there would be insufficient time to discuss all of the material with a health professional during an average detail. The material began with a detailed introductory section titled 'How good could Seretide make your patients feel?' which comprised 6 sections. Some of this material appeared to be similar to that referred to above. There were 10 detailed specialist modules including exacerbations, long-term efficacy, lung function and Seretide use. It was unclear whether all of the specialist modules such as 'Seretide or Symbicort' had been provided by GlaxoSmithKline. The Panel noted that sometimes the material referred to the non-statistically significant primary endpoint when discussing secondary endpoint data and sometimes it did not. The material was inconsistent in this regard and the reason for this inconsistency was unclear. The Panel noted that site architecture might be an important factor. The Panel noted a pop-up box headed 'Towards a Revolution in COPD health (TORCH) was a 3-year randomised multi-centred trial' gave detailed information about the study including, in bold, the primary non-significant outcome. To which pages the pop-up box was linked was unclear. However, the Panel noted its comments above about the use of pop up boxes. The Panel noted that two pages headed '… and benefit over the long-term' in the introductory

section discussed the reduced rate of lung function decline and reduced rate of moderate/severe exacerbations with reference to the TORCH study. A highlighted box 'TORCH study' appeared on the right-hand side. It was unclear whether this was a link to further information about the study and in this regard the Panel noted its comments above about pertinent information necessary for Code compliance appearing in a pop-up box alone. A further page in the introductory section also headed 'and benefits over the long-term' discussed data SGRQ from TORCH with no reference to the primary endpoint or highlighted TORCH tab. A subsequent page in the introductory section was headed 'Seretide 500 Accuhaler improves QoL total score over 3 years' and featured a graph adapted from the TORCH study. The study's primary endpoint result was not referred to. The Panel considered that the failure to refer to the non statistically significant primary end point was such that pages identified above in the introductory section of the secondary care ipad detail aid were misleading. The misleading impression was incapable of substantiation in relation to its reference to secondary endpoint data. A breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that site architecture was more difficult to decipher in the balance of the secondary care campaign ipad material which comprised the specialist modules. Most pages discussing TORCH secondary endpoint data featured the primary endpoint as a prominent and integral part of the page. In the absence of any detailed allegation from the complainant in relation to the secondary care campaign ipad 2012 detail and its layout and noting the complainant bore the burden of proof, the Panel considered the specialist modules provided were not misleading or incapable of substantiation in relation to secondary endpoint data and ruled no breach of Clauses 7.2 and 7.4.

With regard to the allegation that GlaxoSmithKline promotional material based on secondary endpoints from the TORCH study were accessible to the public, the Panel noted GlaxoSmithKline's response and in particular that the complainant's search terms had included 'healthcare professional'. The search had taken the complainant to the section on the GlaxoSmithKline website which stated, *inter alia*, 'For UK Healthcare Professionals, Not a Healthcare Professional? Visit our Public Site'. The Panel noted the supplementary information to Clause 25.1 'Access' which stated that a company website or sponsored website with unrestricted access must provide information to the public as well as health professionals with the sections for each target audience clearly separated and the intended audience identified. That a search including the terms 'health professional, Seretide and TORCH study' identified a promotional site for Seretide did not, in the Panel's view, mean that the site was therefore promoting Seretide to the public. Access to such sites did not have to be restricted to health professionals so long as the requirements in the supplementary information to Clause 25 were met. No breach of Clause 23.1 was ruled.

The Panel noted its rulings of breaches of the Code above. There did not appear to have been a consistent approach in relation to the certification of material which discussed secondary endpoint data from TORCH. Some material was qualified in relation to the non-statistically significant primary endpoint and some was not. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach was ruled accordingly.

**Complaint received** **7 August 2014**

**Case completed** **11 December 2014**

# ANONYMOUS, NON CONTACTABLE v GLAXOSMITHKLINE

## Promotion of Relvar

**An anonymous, non contactable complainant who described him/herself as a prescriber complained that GlaxoSmithKline UK was trying to hide important safety information in relation to promotion of Relvar Ellipta (fluticasone furoate/ vilanterol inhalational powder).**

**The complainant highlighted a claim in an email that 'Relvar is generally well-tolerated in COPD. The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/LABAs' [inhaled corticosteroid and long-acting ß$_2$ adrenoreceptor agonists].**

**The complainant stated that reading the email led him/her to believe that pneumonia was a side-effect associated with COPD only as highlighted on the second page; there was no mention of pneumonia with regard to asthma. The complainant stated that he/she did not think too much about it at the time as pneumonia was associated with the use of ICS/LABA in COPD patients. There was not the same association with asthma so it seemed to be as expected. However, on reading the Drug and Therapeutics Bulletin (DTB) review, the complainant was surprised to note that pneumonia had been reported in asthma patients on Relvar and GlaxoSmithKline had been required by the regulators to study this further.**

**The complainant looked at the GlaxoSmithKline website and noted that the information was similar to that received in the email. A number of screen shots were provided. The website only discussed pneumonia in relation to COPD with no mention of asthma.**

**The complainant noted that pneumonia was mentioned in the SPC with regard to both COPD and asthma. The complainant stated that hidden in the text was the important information that the incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma who took fluticasone furoate/vilanterol 184/22mcg was numerically higher compared with those who took fluticasone furoate/vilanterol 92/22mcg or placebo (see section 4.8). No risk factors were identified.**

**The complainant noted that the incidence of pneumonia was common in asthma patients taking the higher dose. The complainant alleged that for GlaxoSmithKline to discuss pneumonia only in relation to COPD in its advertisements, which was expected for that type of inhaler, while omitting that it was commonly experienced in asthma patients which was an unexpected side-effect, was totally unacceptable and a risk to patient safety.**

**The complainant referred to GlaxoSmithKline's statement that the incidence of pneumonia in COPD patients was similar to that of other commonly used ICS/LABAs quoting the SPCs for Seretide and Symbicort. The complainant noted that GlaxoSmithKline had not included Fostair in the comparison which, although only recently licensed for COPD, was commonly used to treat the condition. Fostair information stated that pneumonia was uncommon and the complainant alleged that this was another example of important safety information being hidden and not included in GlaxoSmithKline materials.**

**The detailed response from GlaxoSmithKline is given below.**

**The Panel noted the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure such complaints were accepted and like all complaints, judged on the evidence provided by both parties. Complainants had the burden of proving their complaint on the balance of probabilities.**

**The Panel noted that the DTB section was headed 'Unwanted effects' and stated 'Although pneumonia is more common in patients with chronic obstructive pulmonary disease (COPD) it has been reported in patients receiving fluticasone/vilanterol for asthma. The company is required to conduct a further study into the risk of pneumonia as an obligatory post-authorisation measure'.**

**The Panel noted the complainant's concern that GlaxoSmithKline was trying to hide important safety information on pneumonia as a side effect associated with using Relvar to treat asthma. The email provided by the complainant specifically highlighted pneumonia as a side effect associated with COPD but not asthma. GlaxoSmithKline stated that the clinical and management considerations for pneumonia in COPD was different to that in asthma. COPD patients were at higher risk of developing CAP than those in the general population and those with asthma. COPD patients with pneumonia had worse clinical outcomes compared with pneumonia patients without COPD in terms of pneumonia severity, intensive care admissions, and mortality (Restrepo *et al*, 2006). The rates of pneumonia seen in COPD were significantly higher than the rates seen in asthma patients, including, importantly, rates of serious and severe events. This was expected based on the different disease profiles and the differing prognoses for pneumonia in the two conditions. That pneumonia was a more important clinical condition in COPD compared with asthma was highlighted by UK and international guidelines. The Panel also noted the Cochrane Review report**

**on inhaled steroids and risk of pneumonia in COPD, Kew *et al* 2014, concluded that budesonide and fluticasone delivered as monotherapy or in combination with a LABA were associated with increased risk of a serious adverse pneumonia event but neither significantly effected mortality compared with controls. The safety concerns highlighted in the review should be balanced with recent cohort data and established evidence of efficacy regarding exacerbations and quality of life.**

**The Panel noted the submission from GlaxoSmithKline that overall, the incidence of pneumonia in asthma was low (≤1.1%) in all treatment groups. The highest incidence of 1.1% for Revlar 200/25 corresponded to five patients. Nonetheless, the Panel noted GlaxoSmithKline's submission that pneumonia was correctly described as a common adverse event in the SPC. The Panel noted the concerns raised about pneumonia in the Discussion of Clinical Safety section of the EMA Revlar assessment report. The regulators required GlaxoSmithKline to continue to gather information about the risk associated with Relvar (a combination of new chemical entities) in both asthma and COPD compared with other licensed ICS/LABAs.**

**The Panel did not consider that mentioning pneumonia in relation to COPD patients in the email meant that it did not have to be considered in asthma patients. The Panel noted GlaxoSmithKline's comments about the importance of pneumonia in COPD compared to asthma. On balance, the Panel considered that it was therefore not unreasonable to mention pneumonia in relation to COPD alone. No breaches of the Code were ruled.**

**The Panel noted the complainant was concerned that GlaxoSmithKline had not compared Relvar to Fostair, which was recently licensed for COPD. The Panel noted the claim in the email stated, 'Relvar is generally well tolerated in COPD. The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/LABAs'. GlaxoSmithKline stated that the most commonly prescribed ICS/LABAs in the UK for COPD were Seretide and Symbicort (June 2013 – June 2014). The FORWARD study (Wedzicha *et al*, 2014), showed that pneumonia occurred in 3.8% of Fostair patients vs 1.8% in the formoterol (LABA alone) group and concluded 'The [Fostair] treatment arm was also associated with a higher incidence of pneumonia. This is in line with recent studies showing a 2-3 fold excess of pneumonia in the ICS/LABA treatment arms of studies compared to the corresponding monotherapy.' Calverley 2010 reported pneumonia in 2.1% of Fostair patients, 2.9% of Symbicort patients and 0.4% in the formoterol group and concluded: 'The rate of reported pneumonia was similar to that reported in placebo controlled trials using budesonide.' GlaxoSmithKline submitted that the association of pneumonia with ICS in COPD was regarded as a class effect and therefore similar risks of pneumonia could be expected with Relvar, Seretide, Symbicort and Fostair.**

**The Panel noted the complainant had not provided any information to support his/her view that Fostair was commonly used to treat COPD. Fostair 100/6 was indicated for symptomatic treatment of patients with severe COPD (FEVI <50% predicted normal) and a history of repeated exacerbations. Pneumonia was listed as an uncommon (≥1/1000 and <1/100) undesirable effect (derived from clinical trials in asthmatic and COPD patients). The SPC included an asterisk next to pneumonia and the explanation 'one related non serious case of pneumonia was reported by one patient treated with Fostair in a pivotal clinical trial in COPD patients'.**

**The Panel noted the complaint was received in August. The email referred to the SMC decision in April 2014 and that AWMSG would be discussing, Relvar in asthma in July 2014. The Panel noted the data provided by GlaxoSmithKline showed that Fostair was not commonly prescribed for COPD around that time. There was a difference in indications. Fostair was only licensed for severe COPD. Although there appeared to be a difference between Fostair and Relvar with regard to whether pneumonia in COPD was common or uncommon as an undesirable effect in the SPCs, the data submitted by GlaxoSmithKline appeared to support similarities between the products. On the evidence before it the Panel did not consider the comparison was misleading and at the time the email was sent GlaxoSmithKline had not 'cherry picked' the information as alleged. No breaches of the Code were ruled.**

**The Panel then considered the allegation about the GlaxoSmithKline website and the screen shot provided by the complainant who had highlighted a section of the website for Budget Holders where three options were provided: 'Making a formulary application in asthma', 'Making a formulary application in COPD' and 'Need a quick reference guide for a formulary application for Relvar Ellipta'. The screen shots provided by the complainant appeared to come from the section 'Need a quick reference guide for a formulary application for Relvar Ellipta'.**

**The Panel noted its comments and rulings above. Bearing in mind that detailed information was provided about pneumonia in asthma in the section 'Making a formulary application in asthma' (as well as pneumonia and COPD in the section 'Making a formulary application in COPD') and each section included links to the prescribing information and SPCs, the Panel considered that information on pneumonia as a side-effect in patients with asthma was available. The Panel did not consider that the section of the website for budget holders 'Need a quick reference guide for a formulary application for Revlar Ellipta' was misleading about the incidence of pneumonia in asthma nor did it fail to reflect the available evidence as alleged. No breaches of the Code were ruled.**

**The Panel did not consider that GlaxoSmithKline had failed to maintain high standards or had brought discredit on the pharmaceutical industry. Thus the Panel ruled no breach including of Clause 2.**

An anonymous, non contactable complainant who described him/herself as a prescriber complained about the promotion of Relvar Ellipta (fluticasone furoate/vilanterol inhalational powder) by GlaxoSmithKline UK Limited and in particular an email (ref UK/FFT/0332/14).

Relvar Ellipta 92/22mcg was indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) was appropriate. The summary of product characteristics (SPC) referred in this regard to patients not adequately controlled with inhaled corticosteroids and as needed inhaled short-acting $beta_2$-agonists. Relvar Ellipta 92/22mcg was also indicated for the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD) with a FEV1 <70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

Relvar Ellipta 184/22mcg was indicated similarly for asthma, it was not indicated for COPD.

The email was sent to subscribers of Nursing in Practice who GlaxoSmithKline submitted had agreed to receive promotional materials from pharmaceutical companies. There were differences between the email supplied by GlaxoSmithKline and the screen shots of the email provided by the complainant which appeared to be incomplete. The GlaxoSmithKline copy was headed RELVAR and had four distinct sections including: Scottish Medicines Consortium (SMC) issues guidance for Relvar in asthma and All Wales Medicines Strategy Group (AWSMG) issues guidance for Relvar in COPD. Both of these sections included the executive summary of the advice and a link to the website where full guidance could be accessed. The third section of the email discussed Relvar Ellipta and its use in asthma and COPD including the indications. The final section consisted of a list of references, the prescribing information and adverse event reporting requirements. The heading and introduction to the SMC section and part of the executive summary to the AWSMG section was missing from the copy supplied by the complainant.

The complainant highlighted a claim, within the Relvar Ellipta summary section, 'Relvar is generally well-tolerated in COPD. The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/LABAs' [inhaled corticosteroid and long-acting $ß_2$ adrenoreceptor agonists].

**COMPLAINT**

The complainant was concerned that GlaxoSmithKline was trying to hide important safety information having seen its advertising in a number of places including the internet, on stands at conferences, in emails and in letters.

The complainant stated that he/she was encouraged to contact the PMCPA after receiving an email regarding Relvar and reading a Drug and Therapeutics Bulletin (DTB) review. The complainant stated that reading the email led him/her to believe that pneumonia was a side-effect associated with COPD only as highlighted on the second page; there was no mention of pneumonia with regard to asthma. The complainant stated that he/she did not think too much about it at the time as pneumonia was associated with the use of ICS/LABA in COPD patients. There was not the same association with asthma so it seemed to be as expected. However, on reading the DTB review, the complainant was surprised to note that pneumonia had been reported in asthma patients on Relvar and GlaxoSmithKline had been required by the regulators to study this further.

The complainant looked at the GlaxoSmithKline website and noted that the information was similar to that received in the email. A number of screen shots were provided. The website only discussed pneumonia in relation to COPD with no mention of asthma.

The complainant then looked at the Relvar SPC and noted that pneumonia was mentioned with regard to both COPD and asthma. The complainant stated that hidden in the text was the important information that the incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma who took fluticasone furoate/vilanterol 184/22mcg was numerically higher compared with those who took fluticasone furoate/vilanterol 92/22mcg or placebo (see section 4.8). No risk factors were identified.

The complainant noted that the incidence of pneumonia was common in asthma patients taking the higher dose. The complainant alleged that for GlaxoSmithKline to discuss pneumonia only in relation to COPD in its advertisements, which was expected for that type of inhaler, while omitting that it was commonly experienced in asthma patients which was an unexpected side-effect, was totally unacceptable and a risk to patient safety. The complainant stated that as a prescriber that was the sort of information he/she wanted to know and that GlaxoSmithKline would want to hide.

The complainant further stated that he/she would like to address the fact that GlaxoSmithKline stated that the incidence of pneumonia in COPD patients was similar to that of other commonly used ICS/LABAs quoting the SPCs for Seretide and Symbicort. The complainant noted that it was true that both of these products had pneumonia commonly reported but GlaxoSmithKline had not included Fostair in the comparison which, although only recently licensed for COPD, was commonly used to treat the condition. Fostair information stated that pneumonia was uncommon and the complainant alleged that this was another example of GlaxoSmithKline cherry-picking the information it used. Important safety information was being hidden and not included in GlaxoSmithKline materials.

The complainant requested that the matter be taken up with GlaxoSmithKline as he/she alleged that it

was dishonest, potentially put patient safety at risk and hid information that prescribers needed to know. The complainant stated that if there were several other inhalers he/she could prescribe, why would he/she give the one that could cause pneumonia to his/her asthma patients. The complainant thought that GlaxoSmithKline should have to send a corrective notification to prescribers as a matter of urgency.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 7.2, 7.3, 7.4, 7.9, 7.10, 9.1 and 2 of the Code.

**RESPONSE**

GlaxoSmithKline explained that Relvar Ellipta was a new inhaled ICS/LABA combination product, which was licensed in the UK for asthma and COPD. It had been generally available since January 2014.

**Asthma indication**

> The regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate:
>
> - patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists.

**COPD indication**

> The symptomatic treatment of adults with COPD with a FEV1 <70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

Two doses were licensed in asthma, 92/22mcg and 184/22mcg; only the 92/22mcg dose was licensed in COPD. The 92/22mcg and 184/22mcg values represented the delivered doses (dose leaving the mouthpiece); this corresponded to pre-dispensed doses of 100/25mcg and 200/25mcg respectively.

**Asthma**

**Relvar and pneumonia in asthma**

GlaxoSmithKline submitted that although pneumonia was more common and seen to be a greater clinical challenge in COPD, it was also reported as a known adverse event associated with ICS/LABA use in asthma. This important point was highlighted clearly within the European Medicines Agency (EMA) Product Assessment Report (EPAR) for Relvar Ellipta (September 2013):

> 'In the asthma programme, the incidence of Community Acquired Pneumonia (CAP) for [fluticasone furoate] containing (ie [fluticasone fuorate and fluticasone fuorate/vilanterol]) groups was within the same range of incidences seen with other ICS.'

Overall, the incidence of pneumonia was low (≤1.1%) in all treatment groups with the 95% confidence intervals for both the incidence and the exposure rate overlapping across treatment groups, including placebo. The data was based on a review of 17 asthma studies from the Relvar clinical development programme, which included 7,199 patients and details from Ellipta EPAR 2013 and GlaxoSmithKline data on file were provided.

GlaxoSmithKline submitted that the data showed that the incidence of pneumonia ranged from 0.6% in the fluticasone 100mcg containing arms to 0.5-1.1% in the fluticasone 200mcg containing arms; this corresponded to event rates/1,000 treatment years of between 8.4 and 20.9 respectively. Furthermore, in absolute terms, this also represented a low number of individual patients; the highest incidence of 1.1% for Relvar 200/25 corresponded to 5 individual patients. Indeed, if pneumonia had only occurred in 4 patients the frequency would have been 0.8% ie uncommon. The incidence in the placebo arm was 0.2% with an event rate/1,000 treatment years of 9.6. GlaxoSmithKline noted that placebo was only included in studies of 6 months' duration compared with a maximum duration of 52–76 weeks for studies of Relvar 200/25mcg and 100/25mcg.

Overall, the incidence of serious pneumonia was low and similar across groups including placebo (0.1-0.3%; 2.8-5.2 events/1,000 treatment years). This was also the case for severe pneumonia (0.0-0.4%; 0-7.4 events/1,000 treatment years). Again absolute numbers of patients for both these parameters were very low (0-5 patients). Serious pneumonia events were those that required hospitalisation, whilst the definition of severe pneumonia was based on the investigator's adjudication on whether an episode was mild, moderate or severe.

Within the Relvar asthma clinical development programme there was one study which directly compared Relvar with a marketed ICS/LABA, Seretide (fluticasone propionate/salmeterol). Within this 24 week study, there were no events of pneumonia in the Relvar arm compared with 2 in the Seretide group including 1 serious pneumonia event. No severe pneumonia events were reported in either treatment group (Relvar Ellipta EPAR 2013).

GlaxoSmithKline stated that as there was only one direct head-to-head study vs a licensed ICS/LABA, of only 24 weeks' duration, it was considered appropriate during the regulatory review process to also submit indirect comparisons with pre-existing studies undertaken for Seretide, an established and commonly used ICS/LABA in the UK. This analysis showed that the rates of pneumonia seen were within the same range as that seen with other ICS/LABAs (Relvar Ellipta EPAR 2013). GlaxoSmithKline noted that the highest incidence seen in the Relvar 200/25mcg group (18.4 events/1,000 treatment years) was very similar to the highest incidence of 19.7 events/1,000 treatment years seen in the Seretide 250/50mcg bd group in the integration of the Seretide studies data from the EPAR was provided. The EMA reached the same conclusion as reported in the Relvar EPAR.

GlaxoSmithKline also provided data for budesonide (BUD) which was the steroid contained in Symbicort, another commonly used ICS/LABA in asthma.

GlaxoSmithKline submitted that here too the percentage of subjects who developed pneumonia was 0.8% and 1.0% for doses of 400mcg and 800mcg respectively, which equated to an event rate/1,000 treatment years of 21.8 and 33.9. However, these values needed to be considered in light of the relatively small number of patients who had events.

O'Byrne *et al* (2011) undertook a retrospective analysis which evaluated studies in asthmatics (n=48,489) which included the use of the inhaled steroids budesonide and fluticasone, as well as placebo. The occurrence of pneumonia in this analysis ranged from 0.5% (rate 10 events/1,000 patient years) and 1.2% (rate 19.3 events/1,000 patient years), with the higher value in the placebo arms. These values once again demonstrated that pneumonia was seen with asthmatic patients who were enrolled in clinical trials and that, as seen with Relvar, these rates were generally low.

Lastly, GlaxoSmithKline noted that prospective studies from the UK, Finland and North America had reported an incidence of community acquired pneumonia diagnosed in the general population of between 5 and 11 per thousand adult population, ie 0.5-1.1% (British Thoracic Society Guidelines for the management of community acquired pneumonia in adults: update 2009).

Therefore, from the above it could be seen that pneumonia was a potential side effect associated with the use of all Relvar doses in patients with asthma. Although classed correctly as a common adverse event, ie with an occurrence of ≥1.0 – <10%, the incidence of pneumonia was low (0.6%-1.1%) and most importantly the rates were similar to those seen with other established, licensed ICS/LABAs which were commonly used for asthma in the UK.

The low numbers of pneumonia events which occurred in the Relvar asthma development programme, coupled with the limitations inherent in indirect analyses meant that the regulators required GlaxoSmithKline to continue to gather ongoing information to further characterise the risk associated with Relvar (a combination of new chemical entities) in asthma compared with other licensed ICS/LABAs. This would be undertaken through continual, proactive pharmacovigilance activities as well as the assessment of pneumonia in the Salford Lung Study; a real world effectiveness study which compared the use of Relvar, in routine clinical practice, with existing therapy.

**COPD**

**Pneumonia in COPD**

GlaxoSmithKline submitted that the clinical picture and management considerations for pneumonia in COPD patients was different to that in asthma. In early COPD, the damage to the innate immune system promoted colonisation and an increase in risk of respiratory tract infections (Vestbo *et al*, 2006). COPD patients were at higher risk of developing community acquired pneumonia than those in the general population and those with asthma. A recent, UK, population-based, retrospective, database study of 40,414 COPD patients estimated the incidence of community acquired pneumonia to be 22.4 episodes/1,000 person years (Mullerova *et al*, 2012). Higher background rates had been reported in the placebo/non-ICS arms of clinical trial populations (52 events/1,000 treatment years; TORCH study, Crim *et al*, 2009). COPD patients with pneumonia had also been shown to have worse clinical outcomes compared with similarly aged pneumonia patients without COPD in terms of pneumonia severity, intensive care admissions, and mortality (Restrepo *et al*, 2006).

**Increased pneumonia risk with inhaled corticosteroids – class effect**

GlaxoSmithKline submitted that there was strong evidence from several independent meta-analyses that the risk of pneumonia in COPD patients was increased with the use of inhaled corticosteroids (ICS) when compared with non-ICS control arms. This was a well established class effect (Kew *et al*, 2014; Symbicort/Seretide/Relvar SPCs). Evidence that the risk of pneumonia in COPD was comparable across all ICS/LABAs, including Relvar, was published in an independent Cochrane meta-analysis (Kew *et al*, 2014). This showed no significant difference in the risk of serious pneumonia leading to hospitalisation for fluticasone furoate, fluticasone propionate or budesonide containing treatments compared with no-ICS controls. A difference in non-serious pneumonias was observed as a consequence of non-standardised pneumonia definitions in the different studies included in the meta-analysis, leading to substantial heterogeneity in the treatment effects, and reduced confidence in the findings.

Additionally, following the review of the available evidence, the 2010 National Institute of Health and Care Excellence (NICE) guideline on COPD concluded that:

> 'meta-analysis showed a statistically-significantly greater incidence of pneumonia in the LABA+ICS arm compared with the LABA arm (where the studies were of greater than six months' duration). The Guidance Development Group (GDG) noted that, although there was a difference, the absolute risk of pneumonia was low. The GDG also considered whether this was a class effect or related to a specific steroid molecule, but the published evidence available at the time of guideline development did not allow them to reach a conclusion on this point.'

**Relvar and pneumonia in COPD**

GlaxoSmithKline stated that an extremely robust approach to the monitoring and reporting of pneumonia was adopted in the Relvar clinical development programme to avoid any potential under reporting of pneumonias: pneumonia was pre-defined as an adverse event of special interest and investigators were provided with a list of specific criteria which could indicate a diagnosis of pneumonia, to standardise the diagnosis. Finally, in the 52 week exacerbation studies, which included patients at higher risk of pneumonia,

chest radiographs were performed at baseline and within 48 hours of any suspected pneumonia or exacerbation.

In the pooled analysis of these 2 one year studies, pneumonia was noted in 6.3% of patients who received Relvar 92/22mcg, compared with 3.3% of patients receiving only vilanterol 22mcg, ie LABA alone (Dransfield *et al*, 2013). The number of pneumonia events/1,000 patient years was 85.7 for the Relvar 92/22mcg arm and 42.3 in the vilanterol 22mcg arm. For severe pneumonia the corresponding number of events/1,000 patient years were 35.5 and 7.6 for Relvar 92/22mcg and vilanterol 22mcg respectively, while for serious pneumonia the corresponding events/1,000 patient years were 42.9 with Relvar 92/22mcg and 12.1 with vilanterol 22mcg (Relvar Ellipta SPC, 2013).

GlaxoSmithKline stated that the rate of pneumonia observed with Relvar 92/22mcg was consistent with that observed for the other ICS/LABA preparations licensed in COPD. The absolute rates of pneumonia would vary from study to study due to differences in study design, baseline patient characteristics and definitions of pneumonia, however, what was expected was that there was a difference (generally 2 fold) between the rates seen in the ICS containing arms vs those seen in the non ICS containing arm. From the TORCH study the estimated 3 year probability of having pneumonia was 19.6% for patients on Seretide 500/50mcg (n=1,546) compared with a rate of 12.3% observed for placebo (n=1,554) (Calverley *et al*, 2007). The Symbicort SPC (2013) stated that since Symbicort contained budesonide and formoterol, the same pattern of undesirable effects as reported for these substances might occur. With respect to pneumonia, the Symbicort SPC stated:

> 'In a 3-year clinical trial with budesonide in COPD, skin bruises and pneumonia occurred at a frequency of 10% and 6%, respectively, compared with 4% and 3% in the placebo group ($p<0.001$ and $p<0.01$, respectively).'

**Fostair and pneumonia in COPD patients**

GlaxoSmithKline stated that the data reviewed for the 2014 Kew Cochrane review the NICE 2010 COPD guidance did not include studies for Fostair, as this only received a COPD licence in 2014. Fostair (beclometasone/formoterol) contained a different steroid component, beclometasone, to that within Seretide, Symbicort or Relvar. However, as highlighted above the evidence indicated that the increased incidence of pneumonia associated with ICS use was a class effect with no difference seen between the different steroid molecules.

The Fostair COPD clinical development programme included two 48 week studies. In the FORWARD study (Wedzicha *et al*, 2014), pneumonia occurred in 3.8% in the Fostair group vs 1.8% in the formoterol (LABA alone) group. The authors of the study concluded:

> 'The [Fostair] treatment arm was also associated with a higher incidence of pneumonia. This is in line with recent studies showing a 2-3 fold excess of pneumonia in the ICS/LABA treatment arms of studies compared to the corresponding monotherapy.'

Within the other study (Calverley 2010), pneumonia was reported in 2.1% of Fostair patients, 2.9% of Symbicort patients and 0.4% in the formoterol group. The authors concluded:

> 'The rate of reported pneumonia was similar to that reported in placebo controlled trials using budesonide.'

Therefore, as could be seen from the above, GlaxoSmithKline submitted that the association of pneumonia with ICS in COPD was regarded as a class effect and therefore similar risks of pneumonia could be expected with Relvar, Seretide, Symbicort and Fostair.

**Clinical importance of pneumonia in COPD and asthma**

GlaxoSmithKline noted that all the pneumonia rates in COPD discussed above were significantly higher than the rates seen in asthma patients, including, importantly, rates of serious and severe events. As discussed above this was expected based on the different clinical and pathophysiological profiles of the diseases involved and the differing prognoses for pneumonia in the two conditions. That pneumonia was a more important clinical condition in COPD compared with asthma was highlighted by UK and international guidelines. In NICE and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD guidelines, pneumonia was discussed as an important risk for COPD patients, with pneumococcal vaccination being recommended for all patients. BTS/Scottish Intercollegiate Guidelines Network (SIGN) and Global Initiative for Asthma (GINA) asthma guidelines did not specifically discuss pneumonia.

**Provision of safety information within promotional material**

GlaxoSmithKline referred to Clauses 7.2, 7.3, 7.4, 7.9 and 7.10 and the Medicines and Healthcare Products Regulatory Agency (MHRA) Blue Guide, 2012. This stated that:

> 'Claims that a medicine is generally well tolerated, including claims relating to the overall incidence of side effects versus placebo in clinical trials, may be acceptable if supported by evidence, provided a misleading impression is not given.'
> 'Care should be taken to ensure that prescribers are not misled by promotional claims in advertising which suggests that a particular product is safer than an alternative medicine unless this is supported by evidence.'

GlaxoSmithKline submitted that the amount of safety information contained in a promotional item (in addition to the prescribing information) varied depending on the item in question. A one page journal advertisement or email would contain less information than a twenty page detail aid. The

amount was also in part determined by how much efficacy information was included, such that any efficacy claims could be appropriately balanced with consideration of the safety profile. Also, certain adverse events which were of particular importance for clinicians and patients, based on factors such as their frequency rate and/or the potential clinical consequences associated with them, should be highlighted in all materials where efficacy data was shared. These factors were taken into consideration when deciding what safety information to include in Relvar promotional materials.

**Response to allegations**

**1 Pneumonia is not an adverse effect associated with ICS/LABAs in asthma; it is only seen in COPD. Relvar Ellipta has a unique safety signal amongst ICS/LABAs in asthma, as pneumonia is a common adverse event in patients taking the higher dose**

The complainant stated that there was not an association between ICS/LABA usage in asthma and pneumonia and thus for pneumonia to be an adverse effect associated with the use of Relvar in asthma was unexpected and a unique safety signal. GlaxoSmithKline stated that this assertion was not correct. As discussed above, pneumonia was a known side effect associated with ICS/LABA usage in asthma. The rates of pneumonia seen in asthma patients in the Relvar clinical trial programme were low (0.6-1.1%) and importantly (as concluded by the EMA) consistent with those seen with other established and commonly used ICS/LABAs in asthma, such as Seretide.

**2 Promotional email with no information on pneumonia in asthma (UK/FFT/0332/14)**

GlaxoSmithKline noted that the first item highlighted by the complainant was a promotional email sent to subscribers of Nursing in Practice who had agreed to receive promotional material from pharmaceutical companies. The first part of the email highlighted that the Scottish Medicines Consortium (SMC) in asthma and the All Wales Medicines Strategy Group (AWMSG) in COPD had issued advice for Relvar Ellipta. The executive summary from the SMC and AWMSG guidance was quoted in full in accordance with their policies. The second half of the email contained the following promotional claims for Relvar as well as the indications in asthma and COPD; GlaxoSmithKline noted that no data was presented.

> 'The first ICS/LABA combination to deliver continuous 24 hour efficacy in a practical once daily dose.'
>
> 'Delivered in a straightforward device.'
>
> 'That offers value to the NHS.'

A limited amount of information was provided here, however in order to present fair balance, a succinct summary of the relevant safety information was also provided. The safety profile for Relvar in asthma, as concluded in the EPAR, was consistent with other ICS/LABAs with regard to the nature, frequency and severity of the adverse effects seen, including, *inter alia*, pneumonia; as a result it could be considered to be generally well tolerated. The use of such a statement was in line with the advice within the MHRA Blue Guide. ICS/LABAs were commonly used asthma treatments and were a class of medicine with which prescribers in primary and secondary care had several years' experience. As highlighted above, pneumonia, due to frequency and clinical characteristics, was not as major a concern in asthma as it was in COPD.

Of all the adverse events associated with ICS/LABAs in COPD it was clear that there was increased clinical importance associated with the potential adverse event of pneumonia. It was important that health professionals should be told that the risk of pneumonia associated with Relvar was similar in magnitude to that associated with other ICS/LABAs. Therefore, an additional statement about pneumonia and COPD was included.

In line with Clause 4.1, prescribing information formed part of this email and this listed all the adverse events, including pneumonia, which might occur in patients with asthma and COPD.

Lastly, the MHRA pre-vetted Relvar promotional material before launch, in line with its commitment to vet advertising for all new active substances. As part of this process, material with a similar balance of efficacy and safety messages was reviewed by the MHRA and no objections regarding these safety statements were raised.

**3 Prescribing information on promotional email UK/FFT/0332/14**

GlaxoSmithKline noted the complainant's concern about the information contained in the prescribing information. He/she stated that GlaxoSmithKline had omitted the fact that pneumonia was an adverse effect in asthma identifying the text contained within the 'Precautions' section. Clause 4.2 of the Code included:

> 'A succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics, together with a statement that prescribers should consult the summary of product characteristics in relation to other adverse reactions.'

The Relvar prescribing information (UK/RESP/0209a/13), which was on all promotional material for asthma, contained pneumonia as a common side effect, thus informing prescribers that, as seen with other ICS/LABAs, there was a risk of pneumonia associated with the use of Relvar in asthma. If this risk had been associated with COPD only it would not appear in prescribing information

for asthma as it would not be relevant to the indication in the advertisement. The Relvar SPC stated the following:

> 'With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently commonly observed in patients with COPD.'

This was deliberately omitted from the prescribing information, as in isolation clinicians might misinterpret this as suggesting that pneumonia only occurred in COPD.

Clause 4.2 required serious adverse events and precautions and contraindications to be succinctly summarised. The precautions section of the Relvar SPC contained a section entitled 'Pneumonia in patients with COPD'. Due to the serious nature of pneumonia in COPD, a precaution about COPD and pneumonia and identified risk factors was included in the prescribing information. The last paragraph of the SPC under this specific heading stated:

> 'The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 184/22 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 92/22 micrograms or placebo (see section 4.8). No risk factors were identified.'

The key information here was that pneumonia was common in asthma patients, however this information was already included in the adverse event listings within the prescribing information and thus further information was not provided in the precautions section. To include the wording 'The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 184/22mcg was numerically higher compared with those receiving fluticasone furoate/vilanterol 92/22mcg or placebo' within the prescribing information would not be appropriate as it would require qualification with the actual numbers involved so that clinicians would know that the incidence rates discussed were 0.6 vs 1.1%. The provision of such detail within the prescribing information would not be appropriate for a succinct summary of adverse events. Using the same rationale specific rates of pneumonia in COPD were also not included in the prescribing information. Finally, as required by the Code, the prescribing information advised prescribers to consult the SPC before prescribing, as the detail contained within the SPC could never be captured by the prescribing information alone.

The prescribing information highlighted above had also undergone MHRA pre-vetting; no objections were raised by the MHRA.

**4 Promotional material on GSK website [UK/FFT/0019e/13(2)]**

GlaxoSmithKline noted that the complainant also highlighted information for Relvar available on health.gsk. This was a GlaxoSmithKline website and the sections discussed were clearly identified as being intended for health professionals. Within the Relvar pages of the website there was a number of sections, including one dedicated to safety. The complainant highlighted information contained within the section entitled 'Budget Holders'. Within this section there were three options the viewer could select including 'Making a formulary application in asthma – Use the Relvar Ellipta asthma pack to support your application'. This section provided a detailed overview of the efficacy and safety data in asthma including an adverse events table which listed pneumonia as the first common adverse event within the organ class of 'Infection and infestations'. Below this table a section entitled 'Pneumonia' stated the following:

> 'In clinical trials of asthma patients the incidence of pneumonia seen with Relvar 92/22mcg was similar to that of placebo. There was a higher incidence of pneumonia with the 184/22mcg compared to the 92/22mcg strength. Few of the pneumonia events lead to hospitalisation with either strength. The number of pneumonia events per 1,000 patient years was 18.4 for fluticasone furoate/vilanterol (Relvar) 184/22mcg vs 9.6 for fluticasone furoate/vilanterol (Relvar) 92/22mcg and 8.0 in the placebo group (<1% overall).'

GlaxoSmithKline submitted that the existence of this information on its website which could be accessed by any UK health professional clearly demonstrated that the company had not hidden information which stated that pneumonia could occur in asthma patients treated with Relvar.

GlaxoSmithKline noted that the complainant, however, had not highlighted this page of the website, but had instead chosen a page within the section for budget holders' 'Need a quick reference guide for a formulary application for Relvar Ellipta?'. Within this page a less detailed, top-line summary was provided of the indications and the key efficacy conclusions. As a result, less safety information was provided with it being stated that Relvar was generally well tolerated in asthma and COPD. Based on the same rationale highlighted above (clinical importance of pneumonia in COPD), further detail was, however, provided for pneumonia in COPD including incidence rates. A link to the prescribing information and SPC was also provided on this page. GlaxoSmithKline noted that this page sat within the overall Relvar website which contained easily accessible sections dedicated to more detailed safety.

**5 Use of the statement 'The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the summary of product characteristics of other commonly used ICS/LABAs'**

GlaxoSmithKline submitted that UK prescription data (Cegedim Longitudinal Patient Database; July 2013 – June 2014) showed that the most commonly prescribed ICS/LABAs in the UK for COPD were Seretide and Symbicort. Details were provided.

In addition, both of these established medicines had been available for use in the UK for COPD for a number of years and as such clinicians would be familiar with prescribing them; Fostair received a marketing authorization in COPD in 2014. Therefore, it was important that health professionals were aware that the risk of pneumonia with a new medicine such as Relvar was similar to that which they knew and were used to dealing with for Seretide and Symbicort.

As discussed above, Fostair was also associated with pneumonia and, as would be expected for a class effect, the risk of pneumonia was no different to Relvar, Seretide or Symbicort.

**Conclusion**

GlaxoSmithKline concluded that:

- Relvar did not have a unique pneumonia safety signal amongst ICS/LABAs used in asthma. The incidence of pneumonia in the Relvar asthma clinical trial programme was low and consistent with other licensed ICS/LABAs.

- The prescribing information for all Relvar asthma materials stated that pneumonia was a common adverse event. Additionally, all Relvar asthma material which contained a significant amount of efficacy data had included in the safety section, as a minimum, a table which highlighted that pneumonia was a common adverse event.

- The increased risk of pneumonia seen in COPD patients treated with ICS/LABAs was a class effect. A similar risk was reported in the clinical trials of Relvar, Seretide, Symbicort and Fostair.

GlaxoSmithKline strongly believed that its Relvar asthma and COPD promotional materials were accurate, balanced, fair, objective and that a clear overview of the safety information had been provided and that this was not misleading, and could be substantiated by data and clinical experience.

The discussion of pneumonia risk in COPD amongst ICS/LABAs was an appropriate comparison of an important, relevant and representative feature. A balanced, objective and up-to-date evaluation of all the evidence had been undertaken and reflected in a manner which could be substantiated.

As a result, Relvar promotional materials encouraged the rational use of the medicine in patients with asthma and COPD.

GlaxoSmithKline therefore refuted any breach of Clauses 7.2, 7.3, 7.4, 7.9 and 7.10. In the absence of these breaches, the company also denied a breach of Clause 9.1 and Clause 2, as it had maintained high standards and had not prejudiced patient safety.

**PANEL RULING**

The Panel noted the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure such complaints were accepted and like all complaints, judged on the evidence provided by both parties. Complainants had the burden of proving their complaint on the balance of probabilities.

The Panel noted the complainant had received a promotional email for Relvar and was concerned GlaxoSmithKline was 'trying to hide important safety information, having seen their advertising in a number of places (internet, stand at conference, e-mail, letter)'.

The Panel noted that the sentence in the DTB highlighted by the complainant was within the section headed 'Unwanted effects' and stated 'Although pneumonia is more common in patients with chronic obstructive pulmonary disease (COPD) it has been reported in patients receiving fluticasone/vilanterol for asthma. The company is required to conduct a further study into the risk of pneumonia as an obligatory post-authorisation measure'.

The Panel noted the complainant's concern that GlaxoSmithKline was trying to hide important safety information on pneumonia as a side effect associated with using Relvar to treat asthma. The email provided by the complainant specifically highlighted pneumonia as a side effect associated with COPD but not asthma. GlaxoSmithKline stated that the clinical picture and management considerations for pneumonia in COPD patients was different to that in asthma. COPD patients were at higher risk of developing CAP than those in the general population and those with asthma. COPD patients with pneumonia had also been shown to have worse clinical outcomes compared with similarly aged pneumonia patients without COPD in terms of pneumonia severity, intensive care admissions, and mortality (Restrepo *et al*, 2006). GlaxoSmithKline further explained that the rates of pneumonia seen in COPD were significantly higher than the rates seen in asthma patients, including, importantly, rates of serious and severe events. This was expected based on the different disease profiles and the differing prognoses for pneumonia in the two conditions. That pneumonia was a more important clinical condition in COPD compared with asthma was highlighted by UK and international guidelines. The Panel also noted the Cochrane Review report on inhaled steroids and risk of pneumonia in COPD, Kew *et al* 2014, concluded that budesonide and fluticasone delivered as monotherapy or in combination with a LABA were associated with increased risk of a serious adverse pneumonia event but neither significantly effected mortality compared with controls. The safety concerns highlighted in the review should be balanced with recent cohort data and established evidence of efficacy regarding exacerbations and quality of life.

The Panel noted the submission from GlaxoSmithKline that although pneumonia was more common and seen to be a greater clinical challenge in COPD, it was also reported as a known adverse event associated with ICS/LABA use in asthma. GlaxoSmithKline submitted that overall, the incidence of pneumonia in asthma was low (≤1.1%) in all treatment groups. The Panel also noted GlaxoSmithKline's submission about the absolute

number of patients. The highest incidence of 1.1% for Revlar 200/25 corresponded to five patients. Nonetheless, the Panel noted GlaxoSmithKline's submission that pneumonia was correctly described as a common adverse event in the SPC. The Panel noted the concerns raised about pneumonia in the Discussion of Clinical Safety section of the EMA Revlar assessment report. The Panel noted that the regulators required GlaxoSmithKline to continue to gather information to further characterise the risk associated with Relvar (a combination of new chemical entities) in both asthma and COPD compared with other licensed ICS/LABAs.

The Panel examined the materials provided by both the complainant and GlaxoSmithKline. The email heading introduction to SMC guidance, part of the AWMSG advice section, and the reference to the Relvar website was missing from the material provided by the complainant. The email started with SMC guidance on the use of Relvar for asthma. The indication was given and the outcome of a study comparing Relvar with another ICS/LABA. The next section reported the AWMSG decision regarding use in COPD. The third section gave information about Relvar including, *inter alia*, it was generally well-tolerated in asthma. A similar statement about COPD was followed by details of the risk of pneumonia in COPD. The prescribing information listed pneumonia as a common side effect. The precautions section of the prescribing information gave details of an increased incidence of pneumonia in COPD patients receiving Relvar.

The Panel did not consider that mentioning pneumonia in relation to COPD patients in the email meant that it did not have to be considered in asthma patients. The Panel noted GlaxoSmithKline's comments about the importance of pneumonia in COPD compared to asthma. On balance, the Panel considered that it was therefore not unreasonable to mention pneumonia in relation to COPD alone. The Panel considered that the failure to discuss pneumonia in asthma did not mean that the email misled either directly or by implication. It was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The information and claims about adverse reactions reflected current evidence and were capable of substantiation. The Panel did not consider GlaxoSmithKline had hidden pneumonia as a side-effect associated with Relvar in patients with asthma as alleged. No breach of Clauses 7.2, 7.4 and 7.9 was ruled.

The Panel noted the complainant was concerned that GlaxoSmithKline had not compared Relvar to Fostair, which was recently licensed for COPD. The complainant believed Fostair was commonly used to treat COPD and the Fostair information stated that pneumonia was uncommon. The Panel noted the claim in the email stated, 'Relvar is generally well tolerated in COPD. The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/LABAs'. The claim was referenced to the Relvar, Seretide and Symbicort Turbohaler SPCs and to Drainsfield *et al* 2013 which looked at Relvar in COPD. The data submitted by GlaxoSmithKline stated that the most commonly prescribed ICS/LABAs in the UK for COPD were Seretide and Symbicort (June 2013 – June 2014) and that clinicians would be familiar with prescribing them. GlaxoSmithKline stated that Fostair received a marketing authorization in COPD in 2014 and contained a different steroid component, beclometasone, to Seretide, Symbicort or Relvar. The Panel noted the data submitted by GlaxoSmithKline. The FORWARD study (Wedzicha *et al*, 2014), showed that pneumonia occurred in 3.8% of Fostair patients vs 1.8% in the formoterol (LABA alone) group and concluded 'The [Fostair] treatment arm was also associated with a higher incidence of pneumonia. This is in line with recent studies showing a 2-3 fold excess of pneumonia in the ICS/LABA treatment arms of studies compared to the corresponding monotherapy.' Calverley 2010 reported pneumonia in 2.1% of Fostair patients, 2.9% of Symbicort patients and 0.4% in the formoterol group and concluded: 'The rate of reported pneumonia was similar to that reported in placebo controlled trials using budesonide.' GlaxoSmithKline submitted that the association of pneumonia with ICS in COPD was regarded as a class effect and therefore similar risks of pneumonia could be expected with Relvar, Seretide, Symbicort and Fostair.

The Panel noted the complainant was uncontactable and had not provided any information to support his/her view that Fostair was commonly used to treat COPD. The Panel noted from the Fostair 100/6 SPC that Fostair was indicated in COPD for symptomatic treatment of patients with severe COPD (FEVI <50% predicted normal) and a history of repeated exacerbations. Pneumonia was listed as an uncommon (≥1/1000 and <1/100) undesirable effect in the SPC which was said to be derived from clinical trials in asthmatic and COPD patients. The SPC included an asterisk next to pneumonia and the explanation 'one related non serious case of pneumonia was reported by one patient treated with Fostair in a pivotal clinical trial in COPD patients'.

The Panel noted the complaint was received in August. The mail referred to the SMC decision in April 2014 and that AWMSG would be discussing, Relvar in asthma in July 2014. The Panel noted the data provided by GlaxoSmithKline showed that Fostair was not commonly prescribed for COPD around that time. There was a difference in indications. Fostair was only licensed for severe COPD. Although there appeared to be a difference between Fostair and Relvar with regard to whether pneumonia in COPD was common or uncommon as an undesirable effect in the SPCs, the data submitted by GlaxoSmithKline appeared to support similarities between the products. On the evidence before it the Panel did not consider the comparison was misleading and at the time the email was sent GlaxoSmithKline had not 'cherry picked' the information as alleged. No breach of Clauses 7.2, 7.3 and 7.10 was ruled. The claim was capable of substantiation. No breach of Clause 7.4 was ruled.

The Panel then considered the allegation about the GlaxoSmithKline website and the screen shot provided by the complainant.

The Panel noted GlaxoSmithKline's submission that the complainant had highlighted information in the section of the website for Budget Holders where three options were provided: 'Making a formulary application in asthma', 'Making a formulary application in COPD' and 'Need a quick reference guide for a formulary application for Relvar Ellipta'. The screen shots provided by the complainant appeared to come from the section 'Need a quick reference guide for a formulary application for Relvar Ellipta'.

The complainant highlighted two parts of a section headed 'safety profile'. These being:

> 'in common with other ICS – containing medicines there is an increased risk of pneumonia in COPD patients treated with Relvar 92/22mcg. The risk of pneumonia with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/ LABAS licenced for the treatment of COPD.
>
> Pneumonia occurred in 6% of patients receiving Relvar 92/22mcg with 3% of patients receiving Vilanterol alone. The number of pneumonia events per 1000 patient years was 85.7 with OD Relvar, 92/22mcg and 42.3 with OD Vilanterol 22mcg.'

The Panel also noted that the section of the website provided by GlaxoSmithKline was headed 'Formulary Application Guide' and included links to the prescribing information as well as the SPCs.

GlaxoSmithKline submitted that a less detailed, top-line summary was provided of the indications and the key efficacy conclusions. As a result, less safety information was provided with it being stated that Relvar was generally well tolerated in asthma and COPD. For the reasons given above, further detail was, however, provided for pneumonia in COPD including incidence rates.

The Panel noted the section 'Making a formulary application in asthma' contained a detailed overview of the efficacy and safety data in asthma, within this section was an adverse events table which listed pneumonia as the first common adverse event within the 'System organ class' of 'Infection and infestations'. Below this table a section entitled 'Pneumonia' stated:

> 'In clinical trials of asthma patients the incidence of pneumonia seen with Relvar 92/22mcg was similar to that of placebo. There was a higher incidence of pneumonia with the 184/22mcg compared to the 92/22mcg strength. Few of the pneumonia events lead to hospitalisation with either strength. The number of pneumonia events per 1,000 patient years was 18.4 for fluticasone furoate/vilanterol (Relvar) 184/22mcg vs 9.6 for fluticasone furoate/vilanterol (Relvar) 92/22mcg and 8.0 in the placebo group (<1% overall).'

The Panel noted its comments and rulings above. Bearing in mind that detailed information was provided about pneumonia in asthma in the section 'Making a formulary application in asthma' (as well as pneumonia and COPD in the section 'Making a formulary application in COPD') and each section included links to the prescribing information and SPCs, the Panel considered that information on pneumonia as a side-effect in patients with asthma was available. The Panel did not consider that the section of the website for budget holders 'Need a quick reference guide for a formulary application for Revlar Ellipta' was misleading about the incidence of pneumonia in asthma nor did it fail to reflect the available evidence as alleged. No breach of Clauses 7.2, 7.4 and 7.9 was ruled.

The Panel did not consider that GlaxoSmithKline had failed to maintain high standards or had brought discredit on the pharmaceutical industry. Thus the Panel ruled no breaches of Clauses 9.1 and 2.

**Complaint received** **18 August 2014**

**Case completed** **13 November 2014**

**CASE AUTH/2731/9/14**

# PULMONOLOGIST v BOEHRINGER INGELHEIM

## Scientific symposium

**A pulmonologist working in Germany complained about a scientific symposium organised by Boehringer Ingelheim at the European Respiratory Society (ERS) Congress held in Munich.**

**The symposium was part of the industry sponsored sessions. It was advertised in the official meeting programme as 'Slowing disease progression in IPF [idiopathic pulmonary fibrosis]: New evidence From Phase III clinical trials'.**

**The complainant stated that his main complaint was that on the main stage, the speakers were allowed to drink beer – with one even dressed in lederhosen. For a serious, fatal condition, this was not appropriate. As two of the speakers were from the UK he assumed the UK rules should apply to them.**

**The detailed response from Boehringer Ingelheim is given below.**

**The Panel noted that the Code applied to the promotion to UK health professionals and administrative staff at international meetings held outside the UK. Further, that the Code also applied to some non-promotional activities including the use of consultants in Clause 20. The Panel noted that two of the four speakers at the symposium were UK health professionals and that Boehringer Ingelheim had sponsored UK health professionals to attend the ERS Congress. The Panel therefore considered that at the very least certain aspects of the arrangements had to comply with the Code. It was an established principle under the Code that the UK company was responsible for acts and omissions of its overseas affiliates that came within the scope of the Code.**

**The Panel considered that the involvement of the UK speakers meant that Boehringer Ingelheim was responsible under the Code for the arrangements for the UK speakers including their travel and subsistence and the impression created by these.**

**The Panel noted that one of the speakers appeared to be drinking beer on stage during the satellite symposium. The Panel considered that the overall impression given was unacceptable. The subsistence in this regard was inappropriate. The Panel considered that high standards had not been maintained. A breach was ruled.**

A pulmonologist working in Germany complained about a scientific symposium organised by Boehringer Ingelheim at the European Respiratory Society (ERS) Congress held in Munich.

The symposium was held on Monday, 8 September as part of the industry sponsored sessions. It was advertised within the official programme for the meeting. The title of the session was 'Slowing disease progression in IPF [idiopathic pulmonary fibrosis]: New evidence From Phase III clinical trials'.

**COMPLAINT**

The complainant stated that at the European Respiratory Society meeting in Munich he attended a symposium arranged by Boehringer Ingelheim on IPF and was hoping to learn about recent clinical trials in IPF.

The complainant stated that his main complaint was that on the main stage, the speakers were allowed to drink beer – with one even dressed in lederhosen. For a serious, fatal condition, this was not appropriate. As two of the speakers were from the UK he assumed the UK rules should apply to them. A photograph of two of the speakers on the stage with a beer was provided.

When writing to Boehringer Ingelheim Limited the Authority asked it to respond in relation to Clauses 7.2, 9.1 and 12.1 of the Code.

**RESPONSE**

Boehringer Ingelheim submitted that whilst it was concerned that the individual making the complaint was clearly disappointed by the event, the Code did not apply in this case:

- The event was organised and run by Boehringer Ingelheim GmbH Co KG. This included the selection, invitation, engagement and briefing of the speakers, the content of the event, and the publicising of the event within the confines of the congress guidelines.

- Boehringer Ingelheim UK stated that its involvement was restricted to the approval of the level of honoraria, subsistence and hospitality offered to the speakers from the UK, via a clearing house system, in advance of the event in accordance with the requirements of Clause 19.1.

- No member of Boehringer Ingelheim UK invited any health professionals to this symposium either by email, flyer, letter or any other means. Any delegate who chose to attend this symposium made that choice themselves.

- This symposium was not specifically aimed at a UK audience. The event took place as part of an internationally renowned congress, and the speakers were an international representation of global expertise in the area of IPF. They came from the UK, the US and Canada.

Boehringer Ingelheim identified the health professional with the beer in the photograph.

Boehringer Ingelheim submitted there was no breach of any clause of the Code since the symposium fell outside the scope of the Code. Previous Panel rulings in Cases AUTH/2512/6/12, AUTH/2419/7/11 and AUTH/2406/5/11 all provided relevant precedent.

In response to a request for further information, Boehringer Ingelheim explained two UK doctors were engaged by Boehringer Ingelheim GmbH Co KG to chair and speak.

Boehringer Ingelheim sponsored 63 UK respiratory health professionals to attend the ERS congress; these were a mixture of primary and secondary care physicians and nurses. Ten were specialists in IPF. No individual was specifically sponsored to attend the symposium. Boehringer Ingelheim reiterated the point that it did not specifically invite any congress delegates to attend the symposium and confirmed that none of their colleagues at Boehringer Ingelheim GmbH Co KG, or any other affiliate, specifically invited any UK delegates to attend the symposium by letter, email, flyer, verbal invitation or inclusion in any company-produced agenda or itinerary. Over 21,000 delegates attended the ERS congress in Munich in 2014, of which 1800 were registered from the UK, representing 8.3% of the total attendees. Over 600 delegates attended the symposium in question however no specific information was collected to identify the country of origin of the attendees so they were not able to state how many were from the UK; it was likely to be a similar proportion as attended the overall congress.

**PANEL RULING**

The Panel noted Boehringer Ingelheim, contrary to the Case Preparation Manager's and Panel's requests, did not respond to the allegations as in its view the complaint was outside the scope of the Code as all aspects of the satellite symposium in question were organised by its parent company in Germany, Boehringer Ingelheim GmBH.

The Panel did not accept Boehringer Ingelheim's submission about the symposium and the scope of the Code. The Panel noted the supplementary information to Clause 1.1, Scope of the Code, stated, *inter alia*, that the Code applied to the promotion to UK health professionals and administrative staff at international meetings held outside the UK. Further, that the Code also applied to some non-promotional activities including the use of consultants in Clause 20. The Panel noted that two of the four speakers at the symposium were UK health professionals and that Boehringer Ingelheim had sponsored 63 UK health professionals to attend the ERS Congress. The Panel therefore considered that at the very least certain aspects of the arrangements had to comply with the Code. It was an established principle under the Code that the UK company was responsible for acts and omissions of its overseas affiliates that came within the scope of the Code. If it were otherwise UK companies would be able to rely on such acts and omissions as a means of circumventing the Code.

The Panel considered that the involvement of UK speakers at the meeting in question meant that Boehringer Ingelheim was responsible under the Code for the arrangements for the UK speakers including their travel and subsistence and the impression created by these.

The Panel noted that one of the speakers appeared to be drinking beer on stage during the satellite symposium. The photograph which had been provided showed three health professionals sitting in a row on stage, above their heads the edge of the screen showing part of a slide was visible. A table between two of the health professionals had two small bottles of water, beside one of these was a large pint glass which appeared to contain some sort of beer. The glass was not full to the top and was close to the UK speaker. Only part of the table was visible. It was unclear from the photograph whether the third health professional had been provided with any subsistence. The supplementary information to Clause 19.1 included the need to keep in mind the impression created by the arrangements for any meeting and Clause 9.1 required that high standards must be maintained at all times. The Panel considered that the overall impression given was unacceptable. The subsistence in this regard was inappropriate. The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

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| **Complaint received** | **16 September 2014** |
| **Case completed** | **19 January 2015** |

# HEAD OF PRESCRIBING SUPPORT UNIT v BOEHRINGER INGELHEIM

## Promotion of Striverdi Respimat

**A prescribing support pharmacist complained that a leavepiece for Striverdi (olodaterol) Respimat issued by Boehringer Ingelheim did not accurately reflect the medicines likely effect in chronic obstructive pulmonary disease (COPD). The front cover showed the photograph of an older woman, smiling and at ease, cycling apparently slightly uphill past a village church. The bicycle basket held a newspaper and a bunch of flowers. The complainant found it hard to believe that the use of Striverdi Respimat would enable COPD patients to cycle away.**

**The detailed response from Boehringer Ingelheim is given below.**

**The Panel noted Boehringer Ingelheim's submission regarding the inclusion criteria for the two studies cited in the leavepiece and that the results meant that on average, patients treated with Striverdi could cycle at 75% of their maximal work rate for 7 minutes in one study and 6.6 minutes in the other.**

**The Panel did not accept Boehringer Ingelheim's submission that it was implied that the woman was cycling for no more than 6 or 7 minutes. There was no unambiguous indication of the nature and duration of the journey.**

**The Panel noted Boehringer Ingelheim's submission that the target patient group for Striverdi included those within the mildest COPD category. The Panel had no information about the severity of COPD of the patients in the studies submitted by Boehringer Ingelheim. The Panel noted that the difference between placebo and Respimat in adjusted mean endurance times after 6 weeks was 52 seconds (p=0.002) in one study and 42 seconds (p=0.0018) in the other study. Guidelines from the National Institute for Health & Clinical Excellence (NICE) recommended bronchodilators as generally the first treatment options to be offered to COPD patients. The Panel considered that given the data provided by Boehringer Ingelheim, including that 36% of patients would be classified as the mildest COPD category and the indication for Striverdi, the artwork was not misleading as alleged. No breach of the Code was ruled.**

A prescribing support pharmacist complained about a leavepiece (ref UK/SVR – 141004(1)) for Striverdi (olodaterol) Respimat issued by Boehringer Ingelheim Limited. Striverdi Respimat was indicated as a maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD) and was a long-acting beta2-adrenergic agonist (LABA).

The front cover of the leavepiece showed the photograph of an older woman, smiling and at ease, cycling apparently slightly uphill past a village church. The basket on the back of the bicycle held a newspaper and a bunch of flowers.

**COMPLAINT**

The complainant alleged that the depiction of a lady cycling on her bicycle did not truely reflect the likely effect of Striverdi Respimat in patients with COPD. Although the inside of the leavepiece referred to a significant increase in exercise endurance time vs control (referenced to data on file) the complainant found it hard to believe that the use of Striverdi Respimat would enable patients with COPD to cycle away.

The complainant referred to the supplementary information for Clause 7.8 which stated that care must be taken to ensure artwork did not mislead as to the nature of a medicine or any claim or comparision. The complainant alleged that the image portrayed by the artwork was misleading.

**RESPONSE**

Boehringer Ingelheim stated that in its two paired, six-week exercise endurance studies cited in the leavepiece, the mean age of subjects was 60.6 ± 7 years. Whilst there were more males than females in each study (116 vs 35 and 116 vs 41) the number of women who smoked and consequently developed COPD in the UK had risen over the last decade.

The inclusion criteria for the studies included a diagnosis of COPD and post-bronchodilator FEV1 (Forced Expiratory Volume in 1 sec) <80% of predicted normal and post-bronchodilator FEV1/FVC of <70% at visit 1; patients also had to be able to perform technically acceptable pulmonary function tests, multiple exercise tests and maintain records.

The primary outcome measure of both studies was exercise endurance time during constant work rate cycle ergometry to symptom limitation at 75% of maximal work capacity, after 6 weeks of treatment. Boehringer Ingelheim submitted that the results meant that on average patients treated with Striverdi Respimat could cycle at 75% of their maximal work rate for 7 minutes in one study and 6.6 minutes in the other.

Boehringer Ingelheim stated that the imagery in the leavepiece was appropriate to the clinical data. The subject was a late, middle aged female undertaking gentle exercise as demonstrated by the use of an old, single-geared bicycle. Her hair did not flow behind her and she did not appear to be exerting herself unduly. The newspaper and flowers in her basket implied that she had ridden a short distance to the

village shop, a journey that could be completed in 6 to 7 minutes.

Boehringer Ingelheim submitted that there might be a general misconception that symptoms in typical COPD patients severely limited their activities of daily living; that they were perhaps housebound or on oxygen. Recently published epidemiological data (Haughney *et al* 2014) which looked at the UK COPD population demonstrated that 36% of patients would be classified with the mildest disease category – Global Initiative for Chronic Obstructive Lung Disease (GOLD) subgroup A (lower risk of exacerbations and fewer symptoms) based on the 2011 assessment criteria.

Both the GOLD and the National Institute for Health and Care Excellence (NICE) guidelines recommended that these were the patients in whom LABA monotherapy such as Striverdi Respimat was considered an appropriate treatment option.

Boehringer Ingelheim submitted that the leavepiece therefore included an image that was appropriate to the target COPD population and included the patient undertaking exercise as supported by clinical trial data. The image did not suggest benefits that could not be substantiated and as such was not in breach of Clause 7.8 of the Code.

**PANEL RULING**

The Panel examined the illustration of an older woman riding a traditional bicycle with a newspaper and flowers in a basket; bright motion swirls had been added around the pedals, the back wheel and for a distance behind the bicycle. The background scenery was a church with a house a short distance away; the road had an incline.

The Panel noted Boehringer Ingelheim's submission regarding the inclusion criteria for the two studies referenced in the leavepiece and that the primary outcome measure for the studies was exercise endurance time during constant work rate cycle ergometry of maximal work capacity, after 6 weeks of treatment. The results meant that on average, patients treated with Striverdi could cycle at 75% of their maximal work rate for 7 minutes in one study and 6.6 minutes in the other.

The Panel did not accept Boehringer Ingelheim's submission that it was implied that the woman would cycle for no more than 6 or 7 minutes. There was no unambiguous indication of the nature and duration of the journey.

The Panel noted Boehringer Ingelheim's submission that the target patient group for Striverdi included those within the mildest COPD category. The Panel had no information about the severity of COPD of the patients in the studies. The Panel noted that the difference between placebo and Respimat in adjusted mean endurance times after 6 weeks was 52 seconds (p=0.002) in one study and 42 seconds (p=0.0018) in the other study. NICE guidelines recommended bronchodilators as generally the first treatment options to be offered to COPD patients. The Panel considered that given the data provided by Boehringer Ingelheim, including that 36% of patients would be classified as the mildest COPD category and the indication for Striverdi, the artwork was not misleading as alleged. No breach of Clause 7.8 was ruled.

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| **Complaint received** | **26 September 2014** |
| **Case completed** | **14 November 2014** |

**CASE AUTH/2735/9/14**

# DOCTOR IN PUBLIC HEALTH v BAYER HEALTHCARE

## Sponsored Journal Supplement

**A doctor in public health, complained about an eight page sponsored supplement 'Venous Thromboembolism – Unblock the System, How to treat DVT [deep vein thrombosis] in the Community', sponsored by Bayer HealthCare.**

**The supplement was distributed as a bound insert in the Health Service Journal (HSJ), 5 September 2014. The Bayer HealthCare company logo appeared in the top right hand corner on the first page of the supplement; running along the bottom edge of the first page was the statement 'Bayer HealthCare sponsored this report. The company has reviewed the data solely to ensure the factual accuracy in relation to Bayer products and compliance with industry guidelines. The views expressed in these articles are not necessarily those of the sponsoring company. Rivaroxaban▼ prescribing information available on page 8'. The Bayer HealthCare logo also appeared at the top of the contents list on page 2. The supplement consisted of four articles, one on service redesign, two GP case studies and one on a charity's perspective.**

**The complainant alleged that a reader who opened the supplement on the double-page spread, pages 4-5 or pages 6-7 would have no indication the material was sponsored by Bayer since it used the same font, layout and general design as the rest of the HSJ and nowhere on those four pages did it state it was a sponsored supplement (this was only stated on pages 1, 2 and 8).**

**The detailed response from Bayer is given below.**

**The Panel noted that the supplement was stapled into the centre of the HSJ. That a sponsored supplement was bound in rather than loose did not necessarily mean that its nature was disguised. The overall impression given to readers was the most relevant factor. The Panel considered that binding a supplement into a journal influenced the way readers would access it; they were not guaranteed to see the first page first and were likely to flick through the journal, often from back to front, and might read an inside page without first seeing the declaration of sponsorship on what would have been the front cover and front inside cover if the supplement were a loose insert. Further, the label 'Health Service Journal supplement' on the bottom of each page in itself was not sufficient to inform the reader that the article was sponsored promotional material produced for a pharmaceutical company.**

**Although the paper quality of the supplement was slightly thicker and glossier than that of the HSJ, in the Panel's view overall the pages of the supplement were not sufficiently dissimilar to the standard editorial pages of the journal. The Panel noted and considered that as a bound in supplement, given the way it would be accessed, some readers would not know from the outset that it was a sponsored promotional piece for Xarelto. Its promotional nature was disguised. A breach of the Code was ruled.**

**The Panel noted its comments above about how readers would access a bound in supplement and considered that the declaration of sponsorship was not adequate. A breach was ruled.**

**The Panel, although noting its rulings above, did not consider that Bayer HealthCare had failed to maintain high standards and ruled no breach.**

A doctor in public health, complained about an eight page sponsored supplement 'Venous Thromboembolism – Unblock the System, How to treat DVT [deep vein thrombosis] in the Community', (ref L.GB.04.2014.6167b) sponsored by Bayer HealthCare.

The supplement was distributed as a bound insert in the Health Service Journal (HSJ), 5 September 2014. Prescribing information for Xarelto (rivaroxaban) appeared on page 8 of the supplement. The Bayer HealthCare company logo appeared in the top right hand corner on the first page of the supplement; running along the bottom edge of the first page was the statement 'Bayer HealthCare sponsored this report. The company has reviewed the data solely to ensure the factual accuracy in relation to Bayer products and compliance with industry guidelines. The views expressed in these articles are not necessarily those of the sponsoring company. Rivaroxaban▼ prescribing information available on page 8'. The Bayer HealthCare logo also appeared at the top of the contents list on page 2. The supplement consisted of four articles, one on service redesign, two GP case studies and one on a charity's perspective.

Xarelto was an anticoagulant indicated, *inter alia*, for the treatment and prevention of DVT.

**COMPLAINT**

The complainant alleged that a reader who opened the supplement on the double-page spread, pages 4-5 or pages 6-7 would have no indication the material was sponsored by Bayer since it used the same font, layout and general design as the rest of the HSJ and nowhere on those four pages did it state it was a sponsored supplement (this information was confined to pages 1, 2 and 8).

When writing to Bayer the Authority asked it to respond in relation to the requirements of Clauses 9.1, 9.10 and 12.1 of the Code.

**RESPONSE**

Bayer noted the complainant's comments and referred to Clause 9.10 of the Code which stated that material sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company. Bayer noted that on the first page of the supplement there was the prominent and clear statement that 'Bayer HealthCare sponsored this report. The company has reviewed the data solely to ensure the factual accuracy in relation to Bayer products and compliance with industry guidelines. The views expressed in these articles are not necessarily those of the sponsoring company. Rivaroxaban▼ prescribing information available on page 8'.

Bayer submitted that Clause 12.1 stipulated that promotional material must not be disguised. In this regard Bayer noted the last sentence of the sponsorship declaration together with the fact that the Bayer HealthCare logo was also on the front cover immediately below the title of the supplement as well as on page 2 under contents. There was also a job code number (L.GB.2014.6167b) and date of preparation. Prescribing information was printed on the last page of the supplement where there was also an adverse event reporting statement directing reporters to Bayer plc.

The company submitted that there was no requirement to declare sponsorship on each and every page of sponsored material. Consequently the supplement was clearly not in breach of Clauses 9.10 and 12.1 and Bayer had thus not failed to maintain high standards (Clause 9.1).

In response to a request for further information, Bayer stated that it approached an agency to discuss opportunities to highlight examples of best practice where the pathway for treating DVT had been moved from the hospital into primary care. The agency recommended the HSJ to write a supplement. Bayer informed the journal about centres where this had happened and recommended some of the individuals to interview. The journal independently interviewed some of the health professionals in the supplement. In addition, the journal proposed that another individual be interviewed. Two of the individuals recommended for interview by Bayer had participated in a Bayer advisory board. Bayer submitted that although it had nominated some of the interviewees, it was not present during the interviews and had no influence over what the interviewees said. The journal wrote the supplement after the interviews.

Bayer reviewed the earlier editions of the supplement to ensure accuracy and readability and compliance with the Code. Upon final approval of the supplement (28 August 2014) the supplement was distributed as a bound insert in the HJS (5 September 2014), 1,000 copies were printed and distributed to the sales force and an email was sent to the sales force with a link to the HSJ supplement.

Bayer provided a copy of the HSJ at issue, the approved concept document with the agency, the contract between the agency and the journal and correspondence and emails regarding the article.

Bayer stated that it strongly believed that there was no breach in this supplement. The supplement was clearly distinct from the rest of the HSJ. The paper quality was different. The pagination was separate from the journal. There was a clear declaration of Bayer's contribution to the journal supplement in page 1, a Bayer logo on pages 1 and 2 and prescribing information on page 8. Most importantly, there was a distinct label 'Health Service Journal supplement' at the bottom of pages 2 to 7.

**PANEL RULING**

The Panel noted it was acceptable for companies to sponsor material. It had previously been decided, in relation to materials aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose.

The Panel noted the requirements of Clause 12.1 and its supplementary information that when a company paid for, or otherwise secured or arranged the publication of promotional material in journals such material must not resemble independent editorial matter.

The Panel noted that the supplement was stapled into the centre of the HSJ. That a sponsored supplement was bound in rather than loose did not necessarily mean that its nature was disguised. The overall impression given to readers was the most relevant factor. The Panel considered that the provision of a supplement, bound into a journal, influenced the way readers would access it; readers were not guaranteed to see the first page first and were likely to flick through the journal, often from back to front, and might thus read one of the inside pages of the supplement without first seeing the declaration of sponsorship on what would have been the front cover and front inside cover if the supplement were a loose insert. Further, the label 'Health Service Journal supplement' appearing at the bottom of each page in itself was not sufficient to inform the reader that the article was sponsored promotional material produced for a pharmaceutical company.

The text of the HSJ itself was written in four columns with a thin black line framing each page, the left hand page was colour coded in the top left hand corner to denote the section of the journal ie news (red), comment (blue) etc. In the news section relevant quotations were reproduced in bold red font within an otherwise normal column of text. The text of the supplement in question was also presented in four columns with a thin black line framing the pages and although the font was identical to that of the HSJ, no colour coding appeared on the left hand pages. Some quotations, however, were reproduced in the same bold red font used in the news section. Although the paper quality of the supplement was slightly thicker and glossier than that of the HSJ itself, in the Panel's view overall the pages of the supplement were not sufficiently dissimilar to the standard editorial pages of the journal. The

Panel noted and considered that as a bound in supplement, given the way it would be accessed, some readers would not know from the outset that it was a sponsored promotional piece for Xarelto. Its promotional nature was disguised. A breach of Clause 12.1 was ruled.

The Panel noted Bayer's submission there was no requirement within the Code for sponsorship to be declared on every page of sponsored material. The supplementary information to Clause 9.10 required the declaration of sponsorship to be sufficiently prominent to ensure that readers of sponsored materials are aware of it at the outset. The Panel noted its comments above about how readers would access a bound in supplement and considered that the declaration of sponsorship was not adequate. A breach of Clause 9.10 was ruled.

The Panel, although noting its rulings above, did not consider that Bayer HealthCare had failed to maintain high standards. Thus no breach of Clause 9.1 was ruled.

During the consideration of this case the Panel noted the supplementary information to Clause 9.10 required the wording of a declaration of sponsorship to be '… unambiguous so that the readers will immediately understand the extent of the company's involvement and influence over the material'. Bayer had suggested many of the individuals who should be approached by the HSJ in the production of the supplement including some health professionals who had previously attended Bayer advisory board meetings. The Panel was concerned to note that the declaration of sponsorship, which appeared on the front cover of the supplement, did not make the extent of Bayer's involvement clear in this regard. The Panel requested that Bayer be advised of its concern.

**Complaint received** **28 September 2014**

**Case completed** **27 November 2014**

**CASE AUTH/2738/10/14**

# VOLUNTARY ADMISSION BY BOEHRINGER INGELHEIM

## Corporate email about Giotrif

**Boehringer Ingelheim voluntarily admitted that an email which had been sent from its corporate headquarters in Germany to LinkedIn members via LinkedIn InMail to a global (including UK) audience was in breach of the Code. The email headed, 'Read new data on treatment outcomes with Giotrif' detailed the results from an abstract presented at the American Society of Clinical Oncology (ASCO) meeting, 2014 (Yang *et al* 2014) also included was an advertisement for Giotrif (afatinib) and a link to a press release.**

**The advertisement referred to overall survival benefit data for certain patients. The press release headed 'New data show Giotrif (afatinib) provided more than one year additional survival for lung cancer patients with the most common type of EGFR [epidermal growth factor receptor] mutation (del19) compared to chemotherapy', gave more detail including that Giotrif was the first treatment to demonstrate an overall survival benefit for certain patients. The press release was marked 'For Ex-US and Ex-UK Media Only'.**

**In accordance with Paragraph 5.6 of the Constitution and Procedure the Director treated the matter as a complaint.**

**Giotrif was indicated for the treatment of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)–naïve adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).**

**Boehringer Ingelheim stated it only knew about these activities when another UK pharmaceutical company brought them to its attention. Inter-company dialogue concluded with Boehringer Ingelheim confirming that it would report the activity to the PMCPA.**

**Boehringer Ingelheim stated that the intended audience was lung cancer health professionals based on the filter of medical, oncology and those who had not opted out of receiving promotional mailings. It was now clear that these filters were not restrictive enough as UK non health professionals were not excluded. The material did not contain the obligatory UK information and was not UK approved or certified.**

**The Giotrif advertisement was not intended for a UK audience and was not used by the UK company; Boehringer Ingelheim Corporate approved and distributed the advertisement. The content, claims and absence of tolerability information might be considered inconsistent with the Code.**

**In order to prevent future issues, the corporate organisation had been reminded not to send by any medium, materials or communications that were not UK certified to any UK recipients.**

**The detailed response from Boehringer Ingelheim is given below.**

**The Panel noted that the email had been created and distributed by Boehringer Ingelheim Corporate in Germany but insomuch as it was sent to UK recipients, that aspect came within the scope of the Code. UK companies were responsible for the activities of overseas affiliates where those activities came within the scope of the Code. Boehringer Ingelheim in the UK was thus responsible for the UK use of the email. As the email had not been certified the Panel ruled a breach of the Code.**

**The absence of prescribing information was also ruled in breach. The Panel ruled no breach of the Code with regard to the need to indicate where the prescribing information could be found. No breach was also ruled as the Panel considered the material satisfied the requirement for providing the date it was drawn up or last revised. The email did not include a prominent statement regarding the mechanism for reporting adverse events or an inverted black triangle. Breaches were ruled. As it was clear which company had sent the email the Panel ruled no breach.**

**The Panel noted that material should only be sent or distributed to those people whose need for, or interest in it could be reasonably assumed. Boehringer Ingelheim had implied that this might not have been so given that the filters defining who the email was sent to were not restrictive enough. The Panel considered that on the balance of probabilities, at least some health professionals with no interest in Giotrif had received the email. A breach was ruled.**

**A member of the public in Australia had received the email. No evidence had been provided to show that a particular member of the UK public had received the email but given the submission that the filters were inadequate, the Panel considered that on the balance of probabilities a member of the UK public had received the promotional email. A prescription only medicine had been promoted to the public and the advertisement would encourage a member of the public to ask their health professional to prescribe Giotrif. Breaches were ruled. The Panel noted Boehringer Ingelheim's submission that as the data did not come from the whole of the Yang *et al* study group it was not balanced and fair. A breach was ruled. The Panel also ruled breaches on**

**the basis that the artwork was misleading and that the material did not encourage the rational use of Giotrif.**

**The Panel ruled that high standards had not been maintained.**

**The Panel considered that Boehringer Ingelheim had been badly let down by its corporate colleagues who appeared to have failed to recognise, the need for the email to be approved for use in the UK. Nonetheless, the Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of the Code was ruled.**

Boehringer Ingelheim Limited voluntarily admitted that an email which had been sent from its corporate headquarters in Germany was in breach of the Code. The email, which was sent to some UK recipients, contained an advertisement for Giotrif (afatinib) and a link to a non-UK Giotrif related press release.

The email was headed 'Read new data on treatment outcomes with Giotrif' and detailed the results from an abstract which had been presented at the American Society of Clinical Oncology (ASCO) meeting, May/June 2014 (Yang *et al* 2014). Within the text was a link to a press release and on the right hand side of the text was an advertisement for Giotrif. The press release was entitled 'New data show Giotrif (afatinib) provided more than one year additional survival for lung cancer patients with the most common type of EGFR [epidermal growth factor receptor] mutation (del19) compared to chemotherapy'. The press release was marked 'For Ex-US and Ex-UK Media Only'.

In accordance with Paragraph 5.6 of the Constitution and Procedure the Director treated the matter as a complaint which was taken up with Boehringer Ingelheim.

**VOLUNTARY ADMISSION**

Boehringer Ingelheim explained that the email was generated and sent in error on 13 August 2014 from its corporate headquarters in Germany to LinkedIn members via LinkedIn InMail to a global (including UK) audience according to the LinkedIn settings described below.

Giotrif was indicated for the treatment of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)–naïve adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

The advertisement referred to overall survival (OS) benefit data for certain patients taken from Yang *et al*. The email included a link to a press release which gave more detail including that Giotrif was the first treatment to demonstrate an overall survival benefit for patients with specific types of EGFR mutation positive NSCLC.

Boehringer Ingelheim stated it was not involved in these activities and did not know about them until another UK pharmaceutical company brought them to its attention on 17 September 2014. Inter-company dialogue with that company concluded with Boehringer Ingelheim confirming that it would report the activity to the PMCPA.

The intended audience for the LinkedIn InMail was lung cancer health professionals based on the filter of medical, oncology and those who had not opted out of receiving promotional mailings through their individual LinkedIn settings. Boehringer Ingelheim stated that it was now clear that these filters were not restrictive enough as UK non health professionals were not excluded. This would not have occurred if Boehringer Ingelheim in the UK had been notified of this activity which might be in breach of Clauses 9.10, 11.1, 23.1 and 23.2 of the Code.

The promotional email, advertisement and press release did not contain the obligatory UK information as the materials were generated and approved by Boehringer Ingelheim Corporate and were not sent for UK approval and certification. As such, this might be considered to be a breach of Clauses 4.1, 4.6, 4.9, 4.10, 4.11, and 25.1.

The Giotrif advertisement was not intended for a UK audience and was not used in the UK by the UK company; Boehringer Ingelheim Corporate had approved and distributed the advertisement. The content, claims and absence of tolerability information might be considered inconsistent with Clauses 7.2, 7.8 and 7.10 of the Code.

The Giotrif related press release, accessible via the link in the email, was also never intended for a UK audience and was never used in the UK by the UK company; again it had been approved and distributed by Boehringer Ingelheim Corporate. The communication was no longer in circulation and had been withdrawn from all UK LinkedIn members. In order to prevent future issues, the corporate organisation had been reminded that under no circumstances should it send by any medium, materials or communications that were not UK certified to any UK recipients.

Boehringer Ingelheim submitted that all corporate communications which fell within the scope of the Code and were directed at a global audience but which had not gone through full UK approval and certification, would be expressly defined as 'for non-UK recipients' and would comply with the digital communications and social media requirements and guidelines as set out by the Code and where relevant with the regulatory frameworks of the other pertinent jurisdictions.

Boehringer Ingelheim stated that it had acted immediately to withdraw the email and put measures in place, in collaboration with corporate colleagues, to ensure greater control on Boehringer Ingelheim Corporate activities in the UK. Boehringer

Ingelheim stated that it took its responsibilities under the Code very seriously.

When writing to the company the Authority asked it to respond to Clauses 9.1 and 2 in addition to the clauses raised by Boehringer Ingelheim. The company was also asked to provide further details including why it considered there might be breaches of Clauses 7.2, 7.8 and 7.10.

**RESPONSE**

Boehringer Ingelheim stated that the intended audience for the email in question was lung cancer health professionals globally, based on the filter of medical, oncology and those who had not opted out of receiving promotional mailings through their LinkedIn settings. It was now clear that these filters were not restrictive enough and did not exclude UK recipients. The email was sent to a global audience with the same filters and the mailing was also received by a member of the public in Australia. As the same filtering criteria were used for all countries it was likely that other members of the public would have received the email outside of the UK. The USA was excluded from these mailings.

Boehringer Ingelheim submitted that the content, claims and absence of tolerability information as written in the email and advertisement were not consistent with Clauses 7.2, 7.8 and 7.10. The information was not balanced and fair as it did not include the data for the whole EGFR mutation positive patient population in the study and provided overall survival data for the del19 mutational sub group (albeit one that represented 50% of the trial population). The graphic image of the pillar in the advertisement was labelled "EFFICACY – PFS [progression free survival] +OS", which implied that afatinib gained its licence based on OS benefit in addition to PFS benefit, rather than on the basis of PFS benefit alone.

Boehringer Ingelheim stated that the material did not mention the tolerability profile which might convey an unbalanced benefit/risk message and raised potential concerns for patient safety if prescribing was based on or influenced by the material. When taken collectively the materials might not encourage the rational use of Giotrif.

With regard to Clauses 9.1 and 2, Boehringer Ingelheim stated it had self-reported the potential breaches instigated by the corporate organisation. It accepted that this activity was not consistent with maintaining high standards. However, as soon as the company knew about this activity it ensured recall and termination of the communications as a matter of urgency. By self- reporting these breaches the company submitted it had demonstrated its strong commitment to maintaining high standards and had introduced robust measures, working collaboratively with corporate colleagues to ensure greater control of all Boehringer Ingelheim Corporate activities in the UK. The materials were not intended for a UK audience and were not used by the UK company. Patient safety and public health had not been compromised with respect to this activity and therefore Boehringer Ingelheim submitted that this was not a breach of Clause 2.

**PANEL RULING**

The Panel noted that the email had been created and distributed by the Boehringer Ingelheim Corporate team in Germany. The supplementary information to Clause 1.9, Applicability of Codes, required that activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national code of the country in which the activities took place or the materials were used. The email in question was issued from a company based in Germany but insomuch as it was sent to UK recipients, the Panel considered that that aspect of its use came within the scope of the Code. The Panel also noted that it was an established principle under the Code that UK companies were responsible for the activities of overseas affiliates where those activities came within the scope of the Code. Boehringer Ingelheim in the UK was thus responsible for the UK use of the email. The Panel noted that the email was promotional and had not been certified for use in the UK and so it ruled a breach of Clause 14.1.

The Panel noted that the email promoted Giotrif but that there was no prescribing information within it. In that regard the Panel ruled a breach of Clause 4.1. The Panel noted that Clause 4.6 of the Code stated that in the case of material included on the Internet, there must be a clear, prominent statement as to where the prescribing information could be found. The Panel noted that although the material at issue was sent electronically, it was not material included on the Internet *per se*; it was an electronic mailing. In that regard the Panel noted its ruling of a breach of Clause 4.1 above. The Panel did not consider that Clause 4.6 applied to emails and so it ruled no breach of that clause. Boehringer Ingelheim had also voluntarily admitted a breach of Clause 4.9 which required that promotional materials, other than advertisements appearing in professional publications, must include a date upon which the material was drawn up or last revised. The Panel noted that the press release linked to the email was dated 1 September 2014 and that the email itself would bear the date upon which it was sent. In that regard the Panel considered that recipients would know when the material was sent and was thus current; no breach of Clause 4.9 was ruled. The email did not include a prominent statement regarding the mechanism for reporting adverse events; a breach of Clause 4.10 was ruled. The Panel noted from the Giotrif summary of product characteristics provided by Boehringer Ingelheim, that the medicine was one which was subject to additional monitoring and thus all promotional material was required to show the inverted black, equilateral triangle symbol. As the email in question did not include that symbol a breach of Clause 4.11 was ruled.

The Panel noted that Clause 9.10 required that all material relating, *inter alia*, to medicines and their uses, whether promotional or not, which was

sponsored by a pharmaceutical company must clearly state that it was sponsored by that company. The Panel noted that to the right of the text of the email was a Giotrif advertisement which clearly showed the Boehringer Ingelheim company logo and name. In addition, the linked press release was headed with the company logo. On balance, the Panel considered that it was clear that the email had been sent on behalf of Boehringer Ingelheim. No breach of Clause 9.10 was ruled.

The Panel noted that Clause 11.1 of the Code required that promotional material only be sent or distributed to those people whose need for, or interest in it could be reasonably assumed. Boehringer Ingelheim had implied that this might not have been so given that the filters defining who the email was sent to were not restrictive enough. The Panel considered that on the balance of probabilities, at least some health professionals with no interest in Giotrif had received the email. A breach of Clause 11.1 was ruled.

Clause 23.1 required that prescription only medicines must not be advertised to the public. Boehringer Ingelheim had submitted that it was possible that some of those who had received the email in the UK were not health professionals and that a member of the public in Australia had received the email. No evidence had been provided to show that a particular member of the UK public had received the email but given the submission that the filters in place did not preclude this from happening, the Panel considered that on the balance of probabilities a member of the UK public had received the promotional email. A breach of Clause 23.1 was ruled. Given its ruling of a breach of Clause 23.1, the Panel also ruled a breach of Clause 23.2 in that the advertisement would encourage a member of the public to ask their health professional to prescribe Giotrif.

The Panel noted Boehringer Ingelheim's submission about the balance of the data within the email. The data included did not come from the whole of the Yang *et al* study group and, according to Boehringer Ingelheim, was thus not balanced and fair. A breach of Clause 7.2 was ruled. The Panel also ruled a breach of Clause 7.8 on the basis that the artwork in the advertisement was misleading as to the basis of the Giotrif licence. A breach of Clause 7.10 was also ruled in that Boehringer Ingelheim had admitted that the material did not encourage the rational use of Giotrif.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel considered that Boehringer Ingelheim had been badly let down by its corporate colleagues who appeared to have failed to recognise that, if sent to UK recipients, the email needed to be approved for use in the UK. Nonetheless, the Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was seen as a sign of particular censure and reserved for such. No breach of Clause 2 was ruled.

During its consideration of this case the Panel queried whether not opting out of receiving promotional material on LinkedIn settings was sufficient, given the very general nature of LinkedIn, to satisfy the requirement in Clause 9.9 of the Code which required recipients to consent to receive promotional material about medicines from pharmaceutical companies. The Panel considered that Boehringer Ingelheim would be well advised to consider how the arrangements for LinkedIn InMail fitted with the Code.

**Complaint received** **31 October 2014**

**Case completed** **9 January 2015**

# CODE OF PRACTICE REVIEW – February 2015

Cases in which a breach of the Code was ruled are indexed in **bold type.**

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|---|---|---|---|---|---|
| **AUTH/2618/7/13** | **AstraZeneca v Chiesi** | **Promotion of Fostair** | **Breaches Clauses 7.2 and 7.4**<br>**Audit and re-audit required by Appeal Board**<br>**Public reprimand required by Appeal Board** | **No appeal**<br>**Report from the Panel to the Appeal Board** | **Page 3** |
| **AUTH/2726/8/14** | **Anonymous, non contactable health professional v GlaxoSmithKline** | **Promotion of Seretide** | **Four breaches Clause 7.2**<br>**Four breaches Clause 7.4**<br>**Breach Clause 9.1** | **No appeal** | **Page 11** |
| AUTH/2728/8/14 | Anonymous, non contactable v GlaxoSmithKline | Promotion of Relvar | No breach | No appeal | Page 21 |
| **AUTH/2731/9/14** | **Pulmonologist v Boehringer Ingelheim** | **Scientific symposium** | **Breach Clause 9.1** | **No appeal** | **Page 32** |
| AUTH/2734/9/14 | Head of prescribing support unit v Boehringer Ingelheim | Promotion of Striverdi Respimat | No breach | No appeal | Page 34 |
| **AUTH/2735/9/14** | **Doctore in public health v Bayer HealthCare** | **Sponsored Journal supplement** | **Breaches Clauses 9.10 and 12.1** | **No appeal** | **Page 36** |
| **AUTH/2738/10/14** | **Voluntary admission by Boehringer Ingelheim** | **Corporate email about Giotrif** | **Breaches Clauses 4.1, 4.10, 4.11, 7.2, 7.8, 7.10, 9.1, 11.1, 14.1, 23.1 and 23.2** | **No appeal** | **Page 39** |

# PMCPA | Prescription Medicines Code of Practice Authority

The Prescription Medicines Code of Practice Authority was established by the Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself. Compliance with the Code is obligatory for ABPI member companies and, in addition, over sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and other relevant decision makers and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including any printed or electronic material used by them
- the supply of samples
- the provision of inducements in connection with the promotion of medicines and inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the sponsorship of attendance at meetings organised by third parties
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio or video-recordings in any format, broadcast media, non-print media, the Internet, interactive data systems, social media and the like.

It also covers:

- the provision of information on prescription only medicines to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- disclosure of tranfers of value to health professionals and organisations
- joint working between the NHS and pharmaceutical companies
- the use of consultants
- non-interventional studies of marketed medicines
- the provision of items for patients
- the provision of medical and educational goods and services
- grants, donations and benefits in kind to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of three of the four members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. One member of the Panel acts as case preparation manager for a particular case and that member does not participate and is not present when the Panel considers it.

Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry. Independent members, including the Chairman, must be in a majority when matters are considered by the Appeal Board.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Further information about the Authority and the Code can be found at www.pmcpa.org.uk

Complaints under the Code should be sent to the Director of the Prescription Medicines Code of Practice Authority, 7th Floor, Southside, 105 Victoria St, London SW1E 6QT

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.