CASE AUTH/2516/6/12

ALLERGAN/DIRECTOR v MERZ

Breach of undertaking

Allergan alleged that a Bocouture (botulinum toxin type A) advertisement, issued by Merz Pharma UK and published in Cosmetic News, June 2012, breached the undertaking given in Case AUTH/2270/10/09. Allergan supplied Botox (botulinum toxin type A). The matter was taken up by the Director as the PMCPA was responsible for ensuring compliance with undertakings.

The advertisement featured a photograph of a vial of Bocouture and a vial of Botox side-by-side above which was the claim 'In glabellar frown lines, clinical studies suggest Bocouture vs Botox: Equal Potency 1:1 Clinical Conversion Ratio'. Below the vials was a thick blue horizontal line beneath which was the statement in smaller black font 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'. This statement and the claim for equal potency were referenced to the Bocouture summary of product characteristics (SPC) June 2010. The claim for a 1:1 clinical conversion ratio was referenced to Sattler *et al* (2010).

Allergan alleged that the advertisement and Merz's ongoing promotional campaign would lead prescribers to conclude that Bocouture and Botox were interchangeable in terms of potency units and delivered equivalent clinical results.

Allergan noted that the current Bocouture SPC (6 March 2012) stated 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.' Allergan was concerned that the advertisement cited the June 2010 SPC which Merz knew would imminently change to remove the statement prominently featured in the advertisement.

The Bocouture 50U SPC (and that of Merz's product Xeomin (botulinum toxin type A)) was changed after Allergan had highlighted to the regulatory authorities potential patient safety concerns with the wording in the Bocouture 50U and Xeomin 50U SPCs. Any reference to equal potency in the Bocouture SPC had been removed.

The statement regarding a 1:1 dosing ratio in Section 4.2 of the Xeomin 50U SPC had been removed. The information from non-inferiority studies in Section 5.1 of the Xeomin 50U SPC was specifically about patients with blepharospasm or cervical dystonia. As previously established, non-inferiority studies did not support claims of equivalence.

The SPCs for Botox 50U, 100U and 200U stated 'Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan units are different from other botulinum toxin preparations.'

Allergan alleged that the claim '1:1 Clinical Conversion Ratio' and the visual of Bocouture and Botox vials side-by-side emphasised a direct 1:1 equivalence/conversion of the two products. In significantly smaller font was the SPC statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.'

Health professionals would assume that Bocouture and Botox were equally potent and could be converted 1:1. Allergan was concerned about Merz's promotion of this 1:1 clinical conversion ratio between Bocouture and Botox. No 'dosing conversion' occurred or should be implied from the non-inferiority study conducted by Merz with its toxin (Sattler *et al*). Allergan submitted that a significant patient safety risk existed with prescribers encouraged to transfer information from one label to another product.

Allergan noted that in Case AUTH/2270/10/09 it was ruled that the results of a non-inferiority study could not be used to claim equivalence. In that case Merz submitted that it had no data to support a claim that Xeomin was equivalent to Botox and this was still so. Therefore, Allergan alleged that the visuals, which implied equivalence/equipotency and the claim '1:1 Clinical Conversion Ratio' between Bocouture and Botox, (ie equivalence), breached the undertaking given in Case AUTH/2270/10/09.

The detailed response from Merz is given below.

The Panel noted that in Case AUTH/2270/10/09 it had considered a complaint from Allergan that the claim by Merz that Xeomin was 'At least as effective as Botox with a similar safety profile' without appropriate context and qualification did not accurately reflect the available evidence and was misleading. Allergan had submitted that to make the claim 'At least as effective as', Merz needed further evidence to confirm equivalent efficacy and clinically relevant superiority. The claim at issue was referenced to Benecke *et al* (2005) and Roggenkamper *et al* (2006) both of which were non-inferiority studies. The Panel considered that there was a difference between showing non-inferiority and showing comparability and that the claim that Xeomin was 'At least as effective as Botox' did not reflect the available evidence. It implied possible superiority of Xeomin and was misleading as alleged; breaches of the Code were ruled. Upon appeal by Merz, the Appeal Board noted Merz's submission that it had no data upon which to claim that Xeomin was equivalent to Botox. The Appeal Board stated that in its view, the claim 'At least as effective as' not only implied equivalence but also possible superiority which was misleading. The Appeal Board did not consider that the claim could

be substantiated by the available data and the Panel's rulings were upheld.

The Panel noted that the material now at issue in Case AUTH/2516/6/12 was different to that at issue in Case AUTH/2270/10/09. In Case AUTH/2270/10/09 the comparison at issue had been between Xeomin and Botox; the comparison now at issue was between Bocouture and Botox. Bocouture and Xeomin, however, were the same product but with different indications.

The Panel noted that the advertisement now at issue had also been at issue in Case AUTH/2496/4/12 in which Allegan had made similar allegations. The Panel's ruling in that case, that the undertaking in Case AUTH/2270/10/09 had not been breached, was overturned upon appeal by Allergan. The Panel considered that the Appeal Board's ruling of a breach of undertaking applied to the case now before it, Case AUTH/2516/6/12. The Panel thus ruled a breach of the Code. The Panel ruled a further breach as high standards had not been maintained.

The Panel noted that it was extremely important that companies complied with undertakings; to do otherwise brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel further noted that there was still no data upon which to base a claim that Botox and Bocouture were clinically equivalent. The Panel was concerned to note that although the advertisement in question had been withdrawn following changes to the Bocouture SPC, Cosmetic News subsequently published it in error. The Panel considered that companies must have robust procedures to ensure that, when required and for whatever reason, materials were withdrawn from all relevant parties including agencies and publishers. Although Merz had reviewed its processes for ensuring publishers used only current and approved advertisements, the Panel considered that the circumstances were such that Merz had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Allergan Limited complained about a Bocouture (Botulinum toxin type A) advertisement (ref 1075/BOC/DEC/2011/JH) issued by Merz Pharma UK Ltd which was published in Cosmetic News, June 2012. Allergan supplied Botox (Botulinum toxin type A).

The matter was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

The advertisement featured a photograph of a vial of Bocouture and a vial of Botox side-by-side. Above the vials was the claim in bold, blue font 'In glabellar frown lines, clinical studies suggest Bocouture vs Botox: Equal Potency 1:1 Clinical Conversion Ratio'. This claim and the photograph took up over half of the advertisement. Below the vials was a thick blue horizontal line beneath which was the statement in smaller black font 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'. This statement and the claim for equal potency were referenced to the Bocouture summary of product characteristics (SPC) June 2010. The claim for a 1:1 clinical conversion ratio was referenced to Sattler *et al* (2010).

COMPLAINT

Allergan alleged that the advertisement and Merz's ongoing promotional campaign had been designed to lead prescribers to conclude that Bocouture and Botox were interchangeable in terms of potency units and delivered equivalent results in clinical practice.

The 'Equal Potency' claim was referenced to the Bocouture SPC, June 2010. The current SPC for Bocouture (which was updated on 6 March 2012) stated:

> **'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.'**

Allergan was concerned that the advertisement which was published in the June 2012 edition of Cosmetic News, prepared in February 2012, referred to an old SPC which Merz knew would imminently change to remove the statement prominently featured in the advertisement.

The UK Bocouture 50U SPC (and that of Merz's product Xeomin (Botulinum toxin type A)) was changed following Allergan's communication to the Pharmacovigilance Working Party (PhVWP) highlighting potential patient safety concerns with the wording in the Bocouture 50U and Xeomin 50U SPCs. Any reference to equal potency in the Bocouture SPC had been removed.

Allergan pointed out that the statement regarding 1:1 dosing ratio in Section 4.2 of the Xeomin 50U SPC, Posology and method of administration, had been removed. The Xeomin 50U SPC still contained information regarding its non-inferiority studies (Section 5.1, Pharmacodynamic properties) but this was in relation to specific patients ie those with blepharospasm or cervical dystonia. As previously established, non-inferiority studies did not support claims of equivalence.

The SPCs for Botox 50, 100 and 200 units stated:

> **'Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan units are different from other botulinum toxin preparations.'**

Allergan noted Merz's use of the claim '1:1 Clinical Conversion Ratio' and visual of Bocouture and Botox vials side-by-side and alleged that this was clearly designed to emphasise a direct 1:1 equivalence/ conversion of the two products. The claim 'In glabellar frown lines, clinical studies suggest' was included. Less prominently and in significantly smaller font was the statement from the SPC 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.'

Allergan considered that health professionals would take away the message that Bocouture and Botox

were equally potent and could be converted 1:1. The promotion by Merz of this 1:1 clinical conversion ratio between Bocouture and Botox was of significant concern. No 'dosing conversion' occurred or should be implied from the non-inferiority study conducted by Merz with its toxin (Sattler *et al*).

Allergan submitted that the direct medical impact was that a significant patient safety risk existed with prescribers encouraged to transfer information from one label to another product.

Allergan noted the ruling in Case AUTH/2270/10/09 that the results of a non-inferiority study could not be used to claim equivalence. Merz's own submission in that case was that it had no data to support a claim that Xeomin was equivalent to Botox. This was still so and Merz had not published any new clinical data to support a claim of equivalence for either Xeomin or Bocouture. Therefore, Allergan alleged that the visuals, which implied equivalence/equipotency and the claim '1:1 Clinical Conversion Ratio' between Bocouture and Botox (ie equivalence), were a breach of the undertaking given in Case AUTH/2270/10/09 and as such were in breach of Clause 25.

When writing to Merz, the Authority asked it to respond in relation to Clauses 2 and 9.1 in addition to Clause 25 cited by Allergan.

RESPONSE

Merz noted that in Case AUTH/2270/10/09 it was found in breach of the Code for claiming that Xeomin was 'At least as effective as Botox with a similar safety profile'. The Panel considered that the claim implied possible superiority of Xeomin vs Botox which was not supported by the available data. The breach was upheld upon appeal.

Merz further noted that in Case AUTH/2496/4/12, claims of 'Equipotent' or 'Equal Potency' were ruled on by the Panel in the context of Case AUTH/2270/10/09 for the advertisement in question (ref 1075/BOC/DEC/2011/JH) and no breaches of Clauses 2, 9.1 or 25 were found.

Merz therefore considered that the advertisement now at issue did not breach the undertaking given in Case AUTH/2270/10/09 and was not in breach of Clauses 2, 9.1 or 25.

Merz submitted that the advertisement in question was withdrawn from circulation (due to the update to the Bocouture SPC) and the last Bocouture insertion was March. No further Bocouture advertising was planned until an updated advertisement had been developed (April and May editions did not contain the advertisement in question). Merz had two full page advertisements booked for the June edition for its dermal fillers, Radiesse and Belotero. On 8 June an updated Bocouture advertisement was sent to the journal for all future use. Cosmetic News erroneously printed the June edition with Radiesse and the old Bocouture advertisement (instead of Belotero). Merz had reviewed its processes for ensuring publishers used only current and approved advertisements.

The withdrawal of the advertisement at issue had already been captured in the undertaking (signed 27 June 2012) to comply with the Panel's ruling in Case AUTH/2496/4/12.

PANEL RULING

The Panel noted that in Case AUTH/2270/10/09 it had considered a complaint from Allegan that the claim by Merz that Xeomin was 'At least as effective as Botox with a similar safety profile' without appropriate context and qualification did not accurately reflect the available evidence and was misleading. Allergan had submitted that to make the claim 'At least as effective as', Merz needed further evidence to confirm equivalent efficacy and clinically relevant superiority. The claim at issue was referenced to Benecke *et al* (2005) and Roggenkamper *et al* (2006) both of which were non-inferiority studies. The Panel considered that there was a difference between showing non-inferiority and showing comparability and that the claim that Xeomin was 'At least as effective as Botox' did not reflect the available evidence. It implied possible superiority of Xeomin and was misleading as alleged and breaches of the Code were ruled. Following an appeal by Merz, the Appeal Board noted Merz's submission that it had no data upon which to claim that Xeomin was equivalent to Botox. The Appeal Board stated that in its view, the claim 'At least as effective as' not only implied equivalence but also possible superiority which was misleading. The Appeal Board did not consider that the claim could be substantiated by the available data and the Panel's rulings were upheld.

The Panel noted that the material now at issue in Case AUTH/2516/6/12 was different to that at issue in Case AUTH/2270/10/09. In Case AUTH/2270/10/09 the comparison at issue had been between Xeomin and Botox; the comparison now at issue was between Bocouture and Botox. Bocouture and Xeomin, however, were the same product but with different indications – Bocouture was indicated for the temporary improvement in the appearance of glabellar frown lines whilst Xeomin was for the symptomatic treatment of blepharospasm, cervical dystonia and post-stroke spasticity of the upper limb.

The Panel noted that the advertisement now at issue had also been at issue in Case AUTH/2496/4/12. In that case, Allegan had similarly alleged that the claims for 'Equal Potency' and '1:1 Clinical conversion ratio' were in breach of the undertaking given in Case AUTH/2270/10/09. The Panel's ruling of no breach of the Code was overturned following an appeal by Allergan. The case was considered in July (ie after the advertisement had reappeared in the June edition of Cosmetic News) and the Appeal Board in its ruling stated:

> 'The Appeal Board noted that the undertaking in [Case AUTH/2270/10/09] related to a claim that not only implied equivalence but also possible superiority; its ruling had been made on both aspects. In the current case, Case AUTH/2496/4/12, Allergan's allegation regarding a breach of undertaking, the subject of the appeal, related only to claims of equivalence.

The Appeal Board noted that to date there was still no data to show whether Xeomin/Bocouture was equivalent to Botox/Vistabel. Now, as when the ruling in Case AUTH/2270/10/09 was made, there were only non-inferiority studies which showed that the medicines were no worse than each other by a clinically acceptable pre-specified margin.

Turning to Case AUTH/2496/4/12, the Appeal Board considered that the Bocouture advertisement (ref 1075/BOC/DEC/2011/JH) claim 'In glabellar frown lines, clinical studies suggest' followed by 'Bocouture vs Botox:', 'Equal potency' and '1.1 Clinical Conversion Ratio' together with the visual beneath of a vial of each of the medicines side-by-side, implied to prescribers that the two products were clinically equivalent and that unit for unit they were interchangeable. The Appeal Board considered that although the claim at issue was not the same as that in Case AUTH/2270/10/09, it was sufficiently similar with regard to a claim for 'equivalence' for it to be covered by the undertaking previously given. The Appeal Board thus ruled a breach of Clause 25. The appeal on this point was successful.

The Appeal Board noted that the Bocouture advertisement included the statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin' and the Xeomin advertisement similarly included the statement 'Always prescribe by brand, unit doses are not interchangeable'. These statements were referenced to the respective products' SPCs and in both advertisements they appeared in a less prominent position and smaller font than the claims and visuals that implied clinical equivalence. The Appeal Board considered that implying that the products were clinically equivalent and hence interchangeable was contrary to statements in the SPCs. The Appeal Board considered that this raised possible patient safety concerns.

The Appeal Board considered that as Merz had no data on which to base the implied claims of clinical equivalence and as it had breached its undertaking and assurance in Case AUTH/2270/10/09 it had failed to maintain high standards and it had thus brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled breaches of Clauses 9.1 and 2. The appeal on this point was successful.'

The Panel considered that the Appeal Board's ruling of a breach of Clause 25 applied to the case now before it, Case AUTH/2516/6/12. The Panel thus ruled a breach of that clause. The Panel considered that as the undertaking had not been complied with, high standards had not been maintained. A breach of Clause 9.1 was ruled.

With regard to the alleged breach of Clause 2, the Panel noted that it was extremely important that companies complied with undertakings; to do otherwise brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel further noted that there was still no data upon which to base a claim that Botox and Bocouture were clinically equivalent. Although the claim for a 1:1 clinical conversion ratio between Bocouture and Botox was referenced to Sattler *et al*, this was a non-inferiority study and so did not substantiate the claim. The Panel was concerned to note that although the advertisement in question had been withdrawn following changes made to the Bocouture SPC, Cosmetic News subsequently published it in error. The Panel considered that companies must have in place robust procedures to ensure that, when required and for whatever reason, materials were withdrawn from all relevant parties including agencies and publishers. The Panel noted Merz's submission that it had reviewed its processes for ensuring publishers used only current and approved advertisements. Nonetheless, the Panel considered that the circumstances were such that Merz had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **15 June 2012**

Case completed **24 August 2012**