CASE AUTH/2953/4/17

TILLOTTS v DR FALK

Promotion of Salofalk Granules

Tillotts alleged that the headline claim in a journal advertisement, that Salofalk Granules (mesalazine, prolonged release) represented a 'step change' in the treatment of ulcerative colitis (UC), implied new features and superiority over other mesalazine products and other UC treatments when such was not so.

Tillotts noted that the advertisement also described how the sachets of granules might be taken once daily and that this might result in patients having a simpler routine. The granule format and once daily posology were not unusual in the mesalazine market and therefore this claim appeared to exaggerate the properties of Salofalk Granules. Further, the language used in the claim, '… even have a tasty vanilla flavour' was not in keeping with the high standards expected of a pharmaceutical company or the health professionals to whom the advertisement was directed.

With regard to the claim, 'if the inflammation is in the distal colon, the granules are pretty good at getting there too', Tillotts submitted that whilst this might be true, it implied an advantage for Salofalk Granules in this area compared with other mesalazine products, which was not supported by evidence. The supporting reference (Leifeld *et al*, 2011) was a pooled analysis of Salofalk Granules vs Salofalk tablets in induction therapy and provided no evidence that Salofalk Granules were superior to mesalazine tablets offered by other manufacturers, particularly those which released mesalazine further down the gastrointestinal tract. As above, this claim appeared to exaggerate the properties of Salofalk Granules. The language used in the claim, 'the granules are pretty good at getting there', was neither clear in its description of the product's properties, nor in keeping with the high standards expected of a pharmaceutical company or the health professionals to whom the advertisement was directed.

Finally, Tillotts noted that the claim 'Optimisation with Salofalk Granules for patients inadequately maintained on previous mesalazine resulted in: 69% fewer days off work, 87% fewer hospital visits due to [UC] flare up, 45% fewer GP visits due to [UC] flare ups, 50% fewer steroid courses used' was referenced to Aldulaimi *et al* (2016a). The reference did not explain what 'optimisation' meant, nor whether patients were previously treated with mesalazine tablets, granules, rectal preparations or brands of mesalazine from other manufacturers. Thus, this reference did not support the claims and also appeared to exaggerate the properties of Salofalk Granules.

Tillotts submitted that in summary, the advertisement appeared to contain a number of claims that were not supported by robust evidence and were therefore potentially inaccurate and exaggerated; might provide misleading comparisons; might not be capable of substantiation; might not encourage rational use of medicines containing mesalazine and potentially disparaged other manufacturers' mesalazine products. Tillotts also alleged that the advertisement demonstrated a failure to uphold high standards.

The detailed response from Dr Falk is given below.

The Panel noted the headline claim 'An oral ulcerative colitis treatment that's a step change, not a step up' followed in more prominent font by 'Now that's progress' and Tillotts' allegation that 'step change' implied new features and superiority over other mesalazine products and other UC treatments which could not be substantiated. Beneath a picture of a granules sachet text in a much smaller typeface stated 'When mesalazine doesn't seem to be working, stepping up to immunosuppressants might not be the only option'. Followed by 'For those patients who could benefit from a simpler routine, Salofalk Granules come in a convenient little sachet, only need to be taken once a day and even have a tasty vanilla flavour' and finally 'Oh, and if the inflammation is in the distal colon, the granules are pretty good at getting there too'.

The Panel noted Dr Falk's submission that it was 'justified to inform health professionals of the option of changing mesalazine rather than moving up to immunosuppressants or biologics' but considered that the claim in question went beyond this. The Panel considered that by describing Salofalk Granules as a step change, followed by the prominent claim 'Now that's progress', some readers might assume that Salofalk Granules represented a significant and progressive change in the treatment of UC compared with other available mesalazines and that was not so. In addition the Panel noted that the qualification 'When mesalazine doesn't seem to be working, stepping up to immunosuppressants might not be the only option' appeared in a separate paragraph and in much smaller white font beneath the depiction of a sachet and bold headline claims. In the Panel's view it would not be immediately obvious that this separate paragraph was meant to qualify the claims above. It also misleadingly implied that changing to Salofalk Granules was the only option to avoid stepping up to immunosuppressants which was not so. The Panel considered that the description of Salofalk Granules as a 'step change' was misleading; the claim exaggerated the effects of Salofalk Granules and could not be substantiated. Breaches of the Code were ruled.

The Panel noted Tillott's allegation that as granules and once daily dosing were not unusual in the mesalazine market the claim 'For those patients who could benefit from a simpler routine, Salofalk

Granules come in a convenient little sachet, only need to be taken once a day and even have a tasty vanilla flavour' exaggerated the properties of Salofalk Granules. The Panel noted Dr Falk's submission that the claim related solely to Salofalk Granules, it was not comparative and was a statement of fact. The Panel noted that 'simpler' was a comparative term and referred to dosing regimens other than once daily. However in the Panel's view the claim did not state or imply that Salofalk Granules were the only mesalazine that could be taken once daily as alleged; it presented Salofalk Granules as an option for those patients who would benefit from a simpler once daily routine. The Panel did not consider that the claim was exaggerated as alleged. No breach of the Code was ruled.

The Panel disagreed with Tillotts' concern that the language used in the claim, including the phrase 'even have a tasty vanilla flavour', was not in keeping with high standards. The advertisement adopted a conversational style which was not unacceptable *per se* so long as the content otherwise complied with the Code. The Panel noted that Tillotts had not explained why it considered high standards had not been maintained and it bore the burden of proof in this regard. No breach of the Code was ruled.

The Panel disagreed with Tillotts' view that the claim '… if the inflammation is in the distal colon, the granules are pretty good at getting there too' implied that Salofalk Granules had an advantage in this area compared with other mesalazine products. The Panel did not consider that the claim was an express or implied comparison. There was no implication that other mesalazine products did not deliver medicine to the distal colon or that Salofalk Granules otherwise had an advantage in this area as alleged. The Panel thus ruled no breach of the Code. The supporting reference, Leifeld *et al*, stated that the favourable effects of mesalazine granules in distal colitis were plausible since the extended release system allowed more 5-ASA to reach the distal parts of the colon. The Panel considered that the claim could be substantiated and ruled no breach of the Code. Further the Panel did not consider that the claim exaggerated the properties of Salofalk Granules as alleged and ruled no breach of the Code.

The Panel noted the allegation that the language used in the claim 'the granules are pretty good at getting there too' was neither clear in its description of the product's properties, nor in keeping with the high standards expected of a pharmaceutical company. The Panel considered that its comments above in relation to the conversational style of the advertisement were relevant here. The Panel also noted its comments above in relation to Leifeld *et al* and rulings of no breach of the Code in relation to the claim in question. The Panel had some concerns about the phrase 'pretty good' but on balance considered that Tillotts had not demonstrated that in using it Dr Falk had failed to maintain high standards. The Panel ruled no breach of the Code.
In relation to the claim 'Optimisation with Salofalk Granules for patients inadequately maintained on previous mesalazine resulted in: 69% fewer days off work, 87% fewer hospital visits due to [UC] flare up, 45% fewer GP visits due to [UC] flare ups, 50% fewer steroid courses used', Tillotts alleged that Aldulaimi *et al* (2016a), did not support the claim as it did not explain what optimisation with Salofalk Granules meant, nor whether the patients involved in the study were previously treated with mesalazine tablets, granules, rectal preparations or brands of mesalazine from other manufacturers. The Panel noted Dr Falk's submission that Tillotts had referred to an incorrect reference; the correct reference, which included additional data was Aldulaimi *et al* (2016b). The Panel noted that the correct reference was cited on the advertisement in question. The Panel noted that Aldulaimi *et al* (2016b) stated that patients were previously treated with various mesalazine therapies; dosing frequencies were provided. The Panel did not consider that the claim in question was incapable of substantiation on the narrow ground alleged. No breach of the Code was ruled.

In relation to the term 'optimisation' the Panel noted that contrary to Dr Falk's submission it was not defined in either study. The only reference to the term was in the introduction to Aldulaimi *et al* (b) which stated 'We have previously reported that optimising oral mesalazine maintenance therapy improved patient and disease outcomes in primary care.' The reference for the previous report was not cited. There was no further reference to the term. Dr Falk had provided a copy of a paper which appeared to be the case study referred to in Aldulaimi *et al* (b) and examined cost reduction and improvements in patient care by improvement of adherence to therapy and patient education. Neither 'optimisation' nor its derivatives were referred to although there was a general reference to dosing frequency in relation to improving adherence and outcomes. The Panel noted the definition of optimisation was 'the act of making the best of something; the state or condition of being optimal' (The New Shorter Oxford English Dictionary). The Panel noted that Aldulaimi *et al* (a and b) evaluated the effect of changing patients inadequately controlled on their current mesalazine therapy to once daily Salofalk Granules. Few details were given in either paper including details of dosages used. The Panel noted that a once daily dose was licensed for treatment of acute episodes of UC. The licensed dosing frequency for maintenance of remission was three times daily although in certain patients the dosing schedule for Salofalk Granules could be adapted to a single daily dose. The title of Aldulaimi *et al* (a and b) referred to maintenance therapy. The position regarding dosage was unclear. The Panel considered that some readers might assume that optimisation meant more than a straightforward switch to a once daily dose. Others might interpret it as a description of the outcomes achieved and described in the claim in relation to days off work etc. The Panel noted that optimisation was however referred to in Taylor and Irving (2011), a review which was not cited in the advertisement in relation to the claim in question: optimisation of conventional

therapy of patients with irritable bowel disease included patient-related factors (adherence and acceptability of treatment) and medicine-related factors (formulation, dose and drug related factors) which could be adjusted to enable successful treatment. The Panel noted that this matter was further complicated as the complainant did not have Aldulaimi *et al* (b) when it made the complaint. The complainant bore the burden of proof. Whilst the Panel had concerns about the claim and data these were not the subject of complaint. The Panel considered that Tillotts had not established that the failure of the study to define optimisation meant that the claim was not capable of substantiation and on the very narrow ground of that allegation it ruled no breach of the Code.

In relation to the allegation that the reference appeared to exaggerate the properties of Salofalk Granules, Tillotts mentioned its failure to detail patients' previous therapies and failure to define optimisation. The Panel noted its rulings above in this regard. The Panel noted it would not rule on the study *per se* but whether given the study the claim was exaggerated for the reasons cited. The Panel noted its comments above about the burden of proof. The Panel noted that at the outset of the study patients were assessed in relation to disease activity (Walmsley Index), use of steroids, days off work, GP and hospital visits. A subgroup of patients were switched to Salofalk Granules once daily maintenance therapy and all patients were reviewed 6 months later. Patient and disease outcomes were compared between those who switched to Salofalk Granules and those retained on their current mesalazine treatment. The Panel noted that Aldulaimi *et al* (a) as provided by Tillotts' stated that patients changing to Salofalk Granules had a higher baseline disease activity Walmsley Index (2.78 vs 1.99 p<0.01) vs those who remained on their mesalazine treatment. The Panel noted that disease activity Walmsley Index was 2.78 vs 1.97 in Aldulaimi *et al* (b) as provided by Dr Falk. Neither Tillotts nor Dr Falk commented on this or the effect if any this might have on the change from baseline of this index and other reported outcomes.

The Panel noted that Tillotts had the burden of proving its complaint on the balance of probabilities; the matter would be judged on the evidence provided by the parties. The Panel did not consider that Tillott's had proven that because the reference did not explain what optimisation with Salofalk granules meant or state the previous therapies that the claim 'Optimisation with Salofalk Granules for patients inadequately maintained on previous mesalazine resulted in: 69% fewer days off work, 87% fewer hospital visits due to [UC] flare up, 45% fewer GP visits due to [UC] flare ups, 50% fewer steroid courses used' exaggerated the properties of Salofalk granules as alleged. The correct reference provided by Dr Falk, Aldulaimi *et al* (b) included additional data. Based on the very narrow allegation, the Panel ruled no breach of the Code.

The Panel did not consider that Tillotts had established that Dr Falk had disparaged other manufacturers' mesalazine products as alleged. No breach of the Code was ruled.

Tillotts Pharma UK Limited complained about an advertisement (ref DrF 17/041) for Salofalk (mesalazine, prolonged release) Granules placed by Dr Falk Pharma UK Ltd and published in Frontline Gastroenterology. The headline claim was 'An oral ulcerative colitis treatment that's a step change, not a step up. Now that's progress'.

Salofalk was indicated for the treatment of acute episodes and the maintenance of remission of ulcerative colitis.

Tillotts marketed Octasa (mesalazine, modified release) tablets which was indicated for the treatment of mild to moderate acute exacerbations and the maintenance of remission of ulcerative colitis.

For the treatment of acute episodes of ulcerative colitis Salofalk Granules were licensed for once daily dosing although it was also possible to take the prescribed daily dose in three divided doses if this was more convenient to the patient. For the maintenance of remission of ulcerative colitis the standard treatment was three times daily. For patients known to be at increased risk of relapse for medical reasons or due to difficulties to adhere to the application of three daily doses the dosing schedule could be adapted to a single daily dose.

COMPLAINT

Tillotts alleged that the statement in the advertisement that Salofalk Granules represented a 'step change' in the treatment of ulcerative colitis implied new features and superiority over other mesalazine products and other treatments for ulcerative colitis. This was not so and was not supported by any evidence. No reference was cited to support the claim and despite a request for such evidence from Dr Falk, none was received. The Cochrane review of mesalazine products used in the treatment of ulcerative colitis (Wang *et al*, 2016) described a meta-analysis of all available clinical data and concluded that 'there do not appear to be any differences in efficacy or safety among the various 5-ASA [mesalazine] formulations'. Tillotts considered that this contradicted the key claim made in the advertisement.

Tillotts noted that the advertisement also described how the sachets of granules might be taken once daily and that this might result in patients having a simpler routine. The granule format and once daily posology were not unusual in the mesalazine market and therefore this claim appeared to exaggerate the properties of Salofalk Granules. Furthermore, the language used in the statement, for example, '… even have a tasty vanilla flavour' was not in keeping with the high standards expected of a pharmaceutical company or the health professionals to whom the advertisement was directed.

Tillotts noted that it was further stated in the advertisement that 'if the inflammation is in the distal colon, the granules are pretty good at getting there too'. Whilst this might be true, it implied that Salofalk Granules had an advantage in this area compared with other mesalazine products, which

was not supported by evidence. The reference cited to support this claim (Leifeld *et al*, 2011) referred to a pooled analysis study in which Salofalk Granules were compared with Salofalk tablets in induction therapy only. Therefore it did not provide evidence that Salofalk Granules were superior to mesalazine tablets offered by other manufacturers, particularly those which might release mesalazine later in the gastrointestinal tract. This point was important, as the majority of oral mesalazine products relied on a pH-dependent modified release mechanism for release of the active ingredient once the tablet or granules reached a certain point in the gastrointestinal tract (the colon was most relevant to those with ulcerative colitis). A higher trigger pH meant the tablet would travel further into the gastrointestinal tract before it released mesalazine, which might result in more mesalazine being available in the distal colon. For example, Asacol (marketed by Allergan) and Octasa tablets began to release at a higher pH than Salofalk tablets, so the results of Leifeld *et al* could not be considered to apply in a comparison between Salofalk Granules and other oral mesalazines. Furthermore, Leifeld *et al* did not provide any evidence of superiority of Salofalk Granules vs Salofalk tablets beyond 8 weeks' treatment and in this regard Tillotts noted that ulcerative colitis was a lifelong condition with mesalazine (or an alternative medicine) being taken for many years. As above, this claim appeared to exaggerate the properties of Salofalk Granules. The language used in the claim, 'the granules are pretty good at getting there', was neither clear in its description of the product's properties, nor in keeping with the high standards expected of a pharmaceutical company or the health professionals to whom the advertisement was directed.

Finally, Tillotts noted the following claim in the advertisement, 'Optimisation with Salofalk Granules for patients inadequately maintained on previous mesalazine resulted in: 69% fewer days off work, 87% fewer hospital visits due to [ulcerative colitis] flare up, 45% fewer GP visits due to [ulcerative colitis] flare ups, 50% fewer steroid courses used' referenced to Aldulaimi *et al* (2016a), a poster displayed at a scientific congress on which Dr Falk's medical director was an author. The reference did not explain what 'optimisation with Salofalk Granules' meant, nor whether the patients involved in the study were previously treated with mesalazine tablets, granules, rectal preparations or brands of mesalazine from other manufacturers. Therefore, this reference did not provide the necessary detail to support the claims and also appeared to exaggerate the properties of Salofalk Granules.

Tillotts submitted that in summary, the advertisement appeared to contain a number of claims that were not supported by robust evidence and were therefore potentially inaccurate and exaggerated; might provide misleading comparisons; might not be capable of substantiation; might not encourage rational use of medicines containing mesalazine and potentially disparaged other manufacturers' mesalazine products. Tillotts also contended that the advertisement demonstrated a failure to uphold high standards. Breaches of Clauses 7.2, 7.3, 7.4, 7.10, 8.1 and 9.1 amongst others were alleged.

RESPONSE

Dr Falk noted the allegation that the term 'step change' 'implied new features and superiority …' and Tillotts' reference to the Cochrane review, which stated that 'there does not appear to be any difference in efficacy or safety among the various [mesalazine] formulations'. Dr Falk submitted that the Cochrane review concluded this on the basis that there were no head-to-head trials between the different mesalazine products. Tillotts alleged that the advertisement contradicted this statement. Dr Falk stated that it agreed with the Cochrane review. The advertisement did not claim or imply differences in efficacy or safety.

Dr Falk recognised that mesalazine products were equally efficacious and safe but noted that the release mechanisms of the various products were different and so they were not considered interchangeable. Dr Falk explained that all mesalazine products were modified release, with the mesalazine being released at different locations within the gastrointestinal tract (pH dependant) due to the different coatings used. The British National Formulary stated that '… the delivery characteristics of oral mesalazine preparations may vary …' and this statement was used in an advertisement by Tillotts which demonstrated its awareness of this fact. In a review of available therapies, Taylor and Irving (2011) stated that 'In any event, swapping to a different formulation might be worth considering in people who are not responding to their current [mesalazine] therapy'. Therefore, whilst in general terms mesalazine products were equally efficacious and safe, patients responded differently depending on the location of disease and might find one product more beneficial than another. Dr Falk concluded that in the advertisement there was no contradiction of the Cochrane review, no statement or implication of superiority or new features and that it was justified to inform health professionals of the option of changing mesalazine rather than moving up to immunosuppressants or biologics.

Dr Falk denied any breach of Clauses 7.2, 7.3, 7.4, 7.10 and 8.1.

Dr Falk noted Tillotts' submission that the claim that Salofalk granules came in a sachet and could be taken once daily for a simpler routine 'appeared to be an exaggeration'. However, it was a statement of fact as the granules did come in a sachet and were taken once daily. There was no claim that Salofalk granules were different to, or better than, any other mesalazine. Dr Falk also noted the allegation that the claim that the granules had a tasty vanilla flavour did not meet high standards. Again, this was a statement of fact, it was not a superlative. Dr Falk considered the statement to be standard English, not in poor taste and that it did not fail to meet the high standards expected.

Dr Falk denied any breach of Clauses 7.2, 7.3, 7.4, 7.10, 8.1 and 9.1.

Dr Falk further noted the allegation that the claim that granules reached the distal colon implied that the granules had an advantage, but Tillotts also admitted that the statement was true, as shown by the reference to Leifeld *et al*. Dr Falk submitted that no comparison was made and there was no claim of superiority and that the language of the factual statement did not fall below the standards expected.

Dr Falk noted that Tillotts discussed the scope of Leifeld *et al* which showed that Salofalk Granules reached the distal region as the study used Salofalk Granules and Salofalk tablets and concluded, 'This pooled analysis supports the hypothesis that mesalazine granules are superior to mesalazine tablets in induction of remission in distal colitis and should be taken once daily' (emphasis added). Consequently, the advertisement correctly stated that Salofalk Granules reached the distal region. It was irrelevant what product Leifeld *et al* compared Salofalk Granules against as the fact remained that Salofalk Granules were shown to reach the distal area as claimed. Other scintigraphic studies confirmed this (Brunner *et al* 2003). The advertisement did not make comparisons with any other product, there was no claim of superiority nor could this be read into the claim. Tillotts then discussed duration of treatment. The advertisement did not mention or allude to duration of treatment; the complaint on this point was therefore not relevant. Dr Falk denied any breach of Clauses 7.2, 7.3, 7.4, 7.10, 8.1 and 9.1.

Dr Falk trusted that, in commenting that the medical director of Dr Falk Pharma UK Ltd was a co-author on Aldulaimi *et al* (2016a), Tillotts had not suggested that the integrity of any author had been compromised but it found it difficult to otherwise understand the point to that comment as the Code did not prevent declared, transparent, authorship. With regard to what 'Optimisation with Salofalk Granules' meant, Dr Falk noted that optimisation was not a new concept and was explained within the referenced paper.

Finally, Dr Falk noted that Tillotts had commented that there was no mention of the products involved in Aldulaimi *et al* (2016a) but in that regard Tillotts had referred to an incorrect reference. The correct reference, which included the data alleged to be missing was Aldulaimi *et al* (2016b). Dr Falk submitted that it was not relevant what mesalazine treatment patients in the study received; standard, validated, assessment methods were used to identify any patients that were inadequately maintained and those patients were offered an alternative treatment. It was not necessary to identify products on which patients were not adequately maintained and no such comparisons were made. Dr Falk did not accept the logic of Tillotts' comment that meant the properties of Salofalk Granules had been exaggerated. The claims in the advertisement were as described by Aldulaimi *et al* (2016b) and represented the outcome from the study, which was an extension to a previous study which was the only quality, innovation, productivity and prevention (QIPP) approved project in lower gastrointestinal disease (Palin 2014). The properties of Salofalk granules had not been exaggerated. The reference provided the necessary detail to support the claims.

Dr Falk denied any breach of Clauses 7.2, 7.3, 7.4, 7.10 and 8.1.

In conclusion, Dr Falk stated that no proof of the complaint had been given and in that regard Tillotts had only alleged that the advertisement might breach Clauses 7.2, 7.3, 7.4, 7.10, 8.1 and 9.1 amongst others. Dr Falk considered that this was not sufficient to prove the complaints and that it had not breached the Code.

PANEL RULING

The Panel noted the headline claim 'An oral ulcerative colitis treatment that's a step change, not a step up' followed in more prominent font by 'Now that's progress' and Tillotts' allegation that 'step change' implied new features and superiority over other mesalazine products and other ulcerative colitis treatments which could not be substantiated. Beneath a picture of a granule sachet followed three paragraphs in a much smaller typeface. The first paragraph stated 'When mesalazine doesn't seem to be working, stepping up to immunosuppressants might not be the only option'. Followed by 'For those patients who could benefit from a simpler routine, Salofalk Granules come in a convenient little sachet, only need to be taken once a day and even have a tasty vanilla flavour' and finally 'Oh, and if the inflammation is in the distal colon, the granules are pretty good at getting there too'.

The Panel noted Dr Falk's submission that the advertisement did not claim or imply differences in efficacy or safety and that whilst in general terms mesalazine products were equally efficacious and safe, patients responded differently depending on the location of the disease and might find one product more beneficial than another. A review of available therapies, Taylor and Irving, noted that there did not appear to be any difference in efficacy between the various formulations of oral 5-ASA and stated that 'In any event, swapping to a different formulation might be worth considering in people who are not responding to their current [5-aminosalicylate] therapy'. The authors further noted that if once daily dosing offered any clinical advantage it probably related to improved adherence. The Cochrane review, Wang *et al*, a meta-analysis noted that there were no differences in efficacy between once daily and conventional dosing for the induction of remission. The authors noted that adherence did not appear to be enhanced by once daily dosing in the clinical trial setting. It was unknown whether adherence was enhanced by once daily dosing in a community based setting. The Panel noted Tillotts' comment that once daily dosing was not unusual in the mesalazine market.

The Panel noted that Taylor and Irving stated that tolerance was rarely a problem with mesalazines, except for sulfasalazine in patients who could not tolerate it and changing to a different mesalazine normally enabled successful treatment. It went on to state that remarkably little evidence supported swapping between 5-aminosalicylates to improve efficacy. The trials reviewed suggested that 5-aminosalicylate dose escalation might be worthwhile in some patients with ulcerative

colitis. Unfortunately, 5-aminosalicylate therapy was often dismissed before maximal doses were reached. A further trial suggested that increasing the duration of therapy might avoid the need to switch to corticosteroids or immunosuppressive drugs. Conversely, a subgroup analysis of data from the ASCEND trials suggested that extending the duration of treatment was worth considering in patients with mild ulcerative colitis, whereas treatment escalation should not be delayed in those with active, severe disease.

The Panel noted Dr Falk's submission that it was 'justified to inform health professionals of the option of changing mesalazine rather than moving up to immunosuppressants or biologics' but considered that the claim in question went beyond this. The Panel noted that 'step change' was defined as a significant change in policy especially one that results in an improvement or increase (on-line English Oxford dictionary). The Panel considered that by describing Salofalk Granules as a 'step change' followed by the prominent claim 'Now that's progress' some readers might assume, not unreasonably, that Salofalk Granules represented a significant and progressive change in the treatment of ulcerative colitis compared to other available mesalazine medicines and that was not so. In addition the Panel noted that the qualification 'When mesalazine doesn't seem to be working, stepping up to immunosuppressants might not be the only option' appeared in a separate paragraph and in much smaller white font beneath the depiction of a sachet and bold headline claims. In the Panel's view it would not be immediately obvious that this separate paragraph beneath was meant to qualify the claims above. It also misleadingly implied that changing to Salofalk Granules was the only option to avoid stepping up to immunosuppressants which was not so. The Panel considered that the description of Salofalk Granules as a 'step change' within the claim 'An ulcerative colitis treatment that's a step change, not a step up. Now that's progress' was misleading and ruled a breach of Clauses 7.2 and 7.3. The Panel considered that the claim in question exaggerated the effects of Salofalk Granules and could not be substantiated. A breach of Clauses 7.4 and 7.10 was ruled.

The Panel noted Tillott's allegation that as the granule format and once daily posology were not unusual in the mesalazine market the claim 'For those patients who could benefit from a simpler routine, Salofalk Granules come in a convenient little sachet, only need to be taken once a day and even have a tasty vanilla flavour' exaggerated the properties of Salofalk Granules. The Panel noted Dr Falk's submission that the claim related solely to Salofalk Granules, it was not comparative and was a statement of fact. The Panel noted that 'simpler' was a comparative term and referred to dosing regimens other than once daily. However in the Panel's view the claim in question did not state or imply that Salofalk Granules were the only mesalazine product that could be taken once daily as alleged. It merely presented Salofalk Granules as an option to consider for those patients who would benefit from a simpler once daily routine. The Panel did not consider that the claim was exaggerated as alleged. No breach of Clause 7.10 was ruled.

The Panel disagreed with Tillotts' concern that the language used in the statement, including the phrase 'even have a tasty vanilla flavour', was not in keeping with the high standards expected of a pharmaceutical company or the health professionals to whom the advertisement was directed. The Panel noted that the advertisement adopted a conversational style, indeed the headline claims were in quotation marks. This was not unacceptable *per se* so long as the content otherwise complied with the Code. The Panel noted that Tillotts had not explained why it considered high standards had not been maintained. Tillotts bore the burden of proof in this regard and had provided no evidence to demonstrate that in using such language Dr Falk had failed to maintain high standards. No breach of Clause 9.1 was ruled in that regard.

The Panel disagreed with Tillotts' view that the claim '... if the inflammation is in the distal colon, the granules are pretty good at getting there too' implied that Salofalk Granules had an advantage in this area compared with other mesalazine products. The Panel noted that the reference cited to support this claim (Leifeld *et al*, 2011) was a pooled analysis in which Salofalk Granules were compared with Salofalk tablets in induction therapy. Whilst the study concluded that its analysis supported the hypothesis that mesalazine granules were superior to mesalazine tablets in the induction of remission in distal colitis, the Panel did not consider that the claim at issue was an express or implied comparison. There was no implication that other mesalazine products did not deliver medicine to the distal colon or that Salofalk Granules otherwise had an advantage in this area as alleged. The Panel therefore ruled no breach of Clause 7.3. Leifeld *et al* stated that the favourable effects of mesalazine granules in distal colitis were plausible and consistent with the galenical properties of this formulation, since the extended release system allowed more 5-ASA to reach the distal parts of the colon. The Panel considered that the claim could be substantiated and ruled no breach of Clause 7.4. Further the Panel did not consider that the claim exaggerated the properties of Salofalk Granules on this point as alleged and ruled no breach of Clause 7.10.

The Panel noted the allegation that the language used in the claim 'the granules are pretty good at getting there too' was neither clear in its description of the product's properties, nor in keeping with the high standards expected of a pharmaceutical company. The Panel considered that its comments above in relation to the phrase 'tasty vanilla flavour' and its conversational style were relevant here. The Panel also noted its comments above in relation to Leifeld *et al* and rulings of no breach of Clauses 7.3, 7.4 and 7.10 in relation to the claim in question. The Panel had some concerns about the phrase 'pretty

good' but on balance considered that Tillotts had not provided evidence to demonstrate that in using such language Dr Falk had failed to maintain high standards. The Panel therefore ruled no breach of Clause 9.1.

In relation to the claim 'Optimisation with Salofalk Granules for patients inadequately maintained on previous mesalazine resulted in: 69% fewer days off work, 87% fewer hospital visits due to [ulcerative colitis] flare up, 45% fewer GP visits due to [ulcerative colitis] flare ups, 50% fewer steroid courses used', Tillotts alleged that what it considered to be the reference, Aldulaimi *et al* (2016a), did not support the claim as it did not explain what optimisation with Salofalk Granules meant, nor whether the patients involved in the study were previously treated with mesalazine tablets, granules, rectal preparations or brands of mesalazine from other manufacturers. The Panel noted Dr Falk's submission that Tillotts had referred to an incorrect reference Aldulaimi *et al* (2016a); the correct reference, which did include some additional data was Aldulaimi *et al* (2016b). The Panel noted that the correct reference (DRF16/057) was cited on the advertisement in question. The Panel noted the narrow nature of the allegation. The Panel noted that Aldulaimi *et al* (2016b) stated that patients were previously treated with mesalazine therapies: Asacol, Pentasa, Mezavant, Octasa and Salofalk. Dosing frequencies were provided. The Panel did not consider that the claim in question was incapable of substantiation on the narrow ground alleged. Details of previous therapies were provided. No breach of Clause 7.4 was ruled.

In relation to the term 'optimisation' the Panel noted that contrary to Dr Falk's submission it was not defined in either study. The only reference to the term was in the introduction to Aldulaimi *et al* (b) which stated 'We have previously reported that optimising oral mesalazine maintenance therapy improved patient and disease outcomes in primary care.' The reference for the previous report was not cited. There was no further reference to the term. Dr Falk had provided a copy of Quality and Productivity:Proven Case Study – A pharmacist-led ulcerative colitis review service: Improving medicines adherence in general practice (Palin). This appeared to be the case study referred to in Aldulaimi *et al* (b) and examined cost reduction and improvements in patient care by improvement of adherence to therapy and patient education. The word 'optimisation' and its derivatives were not referred to although there was a general reference to dosing frequency in relation to improving adherence and outcomes. The Panel noted the definition of optimisation was 'the act of making the best of something; the state or condition of being optimal' (The New Shorter Oxford English Dictionary). The Panel noted that the aim of Aldulaimi *et al* (a and b) was to evaluate the effect of changing to once daily Salofalk Granules in patients inadequately controlled on their current mesalazine therapy. Few details were given in either Aldulaimi *et al* (a and b) including details of dosages used. The Panel noted that a once daily dose was licensed for treatment of acute episodes of ulcerative colitis. The licensed dosing frequency for maintenance of remission was three times daily although in certain patients the dosing schedule for Salofalk Granules could be adapted to a single daily dose. The title of Aldulaimi *et al* (a and b) referred to maintenance therapy. The position regarding dosage was unclear. The Panel considered that some readers might assume that optimisation meant more than a straightforward switch to a once daily dose. Others might interpret it as a description of the outcomes achieved and described in the claim in relation to days off work etc. The Panel noted that optimisation was however referred to in the Taylor and Irving review which was not cited in the advertisement in relation to the claim in question: optimisation of conventional therapy of patients with irritable bowel disease included patient-related factors (adherence and acceptability of treatment) and medicine-related factors (formulation, dose and drug related factors) which could be adjusted to enable successful treatment. The Panel noted the very narrow nature of the allegation: that the reference did not explain what optimisation meant and therefore did not support the claims made. The Panel noted that this matter was further complicated as the complainant did not have Aldulaimi *et al* (b) when it made the complaint. Tillotts bore the burden of proof. Whilst the Panel had concerns about the claim and data these were not the subject of complaint. The Panel considered that Tillotts had not established that the failure of the study to define optimisation meant that the claim was not capable of substantiation and on the narrow ground alleged ruled no breach of Clause 7.4.

In relation to the allegation that the reference appeared to exaggerate the properties of Salofalk Granules, Tillotts mentioned its failure to detail patients' previous therapies and failure to define optimisation. The Panel noted its rulings above in this regard. The Panel noted it would not rule on the study *per se* but whether given the study the claim was exaggerated for the reasons cited. The Panel noted its comments above about the burden of proof. The Panel noted that at the outset of the study patients were assessed in relation to disease activity (Walmsley Index), use of steroids, days off work, GP and hospital visits. A subgroup of patients were switched to Salofalk Granules once daily maintenance therapy and all patients were reviewed 6 months later. Patient and disease outcomes were compared between those who switched to Salofalk Granules and those retained on their current mesalazine treatment. The Panel noted that Aldulaimi *et al* (2016a) as provided by Tillotts' stated that patients changing to Salofalk Granules had a higher baseline disease activity Walmsley Index (2.78 vs 1.99 $p<0.01$) vs those who remained on their mesalazine treatment. The Panel noted that disease activity Walmsley Index was 2.78 vs 1.97 in Aldulaimi *et al* (2016b) as provided by Dr Falk. Neither Tillotts nor Dr Falk commented on this or the effect if any this might have on the change from baseline of this index and other reported outcomes.

The Panel noted that Tillotts had the burden of proving its complaint on the balance of probabilities; the matter would be judged on the evidence provided by the parties. The Panel did not consider

that Tillott's had proven that because the reference did not explain what optimisation with Salofalk granules meant or state the previous therapies that the claim 'Optimisation with Salofalk Granules for patients inadequately maintained on previous mesalazine resulted in: 69% fewer days off work, 87% fewer hospital visits due to [ulcerative colitis] flare up, 45% fewer GP visits due to [ulcerative colitis] flare ups, 50% fewer steroid courses used' exaggerated the properties of Salofalk granules as alleged. The correct reference provided by Dr Falk, Aldulaimi *et al* (2016b) did include some additional data. Based on the very narrow allegation, the Panel ruled no breach of Clause 7.10.

The Panel did not consider that Tillotts had established that Dr Falk had disparaged other manufacturers' mesalazine products as alleged. The Panel thus ruled no breach of Clause 8.1.

Complaint received **18 April 2017**

Case completed **17 August 2017**