CASE AUTH/2706/3/14

WARNER CHILCOTT/DIRECTOR v TILLOTTS

Alleged breach of undertaking

Warner Chilcott UK alleged that an Octasa (mesalazine, modified release (MR)) detail aid produced by Tillotts Pharma UK breached the undertaking given in Case AUTH/2610/6/13. Warner Chilcott marketed Asacol (mesalazine, modified release).

Warner Chilcott noted that in the previous case, Case AUTH/2610/6/13, a supplement produced by Tillotts was ruled in breach of the Code for, *inter alia*, the inclusion of a comparison of the dissolution profiles of Mesren and Asacol. The comparison was made in a section entitled 'Are there any significant differences between Asacol MR and Octasa MR?'; Octasa MR was a rebranded version of Mesren MR. The section contained a graph which demonstrated that the dissolution characteristics of Mesren MR and Asacol MR were very similar. Although the first sentence of the section at issue stated that there had been no clinical comparison of Asacol MR and Octasa MR, the Panel considered that most readers would read the rest of the section and assume that because the in vitro dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to show that this was so. The Panel considered that the supplement was misleading in breach of the Code.

Turning to the detail aid now at issue, page 5 contained a graph which depicted the same dissolution profile of Asacol 400mg MR, Octasa 400mg MR and a reformulated Octasa 400mg MR (which contained the excipient triethyl citrate rather than dibutyl phthalate). The title of this section was 'Comparing Octasa 400mg MR and UK Asacol 400mg MR: Dissolution profiles'. The graph demonstrated that the dissolution profiles for all three were very similar. Warner Chilcott alleged that, similar to the previous case, despite the acknowledgement of absence of clinical data, the reader would assume that, because the dissolution characteristics of Octasa and Asacol were similar, the clinical effects of the two would also be similar. This impression was compounded by the statement immediately below the graph, 'Octasa 400mg MR with triethyl citrate has a comparable mesalazine release profile to Asacol 400mg MR'. There was no data to support a clinical equivalence comparison and Warner Chilcott alleged that this was misleading and contrary to the undertaking given in Case AUTH/2610/6/13. Warner Chilcott also alleged that the breach of undertaking amounted to a breach of Clause 2.

The detailed response from Tillotts is given below.

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/2610/6/13, concerned, *inter alia*, a comparison of the dissolution profiles of Mesren MR and Asacol MR in a journal supplement. During its consideration of that case, the Panel had noted that the section of the supplement entitled 'Are there any significant differences between Asacol MR and Octasa MR?' clearly stated that 'Octasa MR has not been compared directly in a clinical study with Asacol MR'. The Panel considered that most readers would read the rest of the section and assume, even in the acknowledged absence of clinical data, that because the in vitro dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to show that this was so. The Panel considered that the supplement was misleading and a breach of the Code was ruled.

The present case, Case AUTH/2706/3/14, concerned a page headed 'Comparing Octasa 400mg MR and UK Asacol 400mg MR: Dissolution profiles'. The first bullet point included a statement that a new excipient, triethyl citrate, had no effect on the dissolution profile. This was referenced to data on file. Beneath this was a graph which showed that the *in vitro* dissolution profiles of Octasa 400mg MR with triethyl citrate, Octasa 400mg MR with dibutyl phthalate and Asacol 400mg MR, were closely similar. A bullet point below noted that 'Octasa 400mg MR with triethyl citrate had a comparable mesalazine release profile to Asacol 400mg MR. Both products were resistant to dissolution at pH 6.4 and dissolved promptly at pH 7.2'. The final bullet point stated 'There are no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR UK formulation'. The Panel noted Tillotts's submission that its market research supported its submission that the graph and text compared *in vitro* testing and made no clinical claim. The Panel noted that one key issue was whether even if readers were clear that the data derived from *in vitro* testing, the presentation of the data was such that, on the balance of probabilities, readers would assume that the results were, nonetheless, relevant to the clinical situation.

The Panel noted that the previous page stated that Octasa 400mg MR was a branded generic version of Asacol 400mg MR. Turning to the page at issue, the Panel noted that the only reference to 'in vitro dissolution profiles' appeared in a small typeface in the heading to the graph; the heading referred only to 'Dissolution profiles'. The Panel considered the reference to *in vitro* dissolution profiles was not sufficiently prominent to qualify the primary impression of the page; that there was clinical data to support the comparison. The fourth bullet

point which stated there were no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR was insufficient, either alone or in combination with the heading to the graph, was not sufficiently prominent. Further, it was ambiguous as some readers might assume that there were indirect clinical comparisons of Octasa 400mg MR and Asacol 400mg MR and this was not so. The Panel considered that page 5 invited readers to compare the dissolution profiles of Octasa 400mg MR and Asacol 400mg MR and implied that the data presented was directly relevant to the clinical situation. There was no clinical data to support such an implication and the page was therefore misleading. A breach was ruled.

The Panel noted that whilst there were some similarities between the material presently at issue and that considered in Case AUTH/2610/6/13 there were differences in relation to the nature, content and context of the material. That previously considered was a journal supplement which had been used with health professionals involved in medicines budget management. The dissolution data were referred to in a section headed 'Are there any significant differences between Asacol MR and Octasa MR?'. The material presently at issue was a detail aid which, *inter alia,* discussed the use of a new excipient in Octasa 400mg MR, including its effect on the dissolution profile. On balance, the Panel did not consider that the detail aid was in breach of the undertaking previously given and ruled no breach including Clause 2.

Warner Chilcott UK Ltd alleged that an Octasa (mesalazine, modified release (MR)) detail aid (ref UK/OC/0002/0114) produced by Tillotts Pharma UK Limited breached the undertaking given in Case AUTH/2610/6/13. Warner Chilcott marketed Asacol (mesalazine, modified release).

COMPLAINT

Warner Chilcott noted that in the previous case, Case AUTH/2610/6/13, a supplement produced by Tillotts was ruled in breach of the Code for, *inter alia*, the inclusion of a comparison of the dissolution profiles of Mesren and Asacol. The comparison was made in a section entitled 'Are there any significant differences between Asacol MR and Octasa MR?'; Octasa MR was a rebranded version of Mesren MR. The section focused on *in vitro* data and the Panel noted that the supplementary information to Clause 7.2 stated that care should be taken with the use of *in vitro* data and the like so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The section contained a graph which demonstrated that the dissolution characteristics of Mesren MR and Asacol MR were very similar. Although the first sentence of the section at issue stated that there had been no clinical comparison of Asacol MR and Octasa MR, the Panel considered that most readers would read the rest of the section and assume that because the *in vitro* dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to show that this was so. The Panel considered that the supplement was misleading in that regard and a breach of Clause 7.2 was ruled.

Turning to the detail aid now at issue, page 5 contained a graph which depicted the same dissolution profile of Asacol 400mg MR, Octasa 400mg MR and a reformulated Octasa 400mg MR (which contained the excipient triethyl citrate rather than dibutyl phthalate). The title of this section was 'Comparing Octasa 400mg MR and UK Asacol 400mg MR: Dissolution profiles'. The graph demonstrated that the dissolution profiles for all three were very similar. As in the previous case, there was a statement under the graph that there were no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR UK formulation. Warner Chilcott alleged that, similar to the previous case, despite the acknowledgement of absence of clinical data, the reader would assume that, because the dissolution characteristics of Octasa and Asacol were similar, the clinical effects of the two would also be similar. This impression was compounded by the statement immediately below the graph, 'Octasa 400mg MR with triethyl citrate has a comparable mesalazine release profile to Asacol 400mg MR'. There was no data to support a clinical equivalence comparison and Warner Chilcott alleged that this was misleading, in breach of Clause 7.2 and was contrary to the undertaking given in Case AUTH/2610/6/13, in breach of Clause 26. Given that an undertaking to the Authority was an important document and it was very important for the reputation of the industry that companies complied with undertakings; Warner Chilcott alleged a breach of Clause 2.

RESPONSE

Tillotts noted that Paragraph 2.2 of the Constitution and Procedure stated that a complainant had the burden of proving their complaint on the balance of probabilities. Tillotts stated that Warner Chilcott did not come close to doing so in this case; the complaint was both spurious and speculative.

Tillotts stated that more broadly, the foundation of the complaint was that it was alleged that it was misleading to use *in vitro* data to make pharmacological claims about Asacol; in the absence of supporting clinical data, and that the use of *in vitro* data in this way breached the Code. This position was clearly unsustainable and alone showed that the complaint was ill founded.

Tillotts submitted that such an interpretation of the Code would prohibit manufacturers of generic medicines from making fully justified and clearly explained pharmacological claims about their medicines on the basis of *in vitro* data, without first carrying out clinical trials to support the claims. To be able to properly market their products, this would require manufacturers to expend significant financial and other resources on completely unnecessary clinical trials, trials which were not required by the Medicines and Healthcare Products Regulatory Agency (MHRA) as part of the licensing process. The additional costs would inevitably lead to price rises at great expense to consumers and to the taxpayer. It would, in essence, completely undermine the

benefits of generic medicines in the UK market. Tillotts submitted that this could not be the intention of the Code, which was aimed at preventing misleading advertising.

While this unsustainable position was the foundation of the complaint, it was not the complaint's underlying purpose. The complaint had been brought solely for commercial purposes as part of an on-going strategy by Warner Chilcott to inhibit and disrupt the activities of Tillotts; a much smaller competitor, which was successfully increasing its share of a market which Mesren was leading.

Tillotts stated that it treated compliance with the Code seriously in all respects, as was shown by the extensive precautions (detailed below) which it took to ensure that the detail aid was fully compliant before publication. It had given careful and detailed consideration to the allegations. However, Tillotts noted that the Authority was being asked to uphold the complaint solely to damage Tillotts' reputation and market share as part of a commercial strategy. The Authority should consider the complaint in its true context and not be misled into thinking that the complaint had been made to uphold the principles embodied in the Code.

Tillotts submitted that each allegation was without foundation and strongly contested the complaint, for the following reasons:

a The detail aid used *in vitro* data to make a pharmacological comparison between two medicines, in a particular and relevant context and with sufficient clarification to ensure that the reader did not assume that any clinical claim was being made. A health professional would not be misled by this use of data and there had been no breach of Clause 7.2.

b Tillotts had taken the undertaking very seriously and had taken all steps to comply with it. Since there had been no breach of Clause 7.2, there had been no breach of the undertaking. But, in any case, the complaint did not relate to a similar breach such that a breach of Clause 7.2 in this case would be a breach of the undertaking.

c There had been no conduct which merited the allegation of a breach of Clause 2. Tillotts had acted only in accordance with best practice in pre-vetting materials to ensure Code compliance.

Tillotts set out its comments in further detail below.

With regard to Clause 7.2, Tillotts submitted that the detail aid was not misleading and the reader would not assume that because the dissolution characteristics of Octasa and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. Page 4 of the detail aid noted that Octasa 400mg MR was a branded generic version of Asacol (mesalazine) 400mg MR. It set out the respective excipients of Octasa and Asacol and noted that the two had comparable excipients (with the exception of triethyl citrate in Octasa and dibutyl phthalate in Asacol). The detail aid set out the rationale for the change in excipient.

Page 5 of the detail aid set out the effect of the change in excipient on the dissolution profiles of Octasa and Asacol. It would immediately be clear to a health professional that page 5 made no statement regarding clinical effects or clinical equivalence. Tillotts noted the following points in relation to page 5:

a Health professionals reviewing the detail aid would be aware of the impracticality of testing dissolution in vivo due to the number of variables (colon pH varied according to the individual, food the individual had consumed, the individual's stress levels etc) and hence the pharmaceutical industry's consequent reliance on *in vitro* testing for dissolution profiles.

b The heading expressly and clearly stated that it was the dissolution profiles of Octasa and Asacol which were being compared. Terminology such as 'Formulation/dissolution profiles' was used. Readers, based on this use of pharmacological terminology and their appreciation of the testing of dissolution profiles, would be clear from the outset that the content of the page related to *in vitro* testing.

c The main feature on the page was a graph showing *in vitro* dissolution profiles – it was clear that this graph depicted the testing on which all of the conclusions on page 5 were based. It was expressly and clearly stated above the graph that the data was *in vitro* data.

d The page made two points. Firstly, that the substitution of dibutyl phthalate with triethyl citrate in Octasa 400mg MR had no effect on the dissolution profiles; and (consequently) and secondly, that Octasa 400mg MR with triethyl citrate had a comparable mesalazine release profile to Asacol 400mg MR. Contrary to the complaint, it was clear to readers that these two points were taken directly from the *in vitro* data displayed on the graph.

e Further, it was expressly noted in body copy, in font the same size and with no less prominence than the other key points made (and, again, clear to the readers), that there were no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR. This ensured that readers could not form the impression that the detail aid made a clinical comparison between the two medicines.

The detail aid presented *in vitro* data and the conclusions which were readily apparent from that data to make a pharmacological comparison between Octasa and Asacol (in light of the different excipient). The *in vitro* data was not used to make any clinical claim. No express clinical claim was made and the detail aid gave sufficient context and clarification to ensure that readers did not assume that any such claim was made by implication. Consequently no clinical comparison was made.

Tillotts noted the allegation that readers, when presented with dissolution characteristics of Octasa and Asacol would assume that the clinical effects

of Octasa and Asacol would be similar. This was without foundation. In order for readers to assume this, they would need to: ignore the title of page 5, which set out what the purpose of the content was, ignore the broader context of the piece and their wider knowledge and expertise, ignore the prominent text which served to eliminate any possibility of doubt, and assume that the inclusion of similar dissolution profiles must have much broader significance (in absence of any such statement or suggestion in the detail aid).

Tillotts submitted that the intended audience would clearly not be misled by the detail aid in this way. In this context, it should be remembered that readers of the detail aid were clinicians; experienced health professionals with a good understanding of medicines and of the use and purpose of clinical and *in vitro* data. In this regard Tillotts noted that market research testing with health professionals conclusively demonstrated that they would not be misled by the *in vitro* data. The market testing concluded that health professionals would not consider that the detail aid made a clinical claim.

Tillotts submitted that the detail aid was developed in full knowledge of the supplementary information to Clause 7.2 which stated that *in vitro* data should only be extrapolated to the clinical situation where there was data to show that it was of direct relevance and significance. This was shown by the specific wording of the detail aid and by the steps Tillotts took when developing it. The detail aid made no claim that the *in vitro* data was of broader clinical significance, but simply stated the conclusions which could be drawn directly from the dissolution profile graph about the pharmacological similarities between Octasa and Asacol. Tillotts submitted that the detail aid did not extrapolate *in vitro* data to the clinical situation and noted that the Panel had previously considered advertisements where *in vitro* data was referred to and used to make claims relating to the clinical situation. This was not the case with the detail aid, which referred to a formulation change and appropriately presented the dissolution profiles and the pharmacological similarities between the two medicines by reference to their profiles. The title on page 5 clearly stated that any claims related to dissolution profiles (and not to the clinical situation).

Tillotts submitted that it was a misinterpretation of the Code to state, as Warner Chilcott had done, that the mere inclusion of *in vitro* data relating to the pharmacological properties of a medicine must (by implication) mean that such data was being '[extrapolated]... to the clinical situation'.

Tillotts submitted that even if the inclusion of *in vitro* data relating to the pharmacological properties of a medicine necessarily meant it was being extrapolated to the clinical situation, in this case there was ample data to show that the dissolution profiles were of direct relevance and significance. In particular:

a Octasa MR was a branded generic version of Asacol MR. The similarity of the two had been fully accepted by the MHRA and Tillotts had not been required to carry out clinical trials in relation to Octasa MR. For this reason, it was unnecessary for promotional materials to make a clinical comparison between the two medicines as to their clinical effect generally.

b The two medicines had comparable excipients, with the exception of triethyl citrate in Octasa vs dibutyl phthalate in Asacol. Dibutyl phthalate was also previously used in Octasa. The change was important because these excipients were plasticising agents which affected the integrity of the coating of the medicine. The change could legitimately lead to the question of whether the dissolution profile was different and the delivery of the medicine would be affected.

c No clinical trial had been undertaken to compare Octasa MR and Asacol MR and the impact of the change in excipient (and this was clearly stated in the detail aid). Such a trial would be highly expensive and time intensive and the MHRA had not required such a trial to be undertaken.

d However, the *in vitro* dissolution profiles of Octasa MR and Asacol MR could be readily compared and could show whether the change in excipient led to a change in pharmacological properties in this regard.

e Since it was impractical to measure dissolution profiles *in vivo*, the use of *in vitro* dissolution profiles was accepted across the industry. Indeed, the MHRA required such data to be made available as part of the market authorization process, which provided the clearest possible indication of its relevance.

f The *in vitro* data in this case showed that the change had no effect on the dissolution profiles.

g The *in vitro* data had clearly addressed any concerns which the MHRA might have had in this regard since it had authorised Octasa on the basis of *in vitro* dissolution profiles. Clearly, the MHRA considered *in vitro* dissolution profiles to be of direct relevance and significance.

Tillotts submitted that for these reasons, the detail aid complied with the supplementary information to Clause 7.2.

Tillotts submitted that Warner Chilcott's interpretation of Clause 7.2 was that the use of any *in vitro* data to make a pharmacological comparison of two medicines was prohibited, in the absence of clinical data which supported it. This was clearly incorrect because the supplementary information to Clause 7.2 expressly envisaged *in vitro* data being used in certain situations and did not require it to be supported by clinical data and the purpose of Clause 7.2 was to prevent misleading advertising and the use of *in vitro* data in this context, not to indiscriminately prevent its use.

Tillotts noted that the manufacturers of generic medicines were not required to carry out clinical trials to obtain marketing authorisations. However, the implication of the complaint was such that

generics manufacturers would not be able to make pharmacological claims about their medicines in promotional materials based on *in vitro* data as this would breach the Code, even if the material did not mislead. Such manufacturers would then, effectively, be required to conduct clinical trials in order to make pharmacological claims about their medicines. To be able to properly market their products, manufacturers would be obliged to carry out completely unnecessary clinical trials, at considerable expense, leading to an inevitable increase in the prices of such generic medicines and potentially making the model economically unviable. This would ultimately compromise the value (and potentially the availability) of generic medicines, at significant expense to the consumer and to the taxpayer with a potentially highly significant impact on competition in the marketplace. Tillotts submitted that the Code could not possibly be intended to have such an effect.

Tillotts noted that Clause 26 provided that a company must ensure that it complied with an undertaking given in relation to a ruling under the Code. The undertaking stated that Tillotts would 'take all possible steps to avoid similar breaches of the Code occurring in the future'. Tillotts submitted that it had taken the undertaking very seriously and would continue to do so.

For the reasons set out above, the detail aid did not breach Clause 7.2 and so Tillotts submitted that there had been no breach of the undertaking. In any event, the breach alleged here was not a similar breach to that found in Case AUTH/2610/6/13. The presentation and purpose of *in vitro* data in the detail aid, which compared a changed excipient, was different to the material previously considered by the Panel. In Case AUTH/2610/6/13, the Panel made its ruling having considered a section of the supplement entitled 'Are there any significant differences between Asacol MR and Octasa MR'. The Panel considered that, in this context, the use of dissolution profiles would mislead readers. In contrast, the detail aid clearly stated that the data was being used to compare dissolution profiles, rather than to make any broader comparison. The detail aid clearly stated that Octasa MR was a branded generic version of Asacol MR with comparable excipients, with the exception of triethyl citrate used in Octasa. The dissolution profiles were then set out in this context. This was not the case with the supplement considered in Case AUTH/2610/6/13. The Panel's ruling in Case AUTH/2610/6/13 made no suggestion that, merely by including *in vitro* data to make a pharmacological comparison without supporting clinical data, material would breach the Code. Tillotts submitted that it could not have been reasonably expected to assume that this was the impact of the Panel's ruling, such that inclusion of data in future material would lead to a 'similar' breach.

Tillotts stated that it had taken considerable steps to avoid similar breaches (and these were set out further below).

Tillotts noted the wording of Clause 2 and its supplementary information and stated that for the reasons set out above, it had not breached the undertaking and so no circumstances arose which merited an alleged breach of Clause 2 and the allegation was without foundation. Tillotts had provided readers of the detail aid with relevant and significant information to explain the purpose and effect of a different excipient in Octasa vs that used in Asacol. It could not be said that this discredited or reduced confidence in the pharmaceutical industry.

Tillotts also noted that it had taken extensive precautions to ensure compliance with the Code and the undertaking. The company was particularly concerned by this complaint and noted that it appeared to be nothing but an attempt to tarnish its reputation.

Tillotts stated that it took the following steps to ensure compliance with the undertaking:

a In October 2013, before the detail aid was finalised, Tillotts raised the concept of its proposed promotional materials in a meeting with the MHRA. The MHRA representatives fully supported Tillotts setting out positive reasons about why it had changed an excipient in Octasa from that used in Asacol, even in the absence of clinical data comparing the two medicines.

b Tillotts appointed an independent market research agency to test its proposal to include *in vitro* data in promotional materials for Octasa (as used in the detail aid). The purpose of the market testing was to confirm what conclusions health professionals would draw from the materials, including to confirm whether the use of *in vitro* data could be seen as being misleading. The market testing was carried out with 16 health professionals, whose responses confirmed that they had fully understood that the graph and text comparing dissolution profiles resulted from *in vitro* testing and made no clinical claim.

c Throughout the development of the current promotional materials (including the detail aid), the draft materials were challenged against the Code, the ruling in Case AUTH/2610/6/13 and the undertaking and a number of changes were made to ensure compliance.

d Tillotts appointed an additional external consultant, to review materials and provide advice on compliance with the Code, throughout the development of the current promotional materials (including the detail aid). Both the consultant and Tillotts' medical signatory, had considerable experience in working with and ensuring compliance with the Code.

Tillotts stated that in developing the detail aid, it used Zinc. This was an industry standard online review tool, which enabled Tillotts' compliance specialists to add comments to the documents. Even before being uploaded to Zinc, the draft detail aid was initially given consideration with regard to compliance with the undertaking and it went through a number of iterations. The draft detail aid was uploaded to Zinc in December 2013. It was subsequently interrogated for compliance with the

Code by both Tillotts' medical signatory and its external consultant and went through a number of iterations; both interrogated the detail aid in full knowledge of the ruling in Case AUTH/2610/6/13 and the undertaking (and particular terms contained within it). They both approved the detail aid as being compliant with the Code and the undertaking.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/2610/6/13, concerned, *inter alia*, a comparison of the dissolution profiles of Mesren MR and Asacol MR in a journal supplement published in the British Journal of Clinical Pharmacy. During its consideration of that case, the Panel had noted that the section of the supplement entitled 'Are there any significant differences between Asacol MR and Octasa MR?' clearly stated that 'Octasa MR has not been compared directly in a clinical study with Asacol MR'. The relevant section reported that Fadda and Basit (2005) had shown that Mesren and Asacol had similar dissolution profiles and that a more recent study carried out by Tillotts showed very little difference in the dissolution profiles of the two products. The Panel noted that the section at issue focussed on *in vitro* dissolution data. The supplementary information to Clause 7.2 stated that care should be taken with the use of *in vitro* data and the like so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The Panel noted that the first sentence of the section at issue stated that there had been no clinical comparison of Asacol MR and Octasa MR. The Panel further considered that most readers would read the rest of the section and assume, even in the acknowledged absence of clinical data, that because the *in vitro* dissolution characteristics of Mesren and Asacol were similar, the clinical effects of Octasa MR and Asacol MR would also be similar. There was no clinical data to show that this was so. The Panel considered that the supplement was misleading in this regard. A breach of Clause 7.2 was ruled.

The present case, Case AUTH/2706/3/14, concerned page 5 of a detail aid. The page was headed 'Comparing Octasa 400mg MR and UK Asacol 400mg MR: Dissolution profiles'. The first bullet point included a statement that a new excipient, triethyl citrate, had no effect on the dissolution profile. This was referenced to data on file. Beneath this was a graph which showed that the *in vitro* dissolution profiles of Octasa 400mg MR with triethyl citrate, Octasa 400mg MR with dibutyl phthalate and Asacol 400mg MR, were closely similar. A bullet point below noted that 'Octasa 400mg MR with triethyl citrate had a comparable mesalazine release profile to Asacol 400mg MR. Both products were resistant to dissolution at pH 6.4 and dissolved promptly at pH 7.2'. The final bullet point stated 'There are no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR UK formulation'. The Panel noted Tillotts's submission that its market research supported its submission that the graph and text compared *in vitro* testing and made no clinical claim. The market research had not been provided and therefore the Panel did not know either the questions asked nor the material examined. The Panel noted that one key issue was whether even if readers were clear that the data derived from *in vitro* testing, the presentation of the data was such that, on the balance of probabilities, readers would assume that the results were, nonetheless, relevant to the clinical situation.

The Panel examined the context of the material on the page and the impression given to readers. The Panel noted that page 4 of the detail aid stated that Octasa 400mg MR was a branded generic version of Asacol 400mg MR. Turning to the page at issue, the Panel noted that the only reference to '*in vitro* dissolution profiles' appeared in a small typeface in the heading to the graph; the heading to page 5 referred only to 'Dissolution profiles'. The Panel considered the reference to *in vitro* dissolution profiles was not sufficiently prominent to qualify the primary impression of the page; that there was clinical data to support the comparison. The fourth bullet point which stated there were no direct clinical comparisons of Octasa 400mg MR and Asacol 400mg MR was insufficient, either alone or in combination with the heading to the graph. It was not sufficiently prominent to ensure readers were aware of the position. Further, it was ambiguous as some readers might assume that there were indirect clinical comparisons of Octasa 400mg MR and Asacol 400mg MR and this was not so. The Panel considered that page 5 invited readers to compare the dissolution profiles of Octasa 400mg MR and Asacol 400mg MR and implied that the data presented was directly relevant to the clinical situation. There was no clinical data to support such an implication and the page was therefore misleading. A breach of Clause 7.2 was ruled.

The Panel noted that whilst there were some similarities between the material presently at issue and that considered in Case AUTH/2610/6/13 there were differences in relation to the nature, content and context of the material. That previously considered was a journal supplement which had been used with health professionals involved in medicines budget management. The dissolution data were referred to in a section headed 'Are there any significant differences between Asacol MR and Octasa MR?'. The material presently at issue was a detail aid which, *inter alia*, discussed the use of a new excipient in Octasa 400mg MR, including its effect on the dissolution profile. On balance, the Panel did not consider that the detail aid was in breach of the undertaking previously given and ruled no breach of Clause 26 and consequently no breach of Clause 2.

Complaint received **25 March 2014**

Case completed **9 June 2014**