CASE AUTH/1862/7/06

PROSTRAKAN/DIRECTOR v SHIRE

Breach of undertaking

ProStrakan complained that promotional materials for Calcichew-D_3 Forte (calcium carbonate and colecalciferol) issued by Shire were in breach of the undertaking and assurance given in Case AUTH/1825/4/06. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

In Case AUTH/1825/4/06 the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 was preferred over Adcal-D_3 by 80% of patients', which was referenced to Rees and Howe (2001), was ruled to be misleading in breach of the Code. The resultant form of undertaking and assurance, signed on 5 June, indicated that the claim had last been used on 6 April.

ProStrakan alleged however, that the claim at issue was continuing to be used in a journal advertisement, an advertisement on exhibition panels and a leavepiece.

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 future. It was very important for the reputation of the industry that companies complied with undertakings.

The journal advertisement which had appeared in Pulse, 22 June, featured the claim 'She should appreciate a Ten Second chew of Calcichew-D_3 Forte. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients'.

The Panel considered that the advertisement was caught by the undertaking given in Case AUTH/1825/4/06 in that there was insufficient detail about why patients preferred Calcichew-D_3 Forte to Adcal-D_3. The undertaking in the previous case had been signed on 5 June. Due to lead times at the publishers, Shire was unable to cancel the booking. Shire had thus taken steps to comply with its undertaking; publication of the advertisement on 22 June was due to circumstances beyond its control. No breach of the Code was ruled.

An exhibition panel used at a meeting (25-28 June) featured the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients' below which was a brief description of the study by Rees and Howe and a list of the reasons as to why Calcichew-D_3 Forte was preferred (easier to chew/swallow and less chalky/gritty/sticky). Similarly, two leavepieces stated the reasons for preference. The Panel considered that these materials complied with the undertaking previously given and no breach of the Code was ruled which was upheld on appeal by ProStrakan.

With regard to a third leavepiece the Panel noted that although it contained the claim 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3' there was no indication as to why a preference had been expressed. The Panel noted that Shire was in the process of withdrawing the piece because of an unrelated claim. In the Panel's view, however, the leavepiece should have been withdrawn pursuant to the undertaking given in Case AUTH/1825/4/06. Shire had breached its undertaking and high standards had not been maintained and breaches of the Code were ruled. Inadequate action leading to a breach of undertaking was an activity likely to bring discredit to, and reduce confidence in, the industry. A breach of Clause 2 was ruled. These rulings were upheld on appeal by Shire.

ProStrakan Pharmaceuticals complained that promotional materials for Calcichew-D_3 Forte (calcium carbonate and colecalciferol) issued by Shire Pharmaceuticals Ltd were in breach of the undertaking and assurance given in Case AUTH/1825/4/06. The materials in question were a journal advertisement (ref 003/0471), a leavepiece (ref 003/0458) and exhibition panels from the National Osteoporosis Society Annual Meeting. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

In Case AUTH/1825/4/06 ProStrakan had alleged that the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 was preferred over Adcal-D_3 by 80% of patients', which was referenced to Rees and Howe (2001), was misleading. The Panel subsequently ruled the claim in breach of the Code as alleged. The resultant form of undertaking and assurance, signed on 5 June 2006, indicated that use of the claim would cease forthwith and that the advertisement in which it had appeared had last been used on 6 April 2006.

ProStrakan marketed Adcal-D_3 (calcium carbonate and colecalciferol). Both Calcichew-D_3 Forte and Adcal-D_3 were tablets for chewing.

COMPLAINT

ProStrakan noted that there were two instances where the claim at issue was continuing to be used: an advertisement in Pulse, 22 June 2006, where the lead time for this journal was nine days; National Osteoporosis Society Annual Meeting exhibition panels and a leavepiece (ref 003/0458) found on the stand and which was part of a series of leavepieces (ref 003/0446 and ref 003/0456).

ProStrakan alleged that its additional concern was the system of disregard of the Panel's ruling and the implied significant lack of process and oversight in Shire's internal procedures.

When writing to Shire the Authority asked it to respond in relation to Clauses 2, 9.1 and 22 of the Code.

RESPONSE

Shire strongly refuted the statement by ProStrakan alleging 'the system of disregard of the Panel's ruling and the implied significant lack of process and oversight in Shire's internal procedures'.

Shire submitted that prior to the ruling in Case AUTH/1825/4/06, following discussions with ProStrakan, it had withdrawn and modified the advertisements at issue on 31 March 2006. Further, following the Panel's ruling and Shire's undertaking of 5 June 2006, it promptly withdrew the modified advertisements from circulation. Due to print deadlines, publication of the withdrawn advertisements could not be effected immediately. Copies of letters from publishers dated 5 June onwards to confirm Shire's prompt action were provided. In particular a letter of 5 June referred to publication of the advertisement in the 22 June edition of Pulse. The advertisement was withdrawn from the 29 June edition. Shire therefore firmly denied that it was in breach of its undertaking.

Shire submitted that ProStrakan had written to it regarding the 22 June Pulse advertisement on 23 June but did not await Shire's response before complaining to the Authority. With regard to the Panel's ruling in Case AUTH/1825/4/06, Shire noted that the Panel had stated 'Both products had similar indications and although they [Calcichew-D_3 Forte and Adcal-D_3] had different constituents the Panel considered that it was not unreasonable to compare the two' and 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients' was misleading, in breach of Clauses 7.2 and 7.3 of the Code as it was not specified as to why there was a preference and it might imply that taste was the reason for 80% of the patients preferring Calcichew-D_3 Forte over Adcal-D_3.

Shire emphasised again that it had modified the above claim before the original complaint by ProStrakan to the Authority, by omitting the phrase 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise'. The offending material was withdrawn on 31 March 2006.

Shire submitted it had interpreted the qualification in the ruling as meaning that a comparison from this publication could be used, provided that the preferential advantages of Calcichew-D_3 Forte over Adcal-D_3 were clearly listed, thereby ensuring that the comparison would not be misleading.

Shire reviewed its materials and decided that the exhibition panel (ref 003/0442d) and leavepieces (refs 003/0446, 003/0456, 003/0457) were permissible and not misleading because they did not imply that taste was the reason why 80% of patients preferred Calcichew-D_3 Forte over Adcal-D_3. Preferential palatability advantages from Rees and Howe were clearly listed. Results from the one parameter measured (taste), which did not translate into 'good' or 'bad' on the opposite ends of the visual analogue scale (ie 'very sweet' or 'very bitter') and which did not show a significant difference between products, were not quoted.

Shire noted the exhibition panel carried the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients'. It did not include the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise', or similar, against which the Panel had ruled. Further, preferential palatability advantages from Rees and Howe were clearly listed. Nonetheless to avoid further altercations, Shire had promptly removed the exhibition panel at ProStrakan's request.

Shire noted that one copy of the leavepiece (ref 003/0458) was on at its stand. In Shire's regular review of materials this leavepiece was scheduled to be withdrawn as it contained the claim: 'Calcichew-D_3 Forte. Now in a new monthly pack'. As the pack would have been issued one calendar year in July 2006 Shire could no longer state that the pack size was new.

Shire submitted that this leavepiece was modified in April 2006 following Prostrakan's initial complaint to Shire. It was not intended to be used at the National Osteoporosis Society meeting as it was in the process of being withdrawn, for the reason given above. It contained the claim 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3' but had not qualified the reasons (various aspects of palatability) why there was a preference. It did not incorporate the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise', or similar, against which the Panel had ruled. Shire submitted that the claim did not imply that taste was the main reason for the preference – but rather that the overall impression from the respective chewable tablets was the reason for the preference. The detailed significant reasons for the preference were given in Rees and Howe.

Shire submitted that when the leavepiece was discovered on the stand and pointed out by ProStrakan it was removed immediately as it was clear that an error had occurred in it being sent to the meeting as current material. Shire accepted that this was an error on its part and that this leavepiece should not have been on the stand. Since the meeting Shire had ensured that its printers had destroyed all remaining copies of this leavepiece and that all members of the sales force had destroyed any copies that might have still been in circulation.

Shire noted that at the meeting ProStrakan had drawn its attention to the presence of this single leavepiece and was satisfied with its action stated above. ProStrakan had agreed not to take the matter further if Shire complied with its request – which it did. It was not necessary to refer this matter to the Authority.

Shire submitted that it was not in breach of Clauses 22, 9.1 or 2 and it had taken all steps to comply with the Panel's ruling.

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 future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the advertisement which had appeared in Pulse, 22 June, featured the claim 'She

should appreciate a Ten Second chew of Calcichew-D_3 Forte. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients'.

The Panel considered that the advertisement was caught by the undertaking given in Case AUTH/1825/4/06 in that, as with the claim previously at issue 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', there was insufficient detail about why patients preferred Calcichew-D_3 Forte to Adcal-D_3. The undertaking in the previous case had been signed on 5 June 2006; the advertisement at issue was published in Pulse on 22 June. A letter from the publishers, dated 5 June, showed that Shire had tried to cancel bookings for Calcichew advertisements in the June 8, 15 and 22 issues of Pulse but that this had not been possible. The publishers were able to cancel the booking for June 29. The Panel thus noted that Shire had taken steps to comply with its undertaking; publication of the advertisement on June 22 was due to the lead time at the publishers and thus beyond Shire's control. The Panel considered that Shire had complied with its undertaking and so no breach of Clauses 2, 9.1 and 22 was ruled.

The Panel noted that one of the exhibition panels used at the meeting of the National Osteoporosis Society (25-28 June 2006) featured the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients' below which was a brief description of the study by Rees and Howe and a list of the reasons as to why Calcichew-D_3 Forte was preferred (easier to chew/swallow and less chalky/gritty/sticky). Similarly, two of the leavepieces (refs 003/0446 and 003/0456) stated the reasons for preference. The Panel considered that these materials complied with the undertaking previously given and no breach of Clauses 2, 9.1 and 22 was ruled. The ruling of no breach of Clause 22 was appealed by ProStrakan.

With regard to a third leavepiece (ref 003/0458) the Panel noted that although it contained the claim 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3' there was no indication as to why a preference had been expressed. The Panel noted that Shire was in the process of withdrawing the piece because of the claim 'Now in a new monthly pack'. In the Panel's view, however, the leavepiece should have been withdrawn pursuant to the undertaking given in Case AUTH/1825/4/06. The leavepiece had been used almost three weeks after the undertaking had been signed. The Panel considered that Shire had thus breached its undertaking. A breach of Clause 22 was ruled. High standards had not been maintained and so a breach of Clause 9.1 was ruled. These rulings were appealed by Shire.

The Panel noted that the supplementary information to Clause 2 stated that inadequate action leading to a breach of undertaking was an activity likely to bring discredit to, and reduce confidence in, the industry. A breach of Clause 2 was ruled. This ruling was appealed by Shire.

APPEAL BY PROSTRAKAN

ProStrakan appealed the ruling of no breach of Clause 22 with regard to the material used at the National Osteoporosis Society meeting. ProStrakan alleged that Shire had not complied with the letter or the spirit of the ruling in Case AUTH/1825/4/06 and that the comparison between two products with different constituents and clearly identified differences in efficacy was unfair and misleading.

ProStrakan noted the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients' was supplemented with reasons why Calcichew-D_3 Forte was preferred (easier to chew/swallow and less chalky/gritty/sticky). This claim was used in exhibition panels and two leavepieces, 003/0446 and 003/0456. This claim was ruled not in breach of the Clauses 2, 9.1 and 22.

ProStrakan noted that the claim at issue in Case AUTH/1825/4/06 was 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', referenced to Rees and Howe. The amended claim did not comply with the previous ruling.

ProStrakan noted the original reason for complaint was that this comparison was unfair and misleading, as Adcal-D_3 had 250mg of calcium carbonate more per tablet than Calcichew-D_3 Forte and these products were being compared as equivalent. The implication of equivalence was especially misleading as the clinical efficacy data differences for the doses of elemental calcium were very different. This was clearly shown in Section 5.1 of the summaries of product characteristics (SPCs) of both products.

ProStrakan noted from the Adcal-D_3 SPC that there was strong evidence that supplemental calcium and vitamin D_3 could reduce the incidence of hip and other non-vertebral fractures. In a randomised, placebo controlled study, 3,270 patients treated with 1200mg elemental calcium and 800 IU vitamin D_3 daily, ie the same dose delivered by two tablets of Adcal-D_3, the number of hip fractures was 43% lower (p=0.043) and the total number of non-vertebral fractures was 32% lower than among those who received placebo. A positive effect on bone mineral density was also observed.

ProStrakan noted that the SPC for Calcichew-D_3 Forte contained the same data stating the important dose as 1200mg/day of elemental calcium. Calcichew-D_3 Forte was a chewable tablet containing 1250mg calcium carbonate (equivalent to 500mg of elemental calcium) plus 400 IU vitamin D_3 taken twice daily.

ProStrakan noted from the Adcal-D_3 SPC that it was a chewable tablet containing 1500mg calcium carbonate PhEur (equivalent to 600mg of elemental calcium) plus 400 IU colecalciferol (vitamin D_3).

ProStrakan submitted that it had provided a more detailed review of all the relevant data in its complaint in Case AUTH/1825/4/06. There were three elements of comment within the Panel's ruling:

- The Panel had considered that the patients' views on these other parameters (grittiness, chalkiness, taste (bitter or sweet), ease of chewing, ease of swallowing and stickiness of each product) had influenced their preference given that there was no

difference between the two as to perception of taste.

- The Panel was concerned that insufficient detail was given about what it was that patients preferred about treatment with Calcichew-D_3 Forte compared to treatment with Adcal-D_3. The claim implied that not only did patients prefer Calcichew-D_3 Forte to Adcal-D_3 but they also found it pleasant to take. There was no data in that regard.
- The Panel had disagreed with Shire's view that the data on efficacy evaluations and health economics were irrelevant to the current complaint which only dealt with the issue of patient preference. The Panel considered that in addition to palatability a patient's knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products might affect their preference for one or the other. Without such knowledge patients would be unable to express a genuine, well-informed preference.

ProStrakan submitted that the ruling identified the need to be more explicit about preference with regard to grittiness, chalkiness, etc, however, Rees and Howe did not provide the patient with any understanding and 'knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products', therefore, 'Without such knowledge patients would be unable to express a genuine, well-informed preference'. ProStrakan submitted the claim used to imply preference of Calcichew-D_3 Forte to Adcal-D_3 was therefore fundamentally flawed:

- The study compared products of significantly different doses.
- The doses had very different evidence-bases.
- There was no explanation to patients regarding the evidence-based differences therefore patients were unable to express a genuine, well-informed preference.

ProStrakan alleged that the continued use of the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients', was in breach of the original ruling and was still misleading and unfair with or without issues about grittiness, chalkiness etc added.

COMMENTS FROM SHIRE

Shire did not consider that the claims at issue were unfair or misleading. The revised claim used in the exhibition panel and related items strongly implied greater acceptability, with its elements clearly defined (ie ease of chewing, ease of swallowing, chalkiness, grittiness and stickiness) as the observed reasons for preference. Rees and Howe compared acceptability, with no reference to efficacy. Efficacy was not an issue in this claim for the reasons given above. Further, patients were very unlikely to be aware of any differences between products (if they existed) in efficacy for their chronic condition. In any event, the assertion by ProStrakan that treatment with Adcal-D_3 (600mg calcium plus 400 IU vitamin D_3) led to significantly greater efficacy than with Calcichew-D_3 Forte (500mg calcium plus 400 IU vitamin D_3) was inconsistent with overall published data on the relevant calcium/vitamin D medications. There were no published clinical data for Adcal-D_3 apart from Rees and Howe.

FURTHER COMMENTS FROM PROSTRAKAN

ProStrakan stated that it had consistently represented its arguments which established the initial case for the ruling of a breach of the Code in Case AUTH/1825/4/06. The activities and promotion of the study by Rees and Howe, continued to be unfair and misleading.

APPEAL BOARD RULING

The Appeal Board noted that the claims at issue were different to those considered in Case AUTH/1825/4/06 as the parameters used to measure patient preference were clearly stated; easier to chew/swallow and less chalky/gritty/sticky. The Appeal Board considered that these materials thus complied with the undertaking previously given and the Appeal Board upheld the Panel's ruling of no breach of Clauses 2, 9.1 and 22.

APPEAL BY SHIRE

Shire appealed the Panel's rulings of breaches of Clauses 2, 9.1 and 22 with regard to the leavepiece (ref 003/0458). Shire submitted that the leavepiece found at its stand at the meeting did not breach the undertaking because it was not similar to the advertisements ruled in breach by the Panel in Case AUTH/1825/4/06 because:

- The claim in the leavepiece was substantially shorter than that in the advertisement, with a significant amount of text having been removed which the Panel had ruled overall to be misleading. The leavepiece did not incorporate the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise', or similar, against which the Panel had ruled.
- This shortened claim in the leavepiece, 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3' was not misleading in its presented context.

Shire submitted that it followed from its reasons given above that high standards had been maintained and the leavepiece was therefore not in breach of Clause 9.1.

Shire noted that the leavepiece was scheduled to be withdrawn from use for a separate reason and should not have been on the exhibition stand.

Shire submitted that there was no breach of Clause 2, since its actions had not brought discredit on, or reduced confidence in, the pharmaceutical industry. In particular Shire took great care at the conference to minimise open confrontation with ProStrakan that might well have reduced confidence in the industry. There was ample evidence that Shire had endeavoured to comply throughout with the ruling in Case AUTH/1825/4/06.

Shire submitted that it was not in breach of Clauses 2, 9.1 or 22 and it had taken all steps to comply with the ruling.

COMMENTS FROM PROSTRAKAN

ProStrakan stated that the Panel's ruling in Case AUTH/1825/4/06 should be the basis of the appeal. The study and the claims arising from it were unfair and misleading.

ProStrakan noted three elements of comment within the ruling in Case AUTH/1825/4/06. The Panel had considered that the patients' view on these other parameters (grittiness, chalkiness, taste (bitter or sweet), ease of chewing, ease of swallowing and stickiness of each product) had influenced their preference given that there was no difference between the two as to perception of taste. The Panel was concerned that insufficient detail was given about what it was that patients preferred about treatment with Calcichew-D_3 Forte compared to treatment with Adcal-D_3. The claim implied that not only did patients prefer Calcichew-D_3 Forte to Adcal-D_3 but they also found it pleasant to take. There was no data in that regard. The Panel had disagreed with Shire's view that the data on efficacy evaluations and health economics were irrelevant to the current complaint which only dealt with the issue of patient preference. The Panel considered that in addition to palatability a patient's knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products might affect their preference for one or the other. Without such knowledge patients would be unable to express a genuine, well informed preference.

ProStrakan submitted that the ruling identified the need to be more explicit about preference with regard to grittiness, chalkiness etc, however Rees and Howe did not provide the patient with any understanding and 'knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products', therefore, 'without such knowledge patients would be unable to express a genuine, well informed preference'. ProStrakan alleged that the claim used to imply preference of Calcichew-D_3 Forte to Adcal-D_3 was therefore fundamentally flawed:

- The study compared products of significantly different doses.
- The doses had very different evidence-bases.
- There was no explanation to patients regarding the evidence-based differences therefore, patients were unable to express a genuine, well informed preference.

ProStrakan submitted that the continued use of the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients' was in breach of the original ruling and was still misleading and unfair with or without issues re grittiness, chalkiness etc added.

APPEAL BOARD RULING

The Appeal Board noted that the leavepiece at issue (ref 003/0458) featured the claim 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3'. There was, however, no indication as to why such a preference had been expressed.

The Appeal Board considered that the claim at issue was closely similar to that at issue in Case AUTH/1825/4/06 and thus the leavepiece should have been withdrawn pursuant to the undertaking given in that case. Shire had thus breached its undertaking and the Appeal Board upheld the Panel's ruling of a breach of Clause 22. High standards had not been maintained and the Appeal Board thus upheld the Panel's ruling of a breach of Clause 9.1. The appeal on these points was unsuccessful.

The Appeal Board noted that the supplementary information to Clause 2 stated that inadequate action leading to a breach of undertaking was an activity likely to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Appeal Board thus upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **29 June 2006**

Case completed **15 December 2006**