CASES AUTH/1951/2/07 to AUTH/1955/2/07

MEDIA/DIRECTOR v ASTRAZENECA

Insert on statins in The Pharmaceutical Journal

Five letters published in The Pharmaceutical Journal on 3 February criticised a twelve page supplement entitled 'The new NICE [National Institute for Health and Clinical Excellence] guidance on the use of statins in practice - Considerations for implementation' which had been distributed with the journal two weeks previously. The supplement, financially supported by AstraZeneca, had been written by a general practitioner and a pharmacist and it detailed the NICE guidance on the use of statins and charted the evolving guidance on statin use from 2000 until 2005. Optimization of statin treatment strategies was discussed as was the cost of implementing the NICE guidance across a primary care trust population. A cost effectiveness model was presented wherein either atorvastatin or rosuvastatin (AstraZeneca's product Crestor) was used when patients had failed to reach cholesterol targets on simvastatin (the medicine with the lowest acquisition cost). Finally the role of the pharmacist in helping to tackle cardiovascular disease was discussed.

In accordance with established procedure, the letters were taken up by the Director as complaints under the Code.

In Case AUTH/1951/2/07 the complainant stated that she found the inclusion of the AstraZeneca document masquerading as NICE guidance within The Pharmaceutical Journal profoundly depressing. When pharmacists and others were striving to improve the cost-effectiveness and evidence base of statin prescribing here was the pharmacists' own professional journal distributing a document which advocated JBS (Joint British Societies: British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; the Stroke Association) targets which were not national policy and were usually unachievable for the average patient, and the use of a statin [Crestor] for which there was no evidence to demonstrate that it saved lives or reduced cardiovascular events, and which was not even licensed as such.

The NHS statin of first choice for most patients was simvastatin based on a wealth of evidence, as detailed in the NICE guidance, and the targets to reach were those of the National Service Framework for coronary heart disease, affirmed by the cardiovascular disease 'tsar' in December 2006.

In Case AUTH/1952/2/07 the complainant stated that rather than being a useful publication covering the evidence base for the use of statins and practical issues on cost-effective implementation of national guidance, the supplement appeared to be a promotional brochure for Crestor.

The brochure appeared to support the JBS-2 lipid targets of 4 and 2mmol/L although these were not evidence based as recognised by the JBS itself in the statement 'There are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL-cholesterol targets in relation to clinical events' (JBS 2005).

The complainant stated that the Heart Protection Study had provided strong evidence that treating high-risk individuals with simvastatin 40mg/day for five years significantly reduced their chance of having a serious vascular event, irrespective of their lipid level (MRC/BHF Heart Protection Study 2002). The complainant noted that Crestor did not have this sort of patient-oriented evidence to support its use.

The complainant noted that the NICE guidance referred to in the supplement deemed it cost effective to extend access to statins on the NHS. Its cost-effectiveness analysis assumed that half of the prescriptions for statins would be simvastatin 20mg/day and half simvastatin 40mg/day. Arguably, more expensive statins would not be cost-effective and would waste scarce resources.

The complainant submitted that a policy of simvastatin 40mg/day for all those at high risk, irrespective of lipid level, was simple to implement, evidence based and cost effective.

The complainant stated that the bottom line was find the high risk patients, offer them simvastatin 40mg/day, strongly encourage them to take it, and do not worry too much about non-evidence based targets.

In Case AUTH/1953/2/07 the complainant stated that two points were of particular concern. The first was that the supplement, although purporting to be a summary of the NICE guidance, was in fact a marketing case for Crestor and argued heavily for lipid goals of 4 and 2mmol/L. Yet nowhere in the supplement was it stated that confirmed national health policy was for targets of 5 and 3mmol/L. The second was that AstraZeneca's own health economic data showed that if lipid goals of 4 and 2mmol/L were aimed for, nearly 40% of patients would require Crestor 40mg/day, a dose which, due to safety concerns, was restricted to specialist use only (Medicines and Healthcare products Regulatory Agency (MHRA) 2004).

The complainant queried if the requirements for specialist care had been factored into the economic analysis, never mind whether patients would actually want to use this therapy option if presented with the balanced data.

The complainant was concerned that distribution of the supplement via The Pharmaceutical Journal, might have lent it an air of credibility it did not deserve.

This complainant subsequently wrote separately to the Authority and noted that despite the title of the supplement 'The new NICE guidance on the use of statins in practice' the NICE technology appraisal it related to barely featured. Instead the supplement presented a health economic argument for using rosuvastatin (Crestor) in preference to atorvastatin (Lipitor) as it would be more cost effective. The case for lipid goals of 4 and 2mmol/L (as opposed to 5 and 3mmol/L) was heavily featured despite this not being discussed at all in the NICE appraisal. No mention was made that confirmed national health policy was for targets of 5 and 3mmol/L, which had been made absolutely clear by the Department of Health just weeks previously.

The complainant stated that in his view the supplement was essentially an advertisement for rosuvastatin, yet it did not contain appropriate prescribing information. Further despite the fact that the health economic case being strongly argued would end up with nearly 40% of the eligible population (or approximately 5% of the entire population) being treated with the 40mg dose, no mention was made of the MHRA warnings about this dose. Indeed, the supplement stated '… whether all currently marketed statins have a very similar low risk of serious adverse events. Based on the data thus far available, the answer is yes'. The complainant found this hard to reconcile with the MHRA advice and was concerned about the implications it could have for safe prescribing practice.

In Case AUTH/1954/2/07 the complainant was, *inter alia*, disappointed to see that the supplement was included with The Pharmaceutical Journal. Whilst industry supported documents were distributed with journals which relied heavily on advertising revenue, they were promotional and should be declared as such.

This complainant subsequently wrote separately to the Authority. The complainant stated that in his view the supplement was promotional and breached the Code in at least two areas:

- **It took the form of a discussion paper but made claims for the superior cost-effectiveness of rosuvastatin/simvastatin combinations compared to atrovastatin/simvastatin combinations. The evidence to support the claim was referenced as 'Data on File'. The insert was clearly promotional material but was not declared as such.**
- **Prescribing information on rosuvastatin was absent.**

In Case AUTH/1955/2/07 the complainant considered that the supplement was disguised promotion for Crestor, but no prescribing information was included.

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The supplement in question, sponsored/financially supported by AstraZeneca, had been initiated by the company and its communications agency had contacted the two authors. AstraZeneca was aware of the outline of the supplement and had, on request of one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The supplement was reviewed by AstraZeneca to ensure that it was factually correct. The two authors had full editorial control.

The Panel considered that AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Given the company's involvement and content, the Panel considered that the supplement was, in effect, promotional material for Crestor. The supplement should have included Crestor prescribing information. Given that allegations were made in that regard in Cases AUTH/1953/2/07 to AUTH/1955/2/07, breaches of the Code were ruled in those cases. The Panel considered that the supplement was disguised promotion; it appeared to be independently written which was not so, the authors had, in effect, been chosen by AstraZeneca. The statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. A breach of the Code was ruled in all five cases.

The Code required that material relating to medicines and their uses, whether promotional in nature or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company. The Panel concluded that although the phrase 'supported by AstraZeneca' did not give details about the company's role, AstraZeneca's support was clearly stated on the front cover of the supplement. No breach of the Code was ruled in all five cases.

The Panel considered that although the supplement was about the NICE guidance on the use of statins for the prevention of cardiovascular events, the document did not masquerade as NICE guidance as alleged in Case AUTH/1951/3/06. It was clear from the title on the front cover that the supplement discussed the implementation of the guidance. The Panel considered that the supplement was not misleading in that regard and no breach of the Code was ruled.

In its consideration of Cases AUTH/1951/2/07 and AUTH/1952/2/07 the Panel noted that the NICE guidance on statins recognised the body of evidence for reduction in cardiovascular morbidity and overall mortality associated with statin use across a broad spectrum of the population. It did not give targets for cholesterol levels, stating this was outside its remit. With respect to the choice of statin NICE recommended that therapy should usually be initiated with a medicine with a low acquisition cost (taking into account required daily dose and product price per dose). For many patients, the least expensive statin would be simvastatin. The supplement recognised this but put forward arguments for the use of rosuvastatin which was more expensive. By implication, therefore, the supplement advocated the use of rosuvastatin to reduce cardiovascular morbidity. Crestor, however, was not so licensed. Whereas simvastatin (Merck Sharp & Dohme's product, Zocor) was licensed for reduction of cardiovascular mortality and morbidity in certain patients, Crestor was only licensed for primary hypercholesterolaemia or homozygous familial hypercholesterolaemia. There would of course be benefits in lowering cholesterol but there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition. The differences between the licensed indications was not made clear. Thus the Panel considered that by implication the supplement was misleading as to the licensed indication of Crestor. A breach of the Code was ruled in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

The Panel noted in Case AUTH/1951/2/07 that it was stated on the supplement that the date of preparation was December 2006. In November 2006, the national director for heart disease and stroke had issued guidance confirming the current national policy on statin prescribing. This stated that national policy currently accepted 5mmol/L for total cholesterol and 3mmol/L for LDL cholesterol as targets for therapy as per the NSF for CHD and that the JBS-2 guidance was not national policy. This guidance had not been included in the supplement. The Panel noted AstraZeneca's submission that the supplement had been developed before the guidance was written. Nonetheless, the date of preparation of the supplement was a month after the November guidance was issued and the supplement was not distributed until 20 January 2007. Given the time frame involved the Panel considered that it was misleading to distribute the supplement which did not refer to important national guidance and was thus not up-to-date. A breach of the Code was ruled in Case AUTH/1951/2/07. A breach of the Code was similarly ruled in Case AUTH/1953/2/07.

With regard to the allegation in Cases AUTH/1951/2/06 and AUTH/1952/2/07 about unachievable JBS targets, the Panel noted that in the discussion on optimizing statin treatment strategies the supplement asked 'Are more challenging targets such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. In the section discussing the role of the pharmacist, however, readers were urged to 'pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L. A referral back to the GP possibly with a recommendation of change in statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate'. The supplement thus encouraged pharmacists to follow the JBS-2 guidance which was not national policy. In that regard the Panel considered that the supplement was misleading and a breach of the Code was ruled in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

In Case AUTH/1953/2/07 the Panel noted that a cost-effectiveness model was presented in the supplement which showed the budget impact results for patients failing to reach either a total cholesterol target of <5mmol/L or a total cholesterol target of <4mmol/L. Two tables of data detailed the financial implications of having to use atorvastatin or rosuvastatin as second line therapy to simvastatin (the least expensive statin). Both tables referred to rosuvastatin 40mg ie the maximum daily dose which, according to the Crestor summary of product characteristics (SPC), should be under the supervision of a specialist with patients requiring routine follow-up. Crestor appeared to be unique in this regard as specialist supervision was not required with the maximum daily dose of any of the other statins. This important condition on the use of rosuvastatin was not referred to anywhere in the supplement. The Crestor SPC referred to the increased reporting rate of adverse reactions with the 40mg dose compared to lower doses. The maximum dose of 40mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk who did not achieve their treatment goal on 20mg and in whom routine follow up would be performed. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Panel considered that the supplement was misleading and did not encourage the rational use of Crestor 40mg. Breaches of the Code were ruled on this point in Case AUTH/1953/2/07.

The Panel further noted in Case AUTH/1953/2/07 that two tables of cost-effectiveness data only accounted for the acquisition costs of the medicine. This was not entirely clear from the headings, 'Budget impact' and 'Treatment Strategy' and associated text which referred to 'cost-effectiveness', 'financial implications' and the need to look at other 'costs' associated with treatment', which implied more than simply acquisition costs. There was no account taken of the cost of specialist supervision and routine patient follow-up associated with the use of rosuvastatin 40mg which would have an impact on budget. The Panel considered that the data was thus misleading. A breach of the Code was ruled.

In Case AUTH/1954/2/07 the Panel noted that the cost-effectiveness data which showed the financial implications of using either atorvastatin or rosuvastatin as second line therapy in patients who had not reached lipid targets with simvastatin, was referenced to AstraZeneca data on file. The Panel considered that it was not necessarily unacceptable to cite data on file in promotional material. The supplement was thus not misleading in that regard. No breach of the Code was ruled.

Overall the Panel considered that AstraZeneca's failure to recognise that the supplement was, in effect, promotional material for Crestor, meant that high standards had not been maintained. A breach of the Code was ruled in all five cases. The Panel was concerned that the supplement, contrary to national guidance had encouraged pharmacists to follow JBS-2 cholesterol targets. The Panel was further very concerned that although the 40mg dose of rosuvastatin had been referred to in the supplement, there was no reference to the specialist supervision and routine patient follow-up needed with such a dose. The Panel considered that the omission of such information might prejudice patient care. The Panel considered that in these two matters, one or both of which had been raised in Cases AUTH/1951/2/07, AUTH/1952/2/07 and AUTH/1953/2/07, the supplement had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled in these cases. As these matters were not raised in Cases AUTH/1954/2/07 or AUTH/1955/2/07, no breach of Clause 2 was ruled in these cases on the basis of the allegations made.

Upon appeal, the Appeal Board accepted that the views expressed in the material were those genuinely held by the authors. The Appeal Board, however, was called upon to consider the merits of the piece in the context of AstraZeneca's involvement in the generation and production of it. Independent authors were at liberty to publish their views: however, when a pharmaceutical company became involved in such an activity it potentially became subject to the Code.

The Appeal Board noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Appeal Board noted the material in question had been sponsored/financially supported by AstraZeneca. AstraZeneca had paid the authors to write it and The Pharmaceutical Journal to distribute it. In that regard the material was a paid for insert from AstraZeneca; not a supplement sponsored by The Pharmaceutical Journal for which the editor would have been responsible. The insert had been initiated by AstraZeneca and its communications agency following an AstraZeneca statin advisory board meeting organised by AstraZeneca attended by the two authors who were subsequently asked to write the insert. AstraZeneca was aware of the outline of the material and had, when asked to do so by one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The material was reviewed by AstraZeneca to ensure that it was factually correct. The Appeal Board noted from the AstraZeneca representatives that on review of the insert AstraZeneca had suggested the inclusion of a table of budget impact results for a total cholesterol target of <5mmol/L to balance the <4mmol/L results already included, this was accepted by the authors. The Appeal Board noted that although two authors had full editorial control, AstraZeneca took the final decision about whether to publish or not.

The Appeal Board considered that AstraZeneca was inextricably linked to the production of the insert. There was no arm's length arrangement between the provision of the sponsorship and the generation of the material. Given the company's involvement and content, the Appeal Board considered that the material was, in effect, promotional material for Crestor. The Appeal Board considered that it was disguised promotion in that the material appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The Appeal Board upheld the Panel's ruling of a breach of the Code in all five cases.

In Cases AUTH/1953/2/07 to AUTH/1955/3/06 the Appeal Board noted its ruling above and as such considered that the material should have included the prescribing information for Crestor which it did not. The Appeal Board upheld the Panel's rulings of a breach of the Code in all three cases. The appeal on this point was unsuccessful.

The Appeal Board noted that the material stated that the NICE guidance on statins recognised the body of evidence for reduction in cardiovascular morbidity and overall mortality associated with statin use across a broad spectrum of the population. It did not give targets for cholesterol levels, stating this was outside its remit. With respect to the choice of statin NICE recommended that therapy should usually be initiated with a medicine with a low acquisition cost (taking into account required daily dose and product price per dose). For many patients, the least expensive statin would be simvastatin. The Appeal Board noted that the material recognised that simvastatin should be used first-line but put forward arguments for the use of rosuvastatin which was more expensive without stating that it was not licensed to reduce cardiovascular mortality and morbidity. The Appeal Board considered that without a statement to the contrary, the material, by implication, advocated the use of rosuvastatin to

reduce cardiovascular morbidity. Simvastatin was licensed for reduction of cardiovascular mortality and morbidity in certain patients. The Appeal Board considered that the material was misleading as to the licensed indication of Crestor. In this regard the Appeal Board upheld the Panel's rulings of breaches of the Code in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

The Appeal Board noted that the material set out the evolving guidance on statin use. It also noted the timeframe regarding the writing, production and publication of the material. The Appeal Board considered that the timings were such that the statement issued by the national director for heart disease and stroke should have been referred to. By not referring to this important national statement the material was misleading and not up-to-date. The Appeal Board upheld the Panel's ruling of a breach of the Code in Cases AUTH/1951/2/07 and AUTH/1953/2/07 in this regard.

With regard to the allegation in Cases AUTH/1951/2/07 and AUTH/1952/2/07 about unachievable JBS targets, the Appeal Board noted that in the discussion on optimizing statin treatment strategies the supplement asked 'Are more challenging targets such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. In the section discussing the role of the pharmacist, however, readers were urged to 'pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L. A referral back to the GP possibly with a recommendation of change in statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate'. The Appeal Board noted that not only did the material encourage pharmacists to follow the JBS-2 guidance, which was not national policy, it did not advise them that the JBS-2 targets were for high risk patients. From the statement in the material it appeared that the JBS-2 targets should be the aim for all patients which was not so. The Appeal Board considered that the material was misleading in this regard and upheld the Panel's ruling of a breach of the Code in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

The Appeal Board noted, in Case AUTH/1953/3/06, that a cost-effectiveness model was presented in the insert which showed the budget impact results for patients failing to reach either a total cholesterol target of <5mmol/L or a total cholesterol target of <4mmol/L. Two tables detailed the financial implications of having to use atorvastatin or rosuvastatin as second line therapy to simvastatin (the least expensive statin). Both tables referred to rosuvastatin 40mg ie the maximum daily dose. According to the Crestor SPC, in the light of increased reporting rate of adverse reactions with the 40mg dose compared to lower doses a final titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who did not achieve their treatment goal on 20mg and in whom routine follow-up would be preformed. Specialist supervision was recommended when the 40mg dose was initiated. Section 4.4 of the SPC stated that an assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg. Crestor appeared to be different as specialist supervision was not required with the maximum daily dose of any of the other statins. This important condition on the use of rosuvastatin was not referred to anywhere in the insert. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Appeal Board considered that the material was misleading and did not encourage the rational use of Crestor 40mg. The Appeal Board upheld the Panel's rulings of breaches of the Code in this regard in Case AUTH/1953/2/07.

The Appeal Board further noted that the cost-effectiveness data presented in Tables 3 and 4 only accounted for the acquisition costs of the medicine. This was not entirely clear from the headings, 'Budget impact' and 'Treatment Strategy' and associated text which referred to 'cost-effectiveness', 'financial implications' and the need to look at other 'costs' associated with treatment, which implied more than simply acquisition costs. There was no account taken of the cost of specialist supervision and routine patient follow-up associated with the use of rosuvastatin 40mg which would have an impact on budget. The Appeal Board considered that the data was thus misleading. The Appeal Board upheld the Panel's ruling of a breach of the Code in this regard in Case AUTH/1953/2/07.

Overall, in all five cases, the Appeal Board considered that AstraZeneca's failure to recognise that the material was, in effect, promotional material for Crestor, meant that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of the Code in all cases.
The Appeal Board was concerned that the material, contrary to national guidance had encouraged pharmacists to follow JBS-2 cholesterol targets.
The Appeal Board was further very concerned that although the 40mg dose of rosuvastatin had been referred to in the insert, there was no reference to the specialist supervision and routine patient follow-up needed with such a dose. The Appeal Board considered that the omission of such information might prejudice patient care. The Appeal Board considered that in these two matters, the material had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2 in Cases AUTH/1951/2/07 to AUTH/1953/2/07.

Five letters published in The Pharmaceutical Journal, 3 February 2007, criticised a twelve page supplement (ref

P10573) sponsored by AstraZeneca UK Limited. The supplement had been distributed with The Pharmaceutical Journal, 20 January.

The supplement was entitled 'The new NICE [National Institute for Health and Clinical Excellence] guidance on the use of statins in practice - Considerations for implementation' and had been written by a general practitioner and a pharmacist. The supplement detailed the NICE guidance on the use of statins and charted the evolving guidance on statin use from 2000 until 2005. Optimization of statin treatment strategies was discussed as was the cost of implementing the NICE guidance across a primary care trust population. A cost effectiveness model was presented wherein either atorvastatin or rosuvastatin (AstraZeneca's product Crestor) was used when patients had failed to reach cholesterol targets on simvastatin (the medicine with the lowest acquisition cost). Finally the role of the pharmacist in helping to tackle cardiovascular disease was discussed.

The supplement was financially supported by AstraZeneca as acknowledged by the statement 'Supported by AstraZeneca' on the front cover.

In accordance with established procedure, the matters were taken up by the Director as complaints under the Code.

Case AUTH/1951/2/07

COMPLAINT

In a letter from a pharmacist, headed 'Profoundly depressing', the complainant stated that she found the inclusion of the AstraZeneca document masquerading as NICE guidance within The Pharmaceutical Journal profoundly depressing. This was a time when hard working pharmacists and pharmacy technicians were striving to improve the cost-effectiveness and evidence base of statin prescribing through change programmes and advice to patients and prescribers, saving millions of pounds of NHS money to be channelled into other services.

Yet here was the pharmacists' own professional journal distributing a document which advocated JBS (Joint British Societies: British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; the Stroke Association) targets which were not national policy and were usually unachievable for the average patient, and the use of a statin [Crestor] for which there was no evidence to demonstrate that it saved lives or reduced cardiovascular events, and which was not even licensed as such.

The NHS statin of first choice for most patients was simvastatin based on a wealth of evidence well known to all who read the detail of the actual NICE guidance, and the targets to reach were those of the National Service Framework for coronary heart disease, affirmed by the cardiovascular disease 'tsar' in December 2006.

When writing to AstraZeneca, the Authority asked it to respond in relation to the requirements of Clauses 2, 7.2, 7.4, 9.1, 9.10 and 10.1 of the Code.

Case AUTH/1952/2/07

COMPLAINT

In a letter headed 'Concerns over "promotional brochure"', the complainant stated that rather than being a useful publication covering the evidence base for the use of statins and practical issues on cost-effective implementation of national guidance, the supplement appeared to be nothing more than a promotional brochure for Crestor.

The complainant stated that the brochure appeared to support the JBS-2 lipid targets of 4 and 2mmol/L. The complainant noted that these targets were not evidence based as recognised by the JBS itself in the statement 'There are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL-cholesterol targets in relation to clinical events' (JBS 2005). The vast majority of statin trials used fixed doses and were not chasing any particular lipid level.

The complainant stated that the Heart Protection Study had provided strong evidence that treating high-risk individuals (coronary heart disease, cardiovascular disease, peripheral arterial disease, diabetics over 40 years of age) with simvastatin 40mg/day for five years significantly reduced their chance of having a serious vascular event, irrespective of their lipid level (MRC/BHF Heart Protection Study 2002). The complainant noted that Crestor did not have this sort of patient-oriented evidence to support its use. It was patient-oriented evidence that mattered.

The complainant noted that the NICE guidance referred to in the supplement deemed it cost effective to extend access to statins on the NHS. Its cost-effectiveness analysis assumed that half of the prescriptions for statins would be simvastatin 20mg/day and half simvastatin 40mg/day. Arguably, more expensive statins would not be cost-effective and would waste scarce resources.

The complainant submitted that a policy of simvastatin 40mg/day for all those at high risk, irrespective of lipid level, was simple to implement, evidence based and cost effective.

The complainant stated that the bottom line was find the high risk patients, offer them simvastatin 40mg/day, strongly encourage them to take it, and do not worry too much about non-evidence based targets.

When writing to AstraZeneca, the Authority asked it to respond in relation to the requirements of Clauses 2, 7.2, 7.4, 9.1, 9.10 and 10.1.

Case AUTH/1953/2/07

COMPLAINT

In a letter headed 'Perturbed by Journal's distribution of AstraZeneca document', the complainant referred to elements of the supplement which he considered could be tackled at length, but stated that two points were of particular concern.

The first was that the supplement, although purporting to be a summary of the NICE guidance, was in fact a marketing case for Crestor and argued heavily for lipid goals of 4 and 2mmol/L. Yet nowhere in the supplement was it stated that confirmed national health policy was for targets of 5 and 3mmol/L, in simple terms (Boyle 2006). In this way the supplement undermined the NHS approach to managing this important risk factor.

The second concern was that AstraZeneca's own health economic data showed that if lipid goals of 4 and 2mmol/L were aimed for, nearly 40% of patients would require Crestor 40mg/day, a dose restricted to specialist use only due to safety concerns (Medicines and Healthcare products Regulatory Agency (MHRA) 2004).

The complainant queried if the requirements for specialist care had been factored into the economic analysis, never mind whether patients would actually want to use this therapy option if presented with the balanced data.

The complainant was concerned that distribution of the supplement via The Pharmaceutical Journal might have lent it an air of credibility it did not deserve.

Following publication of his letter in The Pharmaceutical Journal, the complainant wrote separately to the Authority. The complainant noted that despite the title of the supplement 'The new NICE guidance on the use of statins in practice' the NICE technology appraisal it related to barely featured. Instead the supplement presented a health economic argument for using rosuvastatin (Crestor) in preference to atorvastatin (Lipitor) as it would be more cost effective. The case for lipid goals of 4 and 2mmol/L (as opposed to 5 and 3mmol/L) was heavily featured despite this not being discussed at all in the NICE appraisal. No mention was made that confirmed national health policy was for targets of 5 and 3mmol/L, which had been made absolutely clear by the Department of Health just weeks previously.

The complainant stated that in his view the supplement was essentially a detailed advertisement for rosuvastatin, yet it did not contain appropriate prescribing information. Further despite the fact that the health economic case being strongly argued would end up with nearly 40% of the eligible population (or approximately 5% of the entire population) being treated with the 40mg dose, no mention was made of the MHRA warnings about this dose. Indeed, the supplement stated '… whether all currently marketed statins have a very similar low risk of serious adverse events. Based on the data thus far available, the answer is yes'. The complainant found this hard to reconcile with the MHRA advice and was concerned about the implications it could have for safe prescribing practice.

When writing to AstraZeneca, the Authority asked it to respond to the matters raised in the published letter in relation to Clauses 2, 7.2, 7.4, 9.1, 9.10 and 10.. When writing to the company about the complainant's additional comments, the Authority asked it to respond in relation to Clauses 4.1, 7.2, 7.4 and 7.10.

Case AUTH/1954/2/07

COMPLAINT

In a letter headed 'Disappointed', the complainant was, inter alia, disappointed to see that the pharmaceutical industry-supported supplement was included with The Pharmaceutical Journal. Whilst such documents were encountered not infrequently with journals which relied heavily on advertising revenue, such advertorials were entirely promotional and should be declared as such. Should readers contest the validity of the supplement's conclusions, as the complainant thought they should, would The Pharmaceutical Journal take editorial responsibility for its content?

Following publication of his letter in The Pharmaceutical Journal, this complainant wrote separately to the Authority. The complainant stated that in his view the supplement was promotional and breached the Code in at least two areas:

- It took the form of a discussion paper but made claims for the superior cost-effectiveness of rosuvastatin/simvastatin combinations compared to atrovastatin/simvastatin combinations. The evidence to support the claim was referenced as 'Data on File'. The insert was clearly promotional material but was not declared as such.
- Prescribing information on rosuvastatin was absent.

When writing to AstraZeneca, the Authority asked it to respond to the matters raised in the published letter in relation to Clauses 2, 9.1, 9.10 and 10.1. When writing to the company about the complainant's additional comments, the Authority asked it to respond in relation to Clauses 4.1, 7.2 and 7.4.

Case AUTH/1955/2/07

COMPLAINT

In a letter headed 'Where is the guidance for advertisers?', the complainant stated that she was a strong advocate of evidence-based medicine and had a strong sense of professional integrity. However, she was disappointed by the standards set by The Pharmaceutical Journal when it distributed the supplement in question.

The complainant considered that the supplement was disguised promotion for Crestor, but no prescribing

information was included as required. The complainant queried how the professional journal for pharmacy allowed this sort of material to be sent out and compared the extensive advice to advertisers issued by the BMJ with the little or no guidance offered by The Pharmaceutical Journal. The complainant, inter alia, asked when would The Pharmaceutical Journal require authors and contributors to declare competing interests? And how did the journal ensure fair and independent reporting on conferences when authors had been funded to attend by a pharmaceutical company.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 4.1, 9.1, 9.10 and 10.1.

Cases AUTH/1951/2/07 to AUTH/1955/07

RESPONSE

AstraZeneca explained that the supplement was developed in 2006. AstraZeneca was told that the supplement would be published in January 2007 but this information was sent to an employee who was off at the time, therefore the company only knew that the supplement had been distributed when it was raised in discussion between a pharmacist and a member of the medical team. As well as the letters published in The Pharmaceutical Journal the editorial board responded in a leading article entitled, 'We call this free speech' which clearly presented its views on the nature and purpose of the article.

In addition, the authors' responses to the readers' comments were published in The Pharmaceutical Journal, 10 February. The journal had not invited AstraZeneca to comment.

During its regular discussions with health professionals, AstraZeneca became aware that they were unclear as to how the recommendations published in the NICE Statin Technology Appraisal in early 2006 should be implemented, taking into consideration seemingly conflicting advice from different sets of guidelines.

The initiation of the supplement arose out of awareness of this issue. AstraZeneca's agency asked if The Pharmaceutical Journal would be interested in such an educational discussion article and when the journal confirmed that it was, the agency contacted two of the health professionals who had previously identified the issue and were interested to co-develop an outline for the article. AstraZeneca was aware of the outline and the health professionals' input to this. These health professionals were well-respected, independent medical authors who frequently contributed articles to the medical press. The two authors wrote the article themselves and had full editorial control. One of the authors requested the cost-effectiveness tables and information from AstraZeneca's data on file and the content was reviewed by her. As required by the Code, AstraZeneca reviewed the document to ensure that it was factually correct and did not contravene the Code or the relevant statutory requirements. Other than this, the authors had full editorial control of the supplement and the views expressed therein. Prior to publication, The Pharmaceutical Journal editorial team reviewed the supplement to ensure it met editorial standards. The supplement had not been distributed by other means.

AstraZeneca noted that in Case AUTH/1951/2/07, the complainant had alleged that the supplement was 'masquerading' as NICE guidance. AstraZeneca noted that the supplement did not present itself as an official NICE document. No Department of Health (DoH), or NICE logos appeared anywhere on the article. The appropriate declaration of sponsorship from AstraZeneca, as required by the Code, was on the front cover. AstraZeneca considered that the title of the document, 'The new NICE guidance on the use of statins in practice - Considerations for implementation', made it clear that this was a review of issues and considerations surrounding the NICE guidance rather than any official document from the institute itself. AstraZeneca therefore denied a breach of Clause 10.1.

In relation to Case AUTH/1951/2/07 with regard to the JBS targets, AstraZeneca submitted that the authors had presented the NICE recommendation in the context of all the available guidelines, as well as indicating how guidelines' target recommendations had changed over time. Indeed in relation to the second edition of the JBS guidelines (JBS-2) the authors wrote, 'Are more challenging targets, such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. The targets available from all existing guidelines were included in a balanced way and represented in a factually accurate manner.

AstraZeneca noted that in Case AUTH/1951/2/07, the complainant had stated that the supplement advocated 'use of a statin for which there was no evidence to demonstrate that it saved lives or reduced cardiovascular events and which was not even licensed as such'. There was, however, no such statement within the supplement either in reference to rosuvastatin or atorvastatin. Where the authors had referred to use of either atorvastatin or rosuvastatin as a second choice statin, this was clearly set in the context of lowering total cholesterol and therefore was consistent with the licensed indication of both medicines. AstraZeneca thus denied breaches of Clauses 7.2 and 7.4.

With regard to the allegation in Case AUTH/1951/2/07 that the supplement ignored affirmation of national policy target made by the cardiovascular disease tsar, AstraZeneca submitted that the affirmation of the targets distributed by Professor Boyle in a DoH circular were not included by the authors as it had not been issued when this section was written. AstraZeneca referred to the authors' own responses on this issue. The company did not accept a breach of Clause 7.2.

With regard to the inference in Case AUTH/1951/2/07 that the supplement was not independent, AstraZeneca noted its involvement in the content and review of the

supplement as explained above. One of the authors had expressed her personal view with regard to this allegation in her own response.

AstraZeneca disagreed with the complainant's view in Case AUTH/1952/2/07 that the supplement was 'nothing more than a promotional brochure – it was neither intended to be or could be considered promotional. There was no intention to use the supplement promotionally; it was a valid educational discussion about the implementation of NICE guidance in relation to statins. The agency, having sought prior confirmation that this would be an interesting and valid education topic for readers of The Pharmaceutical Journal, commissioned two writers to write the article; both were independent of AstraZeneca. AstraZeneca sponsored the supplement, was aware of the proposed outline of the article and had reviewed the item in accordance with the Code to check that the content was not promotional and that the information contained therein was accurate and balanced. On this basis it was not appropriate to include prescribing information in the article.

AstraZeneca noted that a sponsorship statement appeared on the front cover. The company therefore denied a breach of Clause 10.1 in Case AUTH/1952/2/07.

With regard to the complainant's comments in Case AUTH/1952/2/07 about the JBS-2 lipid targets, AstraZeneca submitted that the targets were presented within the article, as well as all the other existing guidelines and evolution of lipid targets in a chronological order. No undue emphasis was placed on advocating the JBS-2 targets. Indeed if the authors had not included the JBS-2 targets then the information presented would not be up-to-date. The JBS guidelines were the most up to date robust clinical guidelines available in the UK. AstraZeneca thus denied breaches of Clauses 7.2 and 7.4.

In its response to Cases AUTH/1953/2/07 and AUTH/1954/2/07 AstraZeneca denied that the content of the supplement was promotional. It was a valid educational discussion about the implementation of NICE guidance in relation to statins. The agency engaged by AstraZeneca, having sought prior confirmation that this would be an interesting and valid educational topic for readers of The Pharmaceutical Journal, commissioned two writers to write the article; both were independent of AstraZeneca. AstraZeneca sponsored the supplement, was aware of the proposed outline of the article and had reviewed the item in accordance with the Code to check that the content was not promotional and the information contained therein was accurate and balanced. The review process confirmed that this was the case and on this basis it was not appropriate to include prescribing information in the article. The AstraZeneca sponsorship statement appeared on the front cover. The company did not accept that there had been a breach of Clause 4.1 or 10.1.

AstraZeneca noted the complainant's concern in Case AUTH/1953/2/07 that there was no mention that health policy was for targets of 5 and 3mmol/L. The title of the supplement clearly sets itself out as a 'considerations' article and therefore mentioned all the relevant existing guidelines and their targets which prescribing health professionals were aware of when making decisions for individual patients. The National Service Framework (NSF) for coronary heart disease, to which the complainant referred, and the General Medical Services contract targets which followed the NSF, were mentioned within the supplement on 7 out of the 9 pages. AstraZeneca knew that re-affirmation of the targets was made in a DoH circular, however as one of the authors indicated in her response, that circular had not been issued at the time she wrote this section. AstraZeneca therefore did not accept a breach of Clause 7.2 or 7.4.

AstraZeneca noted the complainant's concern in Case AUTH/1953/2/07 that the health economic arguments put forward would result in nearly 40% of the eligible population being on rosuvastatin 40mg. AstraZeneca submitted that the health economic page within the supplement contained two budget impact models depending on whether 5 or 4mmol/L was the total cholesterol target aimed for. The complainant had referred only to data presented in Table 4 of the model and not the other table, Table 3, which showed in a balanced way, the model for total cholesterol target of 5mmol/L. The information used by the authors was presented in a balanced and factual way and gave no recommendation or direction to use one treatment strategy over another. In relation to the specific details of the modelling, the cost-effectiveness was based on drug acquisition cost and did not include hospital cost for either the rosuvastatin or atorvastatin options. AstraZeneca denied a breach of Clause 7.10.

In its response to Cases AUTH/1953/3/06 and AUTH/1955/2/07, prescribing information was not included in the supplement as it was a review article written by two independent health professionals, not a promotional item written by AstraZeneca. The information contained within was the opinion of the independent authors and any information relating to rosuvastatin was presented in a balanced, factual and accurate manner taken from peer reviewed publications or publicly available documents (with the exception of the cost-effectiveness data which was supplied by AstraZeneca on request). There were no claims within the supplement that promoted the prescription, supply, sale or administration of rosuvastatin. As indicated in the editorial, 'We call this free speech' The Pharmaceutical Journal also did not consider it to be promotional in nature. AstraZeneca denied a breach of Clause 4.1.

With regard to the complainant's concern in Case AUTH/1953/2/07 that there had been a failure to mention MHRA warnings about the Crestor 40mg dose, AstraZeneca submitted that the supplement was a valid educational discussion item, written independently and over which the authors had full editorial control. AstraZeneca would have expected a balanced comment on safety of statins to be present in the article. Since the authors did not single out the 40mg dose, or any dose of any of the branded statins

for special mention, they did not add any dose specific warnings. AstraZeneca fulfilled its obligation to ensure that the supplement was non-promotional, balanced and accurate in accordance with the Code. The company denied a breach of Clause 4.1.

In its response to Case AUTH/1954/2/07 AstraZeneca submitted that industry support for an independently written article was a legitimate means of providing education and debate for health professionals. The company considered that the supplement provided valid educational content and topical discussion and was produced in accordance with the spirit and letter of the Code. The Pharmaceutical Journal editorial board had separately presented its views on the validity of the distribution and content of the article. The company denied a breach of Clause 10.1.

AstraZeneca stated that the supplement presented itself as a 'considerations' article and did not provide conclusions to direct the reader towards any prescribing recommendations. As indicated within the editorial response, 'We call this free speech' the readers were of course free to debate the validity of the points raised by the authors within the article and to come to their own conclusions, as they would of any article. The complainant in Case AUTH/1954/2/07 had not specifically raised any concerns relating to the validity of the supplement's content, but appeared to question the independence of the authors. AstraZeneca noted that its involvement in the development of the supplement had been explained above. The authors had publicly stated that the content and opinions expressed in the supplement were independent of AstraZeneca. AstraZeneca noted that none of the readers had contested the validity of the summary points presented in the article. The company denied a breach of Clause 7.2.

AstraZeneca reiterated that the cost-effectiveness data was requested for insertion by one of the authors. This data came from an unpublished cost-effectiveness model created by AstraZeneca and so it was correctly referenced as 'AZ Data on File'. Should the complainant in Case AUTH/1954/2/07, or other readers, wish to review this data they could request it from the medical information department. AstraZeneca denied a breach of Clause 7.4.

In response to Case AUTH/1955/2/07 AstraZeneca denied that the supplement was disguised promotion for Crestor as alleged. The title clearly set out the purpose and content of the document. This was an independently written article. AstraZeneca supported the article financially; however, the authors retained full editorial control. AstraZeneca did not accept that there had been a breach of Clause 10.1.

In its response to all five cases AstraZeneca submitted that industry support for an independently written article was a legitimate means of providing education and debate for health professionals. The company considered that the supplement provided valid educational content and topical discussion and had been produced in accordance with the spirit and letter of the Code. AstraZeneca aimed to maintain high standards in all aspects of its internal review process as well as wishing to be considered a respected source of information and education to health professionals. Whilst it was unfortunate that this article prompted the five letters from Pharmaceutical Journal readers, the company considered that this reflected the validity of this topical subject on statins and noted with interest that following publication of the authors' replies, in which they clarified their independence, no further comments had been published. AstraZeneca submitted that these reasons, in addition to the points made in response to the specific complaints, it did not accept that there had been any breaches of Clauses 2, 9.1 or 9.10.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The supplement in question had been sponsored/financially supported by AstraZeneca. The supplement had been initiated by the company and its communications agency had contacted the two authors. AstraZeneca was aware of the outline of the supplement and had, when asked to do so by one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The supplement was reviewed by AstraZeneca to ensure that it was factually correct. The two authors had full editorial control.

The Panel considered that AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Given the company's involvement and content, the Panel considered that the supplement was, in effect, promotional material for AstraZeneca's product Crestor. The supplement should have included the prescribing information for Crestor which it did not. Given that allegations were made in that regard in Cases AUTH/1953/2/07, AUTH/1954/2/07 and AUTH/1955/2/07, breaches of Clause 4.1 of the Code were ruled in those cases. The Panel considered that it was disguised promotion in that the supplement appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. A breach of Clause 10.1 was ruled in all five cases.

Clause 9.10 of the Code required that material relating to medicines and their uses, whether promotional in nature or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company. The Panel concluded that although the phrase 'supported by AstraZeneca' did not give details about the company's role, AstraZeneca's support was clearly stated on the front cover of the supplement. No breach of Clause 9.10 was ruled in all five cases.

The Panel considered that although the supplement was about the NICE guidance on the use of statins for the prevention of cardiovascular events, the document did not masquerade as NICE guidance as alleged in Case AUTH/1951/3/06. It was clear from the title on the front cover that the supplement discussed the implementation of the guidance. The Panel considered that the supplement was not misleading in that regard and no breach of Clause 7.2 was ruled.

In its consideration of Cases AUTH/1951/2/07 and AUTH/1952/2/07 the Panel noted that the NICE guidance on statins recognised the body of evidence for reduction in cardiovascular morbidity and overall mortality associated with statin use across a broad spectrum of the population. It did not give targets for cholesterol levels, stating this was outside its remit. With respect to the choice of statin NICE recommended that therapy should usually be initiated with a medicine with a low acquisition cost (taking into account required daily dose and product price per dose). For many patients, the least expensive statin would be simvastatin. The supplement recognised this but put forward arguments for the use of rosuvastatin which was more expensive. By implication, therefore, the supplement was advocating the use of rosuvastatin to reduce cardiovascular morbidity. Crestor, however, was not so licensed. Whereas simvastatin (Merck Sharp & Dohme's product, Zocor) was licensed for reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy, Crestor was only licensed for primary hypercholesterolaemia or homozygous familial hypercholesterolaemia. There would of course be benefits in lowering cholesterol but there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition. The differences between the licensed indications was not made clear. Thus the Panel considered that by implication the supplement was misleading as to the licensed indication of Crestor. Breaches of Clauses 7.2 and 7.4 were ruled in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

The Panel noted in Case AUTH/1951/2/07 that it was stated on the supplement that the date of preparation was December 2006. In November 2006, the national director for heart disease and stroke had issued guidance confirming the current national policy on statin prescribing. This stated that national policy currently accepted 5mmol/L for total cholesterol and 3mmol/L for LDL cholesterol as targets for therapy as per the NSF for CHD and that the JBS-2 guidance was not national policy. This guidance had not been included in the supplement. The Panel noted AstraZeneca's submission that the supplement had been developed before the guidance was written. Nonetheless, the date of preparation of the supplement was a month after the November guidance was issued and the supplement was not distributed until 20 January 2007. Given the time frame involved the Panel considered that it was misleading to distribute the supplement which did not refer to important national guidance and was thus not up-to-date. A breach of Clause 7.2 was ruled in Case AUTH/1951/2/07. A similar breach was ruled in Case AUTH/1953/2/07 where the Panel also noted a section of the supplement which discussed the role of the pharmacist, urging readers 'to pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L'.

With regard to the allegation in Cases AUTH/1951/2/06 and AUTH/1952/2/07 about unachievable JBS targets, the Panel noted that in the discussion on optimizing statin treatment strategies the supplement asked 'Are more challenging targets such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. In the section discussing the role of the pharmacist, however, readers were urged to 'pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L. A referral back to the GP possibly with a recommendation of change in statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate'. The supplement thus encouraged pharmacists to follow the JBS-2 guidance which was not national policy. In that regard the Panel considered that the supplement was misleading and a breach of Clause 7.2 was ruled in Cases AUTH/1951/2/07 and AUTH/1952/2/07.

In Case AUTH/1953/2/07 the Panel noted that a cost-effectiveness model was presented in the supplement which showed the budget impact results for patients failing to reach either a total cholesterol target of <5mmol/L or a total cholesterol target of <4mmol/L. Two tables of data detailed the financial implications of having to use atorvastatin or rosuvastatin as second line therapy to simvastatin (the least expensive statin). Both tables referred to rosuvastatin 40mg ie the maximum daily dose which, according to the Crestor summary of product characteristics (SPC), should be under the supervision of a specialist with patients requiring routine follow-up. Crestor appeared to be unique in this regard as specialist supervision was not required with the maximum daily dose of any of the other statins (atorvastatin, fluvastatin, pravastatin and simvastatin). This important condition on the use of rosuvastatin was not referred to anywhere in the supplement. The Crestor SPC referred to the increased reporting rate of adverse reactions with the 40mg dose compared to lower doses. The maximum dose of 40mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk who did not achieve their treatment goal on 20mg and in whom routine follow up would be performed. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other

statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Panel considered that the supplement was misleading and did not encourage the rational use of Crestor 40mg. Breaches of Clauses 7.2 and 7.10 were ruled on this point in Case AUTH/1953/2/07.

The Panel further noted in Case AUTH/1953/2/07 that the cost-effectiveness data presented in Tables 3 and 4 only accounted for the acquisition costs of the medicine. This was not entirely clear given the tables were headed 'Budget impact' and 'Treatment Strategy' and the use of terms like 'cost-effectiveness', 'financial implications' and the need to look at other 'costs' associated with treatment', which implied more than simply acquisition costs. There was no account taken of the cost of specialist supervision and routine patient follow-up associated with the use of rosuvastatin 40mg which would have an impact on budget. The Panel considered that the data was thus misleading. A breach of Clause 7.2 was ruled.

In Case AUTH/1954/2/07 the Panel noted that the cost-effectiveness data which showed the financial implications of using either atorvastatin or rosuvastatin as second line therapy in patients who had not reached lipid targets with simvastatin, was referenced to AstraZeneca data on file. The Panel considered that it was not necessarily unacceptable to cite data on file in promotional material. The supplement was thus not misleading in that regard. No breach of Clause 7.2 was ruled.

Overall the Panel considered that AstraZeneca's failure to recognise that the supplement was, in effect, promotional material for Crestor, meant that high standards had not been maintained. A breach of Clause 9.1 was ruled in all five cases. The Panel was concerned that the supplement, contrary to national guidance had encouraged pharmacists to follow JBS-2 cholesterol targets. The Panel was further very concerned that although the 40mg dose of rosuvastatin had been referred to in the supplement, there was no reference to the specialist supervision and routine patient follow-up needed with such a dose. The Panel considered that the omission of such information might prejudice patient care. The Panel considered that in these two matters, one or both of which had been raised in Cases AUTH/1951/2/07, AUTH/1952/2/07 and AUTH/1953/2/07, the supplement had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled in these cases. As these matters were not raised in Cases AUTH/1954/2/07 or AUTH/1955/2/07 no breach of Clause 2 was ruled in these cases on the basis of the allegations made.

APPEAL BY ASTRAZENECA

AstraZeneca appealed against all of the Panel's rulings of breaches of the Code.

The company again explained, as in its response above, the reasons for the supplement and again gave details as to how it was produced and the company's relationship with the authors.

With regard to the ruling of a breach of Clause 10.1 of the Code AstraZeneca noted that the Panel had stated:

> '… AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. … that it was disguised promotion in that the supplement appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca'.

AstraZeneca did not deny a link with the authors, its communications agency contacted them following their discussion with The Pharmaceutical Journal, AstraZeneca sponsored the article and supplied the authors with data on request.

AstraZeneca submitted that it did not per se choose the authors, but acknowledged that this was done by the communications agency acting on its behalf. Although AstraZeneca agreed with the Panel that this meant that 'the two authors had, in effect, been chosen by AstraZeneca' it disagreed strongly with its unequivocally-stated conclusion that this meant 'that it appeared to be independently written which was not so' and that the item was disguised promotion.

AstraZeneca submitted that direct or indirect involvement in the choice of author for items such as company-sponsored journal supplements or inserts was an unavoidable part of the company's role in such projects. Journals and professional societies frequently collaborated with the pharmaceutical industry to produce educational information relevant for their audiences. The expert knowledge that existed within a company in relation to appropriately qualified external experts was commonly utilised.

AstraZeneca submitted that it would be an extreme position to make involvement in the choice of author for company-sponsored educational material a criterion for judging that material to be promotional. There would be very little sponsored educational material left that was not promotional.

AstraZeneca submitted that with respect to the Code, it was considered appropriate for companies to identify external expert presenters for educational meetings that they sponsored. In such situations they were expected to be aware of the presenter's views and might be involved in briefing and approving their materials, both without being subject to automatic allegations that the meeting was promotional. Why should educational supplements be treated any differently from these educational meetings? Elsewhere in the Panel's ruling it had stated it had been established that:

- '… it was acceptable for companies to sponsor material'.
- '… the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose'.

- '… if neither of these applied, the company would be liable if it had been able to influence the content of the material …'
- 'It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.'
- '… the supplement was, in effect, promotional material…'.

AstraZeneca submitted that it was fully aware of the application of the Code in relation to sponsored publications. AstraZeneca endorsed the selection of the two authors as it knew them to be independent, highly-principled medical writers. AstraZeneca made no attempt to abuse its position as sponsors by bringing any influence to bear on the way the article was written. The authors retained full editorial control throughout, including development of the outline. AstraZeneca's involvement was to exercise due diligence in ensuring that the materials could not be considered promotional.

AstraZeneca referred to Case AUTH/1644/10/04 and submitted that it had acted in a way entirely compliant with the Code as written and interpreted by this precedent.

AstraZeneca therefore submitted that its arrangements constituted an 'arm's length arrangement' by any definition.

AstraZeneca submitted that one of the authors in her response to allegations by correspondents in The Pharmaceutical Journal that she was 'motivated by undue influence from the pharmaceutical industry' responded: 'Your readers… imply that my failure to work to national guidelines which I consider… to be contrary to the best interests of patients must be motivated by undue influence from the pharmaceutical industry. I find such accusations offensive in the extreme'.

AstraZeneca submitted that the other author had also refuted allegations that the supplement was not the work of the authors. As well as having responded publicly to the readers' letters he had written to AstraZeneca, stating 'I would like to make it absolutely clear that the words within the supplement were my own based entirely on my own opinion and experience. I am not in the habit of putting my name to the words of others and I take exception to anyone suggesting that this could be otherwise'.

On the basis of the above, AstraZeneca submitted that it was clear that the authors were concerned by the seriousness of the Panel's allegations that the company might have exerted undue influence over them considering that they had previously and publicly confirmed their independence.

AstraZeneca submitted that the editor of The Pharmaceutical Journal, in a leading article entitled 'We call this free speech' in response to the previous week's correspondence, also supported the claim that the article was independent and not promotional, saying that, in their opinion, it 'was neither an advertisement nor an advertorial… As far as the Journal is concerned it was a discussion document written by two health professionals… inviting readers to consider how [NICE] guidance might be implemented'.

The Panel also stated that it considered that the statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. AstraZeneca assumed that the Panel had no issue with the use of 'supported' as a synonym for 'sponsored', there was nothing in its ruling to suggest that there were any issues around this aspect of the item. However AstraZeneca was slightly confused by this point. The Code was straightforward in its advice in relation to sponsored material and the need to make that sponsorship clear at the outset. AstraZeneca had complied with the Code in this regard as the item was not promotional in nature.

As far as any activities beyond the inclusion of the supplement within The Pharmaceutical Journal, it had not and never had the intention to use this supplement in a promotional context.

AstraZeneca noted that the complainant in Case AUTH/1951/2/07 had made other allegations that could be considered as potential breaches of Clause 10.1. The Panel had chosen not to pursue these. On all the points made by the complainant and the Panel AstraZeneca denied a breach of Clause 10.1 of the Code.

AstraZeneca noted that in Cases AUTH/1953/2/07, AUTH/1954/2/07 and AUTH/1955/2/07 because the Panel had ruled the item at issue to be promotional it should have included prescribing information. AstraZeneca denied the item was promotional and hence not in breach of Clause 4.1.

AstraZeneca noted that Clauses 7.2 and 7.4 applied to promotional material. For the reasons already provided this item was not promotional, rather it was a sponsored journal supplement written by independent authors with no editorial input from AstraZeneca.

However, AstraZeneca submitted that the allegations that the item in question promoted Crestor in a manner that was not accurate, balanced, fair, objective, unambiguous and capable of substantiation were unfounded.

AstraZeneca noted as described previously this item, a Pharmaceutical Journal supplement entitled 'The new NICE guidance on the use of statins in practice – Considerations for implementation' covered several topics.

Firstly there was section headed 'The NICE guidance recommendations' covering relevant aspects of Technology Appraisal 94. This provided an outline of the main points from the document, referred to NICE's methodology for assessing risk reduction and introduced NICE's conclusion: LDL cholesterol

reduction resulted in a predictable relative risk reduction for cardiovascular mortality.

This was followed by another section, 'The UK cholesterol story' that summarised the evolution of the various lipid targets affecting UK clinical practice up to and including the 2006 JBS-2.

The next section concerned treatment strategies for achieving targets headed 'Reaching targets by optimising statin treatment strategies'. This unequivocally supported the NICE guidance by endorsing the use of simvastatin first-line in the treatment of dyslipidaemia. AstraZeneca noted that all the descriptions of the relative efficacy of statins in this section referred to their effect on LDL-C.

The next two sections, 'Calculating the cost of implementing NICE guidance across a primary care trust population' and 'Modelling the cost for a local health economy' provided estimates of the cost-effectiveness of the various treatment options for individual patients (as cost per % LDL-C or total cholesterol reduction) and for primary care organisations using the two available first- and second-line strategies (as budget impacts for total cholesterol targets of <5 and <4mmol/L).

The final section, 'Meeting the patient need – the role of the pharmacist' described some of the issues in the management of dyslipidaemia that might affect pharmacists seeing patients with this condition.

AstraZeneca submitted that the standard procedure in the clinical management of dyslipidaemia was in line with NICE guidance which stated 'it is recommended that therapy should usually be initiated with a drug with a low acquisition cost'. Usually this first-line therapy was generic simvastatin. If the patient failed to reach target on this option then they were normally switched to a second-line, more potent statin, usually rosuvastatin or atorvastatin (Lipitor, Pfizer). This treatment algorithm was widely recognised, had been endorsed informally by the DoH and represented, in most people's opinion, a realistic treatment protocol in line with NICE guidance.

AstraZeneca submitted that although the authors suggested that there might be justification for considering the use of a more potent statin first-line in a minority of patients with very severe dyslipidaemia, at no time in the supplement did they question the validity of alternative strategies. In this respect, it was fair to note firstly that NICE recommended that 'Therapy should usually be initiated with a drug with a low acquisition cost'. Secondly, that all the cost-benefit tables used simvastatin first-line before introduction of a more potent treatment option.

AstraZeneca noted that the Panel stated that it considered that:

> '… NICE recommended that therapy should usually be initiated with a medicine with low acquisition cost… For many patients, the least expensive statin would be simvastatin. The supplement recognised this but put forward arguments for the use of rosuvastatin, which was more expensive. By implication, therefore, the supplement was advocating the use of rosuvastatin to reduce cardiovascular morbidity…. Crestor was only licensed for primary hypercholesterolaemia …. There would of course be benefits in lowering cholesterol but there was a difference between promoting a product for a licensed indication and promoting the benefits of treating the condition. The differences between the licensed indications was not made clear.'

AstraZeneca submitted that the use of rosuvastatin as a more expensive replacement for simvastatin was only mentioned in the article in the context of it usually being an alternative treatment where patients had failed to reach target on first-line simvastatin. The text and figures on pages 6 to 8 of the supplement made this abundantly clear.

In relation to the Panel's concerns that there was an implied outcome benefit, AstraZeneca pointed out that NICE had accepted the relationship of cholesterol lowering and outcomes and included rosuvastatin in its guidance and analysis. NICE did not discriminate against it based on the fact that outcome data was still awaited. Therefore it was appropriate that rosuvastatin be included in a discussion in relation to the NICE guidance.

AstraZeneca submitted that whether it was blood pressure in hypertension, LDL-C in dyslipidaemia or HbA1c in diabetes there was an implied effect on outcomes in any discussion of surrogate endpoints in disease management. The role of a responsible company in dissemination of information in therapy areas where surrogate endpoints were the principal consideration was to ensure that it was entirely clear what was being discussed. This supplement presented the facts appropriately and without misleading: all of the figures and the text were unambiguous in referring to rosuvastatin's efficacy in managing LDL-C/total cholesterol and achieving targets.

AstraZeneca submitted that in this context, it was not inappropriate to mention that NICE had referred to rosuvastatin's efficacy in lowering LDL-C.

AstraZeneca noted that the Panel had not referred to Clause 3.2.

AstraZeneca noted that the Panel had further noted that:

> 'In November 2006 the national director for heart disease and stroke had issued guidance confirming the current national policy …. The date of preparation of the supplement was a month after the November guidance was issued and the supplement was not issued until 20 January …. It was misleading to distribute the supplement which did not refer to important national guidance and was thus not up-to-date …. Readers were urged "to pick up on those patients not reaching the JBS-2 targets …. A referral back to the GP possibly with a

recommendation of change of statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate". The supplement thus encouraged pharmacists to follow the JBS-2 guidance which was not national policy.'

AstraZeneca submitted that it had previously acknowledged that the reminder of the National Service Framework (NSF) targets distributed by Professor Boyle in a DoH circular were not included by the authors as it had not been issued when this section had been written. The NSF targets were however specifically included within the supplement. The letter from Professor Boyle, the National Director for Heart Disease, was not a new national policy, nor was it a new review of the evidence base. It was merely a reminder of the NSF targets, which were included in the discussion within the supplement. Therefore, the article represented the balance of evidence by citing the various guideline targets, including the NSF.

AstraZeneca submitted that it was pleased to clear up any misunderstanding about the date of preparation included on the item. Many items took several months to prepare, this one was a case in point. In these instances it was common industry practice to insert the date of preparation at the time of issue of the item. On this occasion the final text of the article was agreed and the content reviewed and approved internally by 3 October 2006. For this reason the date of preparation was initially stated as November 2006 despite the fact the article was completed in advance of this date. On November 7 Professor Boyle posted his clarification of lipid targets. Subsequent delays to the preparation of the final layout and printing of the supplement meant the date of preparation was changed again, this time to December 2006, the anticipated date of inclusion in The Pharmaceutical Journal. Further administrative delays meant the supplement was not included in the journal until January 2007. AstraZeneca repeated its assertion that the circular was issued after the supplement had been completed. This was also referred to in the author's own response on this issue.

Notwithstanding the national director's awareness of the debate on lipid targets and his reaffirming of the existing NSF target of total cholesterol <5mmol/L, AstraZeneca noted that several areas of the UK had local lipid guidelines based on the JBS-2 recommendations. Numerous other local guidelines issued by primary care organisations included lipid targets based on JBS-2 (provided). Included in the list of organisations setting JBS-2 targets was the PCT of one of the authors. He mentioned this in response to criticism about his support of JBS-2 that was published in The Pharmaceutical Journal.

AstraZeneca submitted that several prominent GPs and cardiovascular clinicians considered that the debate on QOF/NSF targets of 5 or 5 and 3mmol/L or the JBS-2 recommendation of 4 and 2mmol/L for total cholesterol and LDL-C was valid. AstraZeneca was concerned that the Authority might stifle a relevant and perhaps critical debate on this important clinical issue by ruling AstraZeneca to be in breach of the Code. AstraZeneca had included a number of quotations from the medical press on this subject. All of these supported the position of the authors that the debate on whether the JBS-2 targets were viable in today's economic climate was far from over.

Wherever the national debate might be leading, AstraZeneca submitted that it was still appropriate to encourage pharmacists to assume a role in the management of dyslipidaemia working to whichever target applied in their area. In many instances this target would be based on JBS-2.

On all the points made by the complainant and the Panel AstraZeneca denied a breach of Clauses 7.2 and 7.4.

With regard to the rulings of breaches of Clauses 2 and 9, AstraZeneca noted that the Panel had stated:

> '… failure to recognise that the supplement was, in effect, promotional material for Crestor, meant that high standards had not been maintained. … by encouraging pharmacists to go beyond national policy …'.

AstraZeneca refuted that the supplement was intended to be promotional and that it was therefore disguised promotion and submitted that it had adequately covered this aspect of this complaint already.

AstraZeneca submitted that The Pharmaceutical Journal was an important part of the available range of UK health journals. One of the strengths of The Pharmaceutical Journal was the lively debate that frequently took place on its correspondence pages and the activities of the pharmaceutical industry were often debated. It was of note that five readers complained but these cases should be judged on the evidence pertaining to the development of the supplement. AstraZeneca welcomed the complainants' response to the clinical debate which showed that the matters covered in the article by the two independent writers were very topical.

AstraZeneca therefore also denied the associated breaches of Clauses 2 and 9.1.

COMMENTS FROM THE COMPLAINANTS

No comments were received in relation to Cases AUTH/1951/2/07 and AUTH/1953/2/07 to AUTH/1955/2/07.

Case AUTH/1952/2/07

The complainant alleged that it was clear that AstraZeneca had initiated the article. It must have anticipated some advantage from doing this. The two authors seemed to have been chosen because they were interested in the subject. Many had written on this subject in the medical and pharmaceutical press, so why were these two people chosen? Was it because their points of view were in line with those of AstraZeneca? AstraZeneca had submitted that the authors were well-respected, independent medical

authors who frequently contributed to articles to the medical press. The complainant noted that he had frequently written for both the medical and pharmaceutical journals and had had articles published in the BMJ, The New Generalist, The Pharmaceutical Journal, Pharmacy in Practice, and Prescriber among others, including discussions on appropriate statin use. The complainant was not asked to contribute and he suspected that this was because he would have written a very different article. The complainant did not dispute that the authors had written the article themselves but the complainant alleged that they were chosen for what they were likely to write and AstraZeneca was in fact inextricably linked to the production of this supplement. As this was in effect an opinion piece, were any independent editorial advisers involved? The complainant questioned if the authors wrote this altruistically because of their concerns about inappropriate use of statins or were they paid to write it? If the latter, then this was a potential conflict of interest and should have been declared. There would then inevitably be a perceived association with AstraZeneca.

In the complainant's experience sponsored supplements such as this normally included prescribing information for the sponsor's medicines. Was this not a requirement? The inclusion of such prescribing information would have enabled readers to know that one of the proposed treatment strategies was inappropriate in that rosuvastatin was not licensed for the prevention of cardiovascular events. As the reason for the supplement was to discuss the implementation of the NICE guidance and the NICE guidance was about the prevention of cardiovascular events and there were three other statins licensed for this indication, then this was seriously misleading. In addition, the rosuvastatin strategy included the use of the 40mg dose. The SPC for Crestor stated 'Specialist supervision is recommended when the 40mg dose is initiated'. This was not mentioned in the supplement despite the increased risk of adverse events with this dose and this was a serious omission.

The complainant alleged that the strategy suggested that simvastatin 40mg would only achieve a total cholesterol target of <5mmol/L in 63.7% of patients and used data on file to support the claim. This ignored published evidence to the contrary and was therefore misleading. The two randomised controlled trials that involved the use of dose-adjusted simvastatin strongly suggested that the vast majority of people given simvastatin 40mg would achieve a total cholesterol of <5mmol/L. In the 4S (Lancet 1994) and IDEAL studies (Pedersen et al 2005) patients were started on simvastatin 20mg and moved up to 40mg daily if necessary to achieve a total cholesterol <5.2mmol/L in 4S and <5mmol/L in IDEAL. The mean simvastatin dose in 4S was 27mg daily and in IDEAL 25mg daily, suggesting that most people would get below 5mmol/L on 40mg daily. The strategies also ignored simvastatin 80 mg daily as the appropriate step 1, as advocated in the widely publicised University College London Hospitals statin guideline 'Switching Statins' (BMJ 2006). These two adjustments would have had a dramatic effect on the cost-effectiveness analysis, which was therefore misleading.

The complainant noted the recently published Health Technology Assessment (HTA) review of statins for the prevention of coronary events (2007) was pertinent to the debate about the promotion of rosuvastatin without clinical endpoint evidence. It stated 'although there is evidence to suggest that rosuvastatin is more effective than atorvastatin, pravastatin and simvastatin in reducing both total cholesterol and LDL-C, it is not possible to prove that these reductions translate into comparable reductions in clinical events' and 'in the absence of strong and conclusive evidence on the exact relationship between cholesterol lowering and clinical end-points, cost-effectiveness results for rosuvastatin are subject to additional uncertainty'.

The complainant noted that the supplement put forward the strategies of either atorvastatin or rosuvastatin as appropriate second-line statins and therefore implied that they would have similar patient benefits. As atorvastatin had patient-orientated outcome evidence to support it and rosuvastatin had not, this was misleading. The majority of trusts would have atorvastatin as their second-line statin because it had been proven to reduce cardiovascular morbidity, unlike rosuvastatin. Reduction in cardiovascular morbidity could not be assumed from surrogate outcomes. There were too many examples where this had been shown not necessarily to follow. Such risks could not be taken with people's health when evidence-based medicines were available. The complainant alleged that AstraZeneca had been selective in providing guidelines that included its medicine when the majority did not.

The complainant noted that it was well known that the NSF cholesterol targets were still national policy and they were reflected in the QoF targets. The supplement did not highlight this fact and implied that it was appropriate to aim to achieve for JBS2 targets. Professor Boyle's letter was only issued because of activities leading to inappropriate promotion of the JBS-2 targets. Whether the supplement preceded the letter or vice versa was not actually relevant. The supplement encouraged following JBS-2 guidance rather than national policy and this reduced confidence in the integrity of the pharmaceutical industry. It was also well known that the JBS-2 targets were not evidence-based as the JBS admitted in its own document as highlighted in the letter to The Pharmaceutical Journal. The vast majority of trusts would have the national targets not the JBS-2 targets in their guidelines as it was well recognised that they were neither achievable or affordable. Once again AstraZeneca had been selective in the guidelines it had presented. It was of interest to note that the Scottish Intercollegiate Guidelines Network (SIGN), which one of the authors in his letter seemed to think would support his stance, rejected the JBS-2 targets and promoted simvastatin 40mg daily. Also, a recently published quality assessment (Minhas 2007) concluded that the JBS guidelines 'contain serious deficiencies, are of low quality and should not be recommended for clinical practice', thereby supporting the position of the majority of trusts with their evidence-based, cost-effective guidelines.

AstraZeneca argued that NICE referred to rosuvastatin in their guidance. The NICE guidance stated that specialist supervision was recommended when rosuvastatin 40mg was initiated and the 40mg dose was contraindicated in those of Asian origin, neither of which were mentioned in the supplement. NICE also stated that the guidance related only to the use of statins within their licensed indications, which effectively ruled out rosuvastatin, as it was not licensed for the prevention of cardiovascular events.

The complainant alleged that this was a promotional supplement and remained convinced that the Panel had made the correct decision and the appeal should be rejected.

APPEAL BOARD RULING

The Appeal Board accepted that the views expressed in the material were those genuinely held by the authors. The Appeal Board, however, was called upon to consider the merits of the piece in the context of AstraZeneca's involvement in the generation and production of it. Independent authors were at liberty to publish their views; however when a pharmaceutical company became involved in such an activity it potentially became subject to the Code.

The Appeal Board noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Appeal Board noted the material in question had been sponsored/financially supported by AstraZeneca. AstraZeneca had paid the authors to write it and The Pharmaceutical Journal to distribute it. In that regard the material was a paid for insert from AstraZeneca; not a supplement sponsored by The Pharmaceutical Journal for which the editor would have been responsible. The insert had been initiated by AstraZeneca and its communications agency following an AstraZeneca statin advisory board meeting organised by AstraZeneca attended by the two authors who were subsequently asked to write the insert. AstraZeneca was aware of the outline of the material and had, when asked to do so by one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The material was reviewed by AstraZeneca to ensure that it was factually correct. The Appeal Board noted from the AstraZeneca representatives that on review of the insert AstraZeneca had suggested the inclusion of a table of budget impact results for a total cholesterol target of <5mmol/L to balance the <4mmol/L results already included, this was accepted by the authors. The Appeal Board noted that although two authors had full editorial control, AstraZeneca took the final decision about whether to publish or not.

The Appeal Board considered that AstraZeneca was inextricably linked to the production of the insert. There was no arm's length arrangement between the provision of the sponsorship and the generation of the material. Given the company's involvement and content, the Appeal Board considered that the material was, in effect, promotional material for Crestor. The Appeal Board considered that it was disguised promotion in that the material appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The Appeal Board upheld the Panel's ruling of a breach of Clause 10.1 in all five cases. The appeal on this point was unsuccessful.

In Cases AUTH/1953/2/07, AUTH/1954/2/07 and AUTH/1955/3/06 the Appeal Board noted its ruling of a breach of Clause 10.1 and as such considered that the material should have included the prescribing information for Crestor which it did not. The Appeal Board upheld the Panel's rulings of a breach of Clause 4.1 of the Code in all three cases. The appeal on this point was unsuccessful.

The Appeal Board noted that the material stated that the NICE guidance on statins recognised the body of evidence for reduction in cardiovascular morbidity and overall mortality associated with statin use across a broad spectrum of the population. It did not give targets for cholesterol levels, stating this was outside its remit. With respect to the choice of statin NICE recommended that therapy should usually be initiated with a medicine with a low acquisition cost (taking into account required daily dose and product price per dose). For many patients, the least expensive statin would be simvastatin. The Appeal Board noted that the material recognised that simvastatin should be used first-line but put forward arguments for the use of rosuvastatin which was more expensive without stating that it was not licensed to reduce cardiovascular mortality and morbidity. The Appeal Board considered that without a statement to the contrary, the material, by implication, advocated the use of rosuvastatin to reduce cardiovascular morbidity. Simvastatin (Merck Sharp & Dohme's product, Zocor) was licensed for reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy. In this regard the Appeal Board noted that Lipitor was indicated for primary prevention in type II diabetes for reducing the risk of cardiovascular events in diabetic patients with at least one additional risk factor, without clinically evident coronary heart disease irrespective of whether cholesterol was raised. The Appeal Board considered that the material was misleading as to the licensed indication of Crestor. In this regard the Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4 in Cases AUTH/1951/2/07 and

AUTH/1952/2/07. The appeal on this point was unsuccessful.

The Appeal Board noted that the material set out the evolving guidance on statin use. It also noted the timeframe regarding the writing, production and publication of the material. The Appeal Board considered that the timings were such that the statement issued by the national director for heart disease and stroke should have been referred to in the insert. By not referring to this important national statement the material was misleading and not up-to-date. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code in Cases AUTH/1951/2/07 and AUTH/1953/2/07 in this regard. The appeal on this point was unsuccessful.

With regard to the allegation in Cases AUTH/1951/2/07 and AUTH/1952/2/07 about unachievable JBS targets, the Appeal Board noted that in the discussion on optimizing statin treatment strategies the supplement asked 'Are more challenging targets such as JBS-2, really achievable - and, more importantly, can they be achieved safely?'. In the section discussing the role of the pharmacist, however, readers were urged to 'pick up on those patients not reaching the JBS-2 targets of total cholesterol <4mmol/L and LDL cholesterol <2mmol/L. A referral back to the GP possibly with a recommendation of change in statin dose or drug entity (in accordance with NICE guidelines) might be seen as appropriate'. The Appeal Board noted that not only did the material encourage pharmacists to follow the JBS-2 guidance, which was not national policy, it did not advise them that the JBS-2 targets were for high risk patients. From the statement in the material it appeared that the JBS-2 targets should be the aim for all patients which was not so. The Appeal Board considered that the material was misleading in this regard and upheld the Panel's ruling of a breach of Clause 7.2 in Cases AUTH/1951/2/07 and AUTH/1952/2/07. The appeal on this point was unsuccessful.

The Appeal Board noted, in Case AUTH/1953/3/06, that a cost-effectiveness model was presented in the insert which showed the budget impact results for patients failing to reach either a total cholesterol target of <5mmol/L or a total cholesterol target of <4mmol/L. Two tables detailed the financial implications of having to use atorvastatin or rosuvastatin as second line therapy to simvastatin (the least expensive statin). Both tables referred to rosuvastatin 40mg ie the maximum daily dose. According to the Crestor SPC, in the light of increased reporting rate of adverse reactions with the 40mg dose compared to lower doses a final titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who did not achieve their treatment goal on 20mg and in whom routine follow-up would be performed. Specialist supervision was recommended when the 40mg dose was initiated. Section 4.4 of the SPC stated that an assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg. Crestor appeared to be different as specialist supervision was not required with the maximum daily dose of any of the other statins (atorvastatin, fluvastatin, pravastatin and simvastatin). This important condition on the use of rosuvastatin was not referred to anywhere in the insert. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Appeal Board considered that the material was misleading and did not encourage the rational use of Crestor 40mg. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10 in this regard in Case AUTH/1953/2/07. The appeal on this point was unsuccessful.

The Appeal Board further noted that the cost-effectiveness data presented in Tables 3 and 4 only accounted for the acquisition costs of the medicine. This was not entirely clear given the tables were headed 'Budget impact' and 'Treatment Strategy' and the use of terms like 'cost-effectiveness', 'financial implications' and the need to look at other 'costs' associated with treatment, which implied more than simply acquisition costs. There was no account taken of the cost of specialist supervision and routine patient follow-up associated with the use of rosuvastatin 40mg which would have an impact on budget. The Appeal Board considered that the data was thus misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 in this regard in Case AUTH/1953/2/07. The appeal in this point was unsuccessful.

Overall, in all five cases, the Appeal Board considered that AstraZeneca's failure to recognise that the material was, in effect, promotional material for Crestor, meant that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1 in all cases.

The Appeal Board was concerned that the material, contrary to national guidance had encouraged pharmacists to follow JBS-2 cholesterol targets. The Appeal Board was further very concerned that although the 40mg dose of rosuvastatin had been referred to in the insert, there was no reference to the specialist supervision and routine patient follow-up needed with such a dose. The Appeal Board considered that the omission of such information might prejudice patient care. The Appeal Board considered that in these two matters, the material had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2 in Cases AUTH/1951/2/07, AUTH/1952/2/07 and Case AUTH/1953/2/07. The appeal on these points was unsuccessful.

Proceedings commenced **5 February 2007**

Cases completed **3 July 2007**