CASE AUTH/2460/11/11

MERZ/DIRECTOR v ALLERGAN

Breach of undertaking

Merz alleged that at a meeting and through the conduct of one of its representatives, Allergan had continued to misrepresent data relating to the relative potencies of its medicines Vistabel/Botox (botulinum toxin type A (onabotulinumtoxinA)) vs Merz's medicines Bocouture/Xeomin (botulinum toxin type A (incobotulinumtoxinA)). As Merz alleged that Allergan had breached the undertakings given in Cases AUTH/2183/11/08 and AUTH/2346/8/10 this case was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

The detailed response from Allergan is given below.

The presentation at issue was given by an Allergan scientific services manager at an aesthetic practitioners meeting. Merz alleged that claims were made about the relative potency of Vistabel vs Bocouture – a comparison which had been the subject of Case AUTH/2346/8/10 – and built the case that the units of potency of the products were not interchangeable and that Bocouture was less potent than Vistabel. The presentation specifically did not reflect the Bocouture summary of product characteristics (SPC) which stated: 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency'.

Merz submitted that in Case AUTH/2346/8/10 the Appeal Board stated that 'both the Bocouture SPC and data on file that support the SPC statement were available to Allergan when the presentation [at issue in that case] was delivered but were nonetheless not included'. Allergan had again presented a discussion about product potency excluding not only the regulator's view but now also that of the Appeal Board. No new independent data to change understanding of relative potencies had been published. In fact since the Appeal Board's ruling a 1:1 conversion ratio between Botox (Vistabel) and Xeomin (Bocouture) had been made even more clear with the publication of the Xeomin 50 unit SPC in May 2011 which stated: 'Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1'.

Merz alleged that the Allergan presentation referred to non-interchangeability of unit doses directly quoted from the product SPCs yet it again failed to mention the regulatory view of the relative potencies. Merz noted that the botulinum toxin in both Vistabel and Bocouture came from the Hall strain of clostridium botulinum and as such would not be expected to demonstrate different clinical effect.

The Allergan speaker then presented data from Moers-Carpi *et al* (2011) to further develop the impression that Bocouture was less potent than Vistabel. Merz submitted that the design of this study was open to significant question as there was no control arm and unmatched doses of each product were used.

Merz stated that prior to the publication of this recent data it had been established, and reflected in the SPCs, that the correct starting dose for Vistabel and Bocouture in the treatment of moderate to severe glabellar frown lines was 20 units. Carruthers *et al* (2005) demonstrated that Botox 20U and 30U showed no measurable clinical difference in the treatment of moderate to severe frown lines and postulated that in most patients a 20U dose was sufficient to saturate the local nerve endings so that additional dosing had little or no incremental clinical effect.

The new Allergan study compared 30U of Bocouture with 20U of Vistabel in moderate to severe frown lines. Merz alleged that the crafting of this presentation, the selective use of data, and what could only be a deliberate omission of the established regulatory position to leave the impression of reduced potency of Bocouture to Vistabel was cynical and in breach of previous undertakings made by Allergan.

The Panel noted that in Case AUTH/2346/8/10, the Appeal Board considered that a presentation by Allergan had implied that Botox was more potent than Xeomin which was inconsistent with the SPCs and clinical data. Although the material at issue in Case AUTH/2346/8/10 differed from that in Case AUTH/2183/11/08, the Appeal Board considered that the overall effect was sufficiently similar to the point at issue in Case AUTH/2183/11/08 for it to be caught by the undertaking in that case and so breaches of the Code were ruled including a breach of Clause 2.

The Panel noted that Bocouture/Xeomin contained the same active constituent as Botox/Vistabel, ie botulinum toxin type A (BONT/A). In all of the products the neurotoxin was derived from an identical strain.

The Panel noted that there appeared to be no standard assay method for the two BONT/A preparations. The SPCs for Botox/Vistabel referred to Allergan Units/vial and the Bocouture/Xeomin SPCs referred to LD50 units per vial. The Xeomin SPC stated that due to differences in the LD50 assay, these units were specific to Xeomin and were not interchangeable with other botulinum toxin preparations. All of the SPCs stated that as the botulinum toxin units differed from product to product, doses recommended for one product were not interchangeable with those for another. The

Bocouture SPC, however, stated that comparative clinical study results suggested that Bocouture and the comparator product containing conventional botulinum toxin type A complex (900kD) [Botox/ Vistabel] were of equal potency. The Xeomin 50 units SPC contained the equivalent statement but added 'when used with a dosing conversion ratio of 1:1'. In this regard the Panel noted that Sattler *et al* (2010) demonstrated the non-inferiority of 24 units each of Bocouture/Xeomin to Botox/Vistabel in the treatment of frown lines. The SPCs for Bocouture and Vistabel stated identical recommended unit doses for the treatment of moderate to severe frown lines, ie five injections each of 4 units. The Bocouture SPC stated that the dose might be increased to up to 30 units if required by the individual needs of the patient.

The title of the presentation at issue was 'Botulinum Toxin Review and Update'. The second slide stated that the most potent of the seven botulinum neurotoxin serotypes was type A, the active constituent of Vistabel and Bocouture. It was also stated that unit doses of botulinum toxin were not interchangeable from one product to another. Slide 14 of the presentation depicted the SPCs for, *inter alia*, Bocouture and Vistabel and the heading referred to the 'non-interchangeability of units of BONT-A products'. Although the relevant statement in the Bocouture SPC was highlighted, the subsequent statement that comparative clinical study results suggested that Bocouture and Botox/ Vistabel were of equal potency was not and nor was this information given in any other slide.

The final section of the presentation headed 'Introduction to Clinical Trials' discussed non-inferiority studies in general and the last 19 slides in particular detailed the results of Moers-Carpi *et al* which compared the efficacy of Vistabel (20 units) vs Bocouture (30 units) in the treatment of patients with moderate/severe glabellar lines. There was no explanation as to why different doses of the two medicines had been chosen despite the doses (in numbers of units) recommended in the respective SPCs being identical. The slide which introduced the study stated that 20 units of Vistabel and 30 units of Bocouture both represented labelled doses. It did not appear, however, that information about the doses chosen in the study had been presented within the context of the SPC recommendations, ie that the starting dose for Bocouture was 20 units which could be increased to up to 30 units if required. The slide headed 'Study Conclusions' stated that Vistabel (20 units) was as effective as Bocouture (30 units) in the treatment of glabellar lines and that the study reinforced the data previously reported by Hunt *et al* (2010). The Panel noted that there was no reference in the presentation to Sattler *et al* although the speaker submitted he/she had mentioned that the study had shown that in the same therapy area 24 units of Bocouture was non-inferior to 24 units of Vistabel.

The Panel also noted that there was no reference in the presentation to Carruthers *et al*, the dose ranging study with Botox/Vistabel which had shown that in the treatment of frown lines doses of 30 or 40 units did not produce statistically significantly better results than a dose of 20 units and that the majority of patients responded well to 20 units with some needing a higher dose to achieve the same effect. Although this was a Botox/Vistabel study, the Panel considered that it demonstrated an important point which would have helped to provide context to the rest of the presentation. The Panel noted that Allergan had provided a copy of data on file from Merz which it stated demonstrated a dose response for Bocouture/Xeomin between 10, 20 and 30 units when used to treat frown lines. When determined by the investigator at day 30, the percentage of responders to 20 units and 30 units was 74.5 and 91.7 respectively. It was not stated in the information before the Panel whether this was a statistically significant difference.

Overall, the Panel considered that the presentation did not reflect the balance of evidence with regard to the relative potencies and was concerned to note that, as acknowledged by Allergan, it had not been reviewed or approved for use at the meeting. In the Panel's view the presentation implied that Botox/Vistabel was more potent than Bocouture/ Xeomin. In that regard the Panel considered that this was sufficiently similar to the point at issue in Case AUTH/2346/8/10 for it to be covered by the undertaking in that case and to breach undertakings given previously. In that regard high standards had not been maintained. Breaches of the Code were ruled.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking was such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Panel ruled a breach of Clause 2.

Merz stated that an Allergan sales representative, in a visit to a customer who used Bocouture, used the Moers-Carpi *et al* poster to support the assertion that the potency of Bocouture was inferior to that of Vistabel. The poster directly referred to the Hunt and Clark data that was the subject of the breach of undertaking in Case AUTH/2346/8/10. The customer was clearly left with the message that Bocouture did not possess the same clinical potency per unit as Vistabel.

The Panel noted that the Vistabel sales aid provided by Allergan as the only promotional item that referred to Moers-Carpi *et al* was entitled 'Not all toxins are Vistabel'. The front cover included with the statement 'Vistabel unit doses are not interchangeable with other preparations of botulinum toxins'. One page was headed 'Head-to-head data review of glabellar lines' beneath which were a very brief description of Sattler *et al* and a more detailed description of Moers-Carpi *et al*. Subsequent pages of the sales aid detailed the results of Moers-Carpi *et al* with the use of a bar chart and graph. The back page included the claim 'A recently conducted equivalence study confirms that unit doses of Vistabel and Merz toxin are not interchangeable in clinical practice' referenced to Moers-Carpi *et al*. There was no reference on the

back page to Sattler *et al*. There was no mention of the statement in the Bocouture SPC that clinical data suggested equal potency.

There was no complaint about the sales aid. However, the Panel considered it was relevant to the allegation that the customer was left with the message that Bocouture did not possess the same clinical potency per unit as Vistabel.

The Panel noted that the Moers-Carpi *et al* poster was not available for representatives to distribute; if customers asked for a copy the representatives had to ask medical information to send a copy or receive a copy themselves in a sealed envelope for delivery. Allergan had acknowledged that three customers had asked the representative for a copy of the poster.

The Panel noted that it was impossible to know what the representative had said or whether the representative had used the sales aid. However, the Panel considered that, given the content of the sales aid, on the balance of probabilities, the representative had used the Moers-Carpi *et al* poster to inform the health professional that in order to achieve the same clinical outcome in the treatment of glabellar lines 20 units of Vistabel was needed vs 30 units of Bocouture ie unit for unit, Bocouture, was less potent than Vistabel.

The Panel noted its comments above with regard to the clinical data and the statement in the Bocouture SPC. Noting the content of the sales aid the Panel considered that the arranged provision of the Moers-Carpi *et al* poster by the representative would, on the balance of probabilities, leave the health professional with the impression that Bocouture did not possess the same clinical potency as Vistabel as alleged. In the Panel's view this breached the undertakings previously given. In that regard high standards had not been maintained. Breaches of the Code were ruled.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

The Panel noted that Allergan had again breached undertakings with regard to claims about the relative potency of its botulinum toxin vs that of the Merz product. In the Panel's view, the repeated and serious nature of such breaches of the Code raised concerns about the company's procedures and warranted consideration by the Appeal Board. In accordance with Paragraph 8.2 of the Constitution and Procedure, the Panel reported the company to the Appeal Board.

The Appeal Board noted that Allergan had accepted the breaches of the Code and that it had already undertaken meaningful action to improve its culture and processes to avoid similar errors in the future. Further steps to improve compliance were planned.

The Appeal Board considered that the company's comments on the report and presentation revealed a marked lack of insight and objectivity. Given that potency comparisons between Botox and Xeomin had previously resulted in two breaches of undertaking it was vital that Allergan briefed, trained and had systems in place such that its staff did not use material that could result in a further breach of undertaking or the use of unapproved slides. The Appeal Board considered that an undertaking and assurance was an important document and it was extremely concerned that Allergan had now breached its undertaking and assurance on three separate occasions in a short space of time. This was completely unacceptable.

The Appeal Board decided that Allergan should be publicly reprimanded for successive breaches of its undertaking. The Appeal Board also decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require an audit of Allergan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in April 2012. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

On receipt of the April 2012 audit report the Appeal Board considered that Allergan's procedures were not satisfactory. The Appeal Board was extremely disappointed that there was insufficient responsibility taken across the company for Code compliance. Company culture did not appear to support compliance with the Code. The Appeal Board noted that it had already publicly reprimanded Allergan.

The Appeal Board decided that Allergan should be re-audited in three months' time at which point it expected there to be significant improvement. As part of the usual re-audit process Allergan would be asked to provide an update of its response to the first audit report with actions and timelines. Upon receipt of the report for the re-audit, the Appeal Board would decide whether further sanctions were necessary.

The Appeal Board subsequently decided in Cases AUTH/2487/3/12 and AUTH/2489/3/12 to require an audit which would be conducted at the same time as the re-audit required in this case (Case AUTH/2460/11/11).

On receipt of the August 2012 audit report the Appeal Board was disappointed at the lack of progress demonstrated. However the company appeared to have taken action including setting time frames for the bulk of the processes and work to be completed by the end of 2012. The Appeal Board was concerned that the amendments to some of the standard operating procedures (SOPs) had not been finalized. The Appeal Board noted that there were plans to significantly change the company structure and the interim country manager would be replaced in 2013. A UK medical director was due to be appointed. The Appeal Board considered that Allergan should be re-audited in January 2013 at which point it expected there to be significant improvement.

Upon receipt of the January 2013 audit report, the Appeal Board noted that although Allergan had made progress, further improvement was necessary. The Appeal Board noted that one key change in senior personnel would take place shortly and another in due course. Given that further improvement was required, the Appeal Board considered that Allergan should be re-audited in September 2013. Upon receipt of the next audit report, the Appeal Board would decide whether further sanctions were necessary.

Upon receipt of the September audit report, the Appeal Board noted that Allergan had made progress since the re-audit in January. The company had undergone four audits since April 2012. It was important that the progress shown in the September 2013 audit was continued and maintained. Every opportunity should be taken for improvement. The Appeal Board noted that Allergan needed to ensure that it updated its processes in good time to reflect the 2014 Code and that relevant staff were trained on the new Code. Allergan provided details of its plans to implement the recommendations in the audit report. On the basis that this work was completed, the Appeal Board decided that no further action was required.

Merz Pharma UK Ltd alleged that Allergan Limited had continued to misrepresent data relating to the relative potencies of its medicines Vistabel/Botox (botulinum toxin type A (onabotulinumtoxinA)) vs Merz's medicines Bocouture/Xeomin (botulinum toxin type A (incobotulinumtoxinA)). As Merz alleged that Allergan had breached the undertakings given in Cases AUTH/2183/11/08 and AUTH/2346/8/10 this case was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Merz explained that in accordance with Paragraph 5.3 of the Constitution and Procedure it had not sought to resolve this matter through inter-company dialogue with Allergan. It was apparent that despite repeated reinforcement of the importance of undertakings this consistent behaviour suggested either poor understanding of the Code coupled with systemic compliance incompetence or contempt; neither was appropriate within the industry.

By way of background Merz noted that in Case AUTH/2183/11/08 Allergan was ruled in breach of the Code for suggesting that Xeomin (the same pharmaceutical product as Bocouture) was less potent than Botox (the same pharmaceutical product as Vistabel). Following this Allergan entered into an undertaking not to use this or similar claims. This undertaking was breached twice in Cases AUTH/2335/7/10 and AUTH/2346/8/10 and Allergan entered into yet another undertaking. It was clear that Allergan had again breached the undertaking and the fact that two employees from different parts of the business had delivered the same message within a week of each other suggested this was a behaviour born out of a clear brief.

Merz was concerned that Allergan was relentless in its pursuit of the message that the Bocouture and Xeomin units were less potent than the Vistabel and Botox units against all the clinical evidence and the view of the Medicines and Healthcare products Regulatory Agency (MHRA) and the wider European regulators. In pursuit of this message Allergan was clearly as contemptuous of the PMCPA, the Code of Practice Appeal Board and its undertakings as it was of the regulators and the peer reviewed published evidence.

By way of background, Allergan explained that it did not accept the allegations from Merz that it had made 'disparaging, misleading and unsubstantiated' claims about the relative potency of Bocouture/Xeomin vs Vistabel/Botox or that these claims constituted a breach of undertaking. Allergan took exception to the tone and language within Merz's complaint and strongly refuted the serious and disparaging allegations made. Allergan was aware and fully understood the undertakings made with respect to Case AUTH/2183/11/08 and Case AUTH/2346/8/10 (which was ruled on along with Case AUTH/2355/7/10). It took any undertaking seriously and certainly would not treat them with contempt as erroneously suggested by Merz.

The undertakings in all three cases fundamentally related to the use of animal data (Hunt and Clarke, 2006 and 2009). More specifically, the undertaking in Case AUTH/2183/11/08 centred around the use of these animal data, which should not be extrapolated to the clinical situation unless there were data to show it was of direct relevance and significance.

Case AUTH/2346/8/10 (and Case AUTH/2335/7/10) again centred on the use of Hunt and Clarke data and the fact that it implied that Botox was more potent than Xeomin, which was inconsistent with the summaries of product characteristics (SPCs) and the recently available clinical data from Merz. The data had not been sufficiently contextualised and therefore the presentations at issue in both cases were found in breach of the ruling in Case AUTH/2183/11/08.

With respect to the current alleged breach of undertaking at two events, no animal data relating to the Hunt and Clarke study (at the centre of the original undertaking in Case AUTH/2183/11/08) nor indeed any animal potency determination data were presented. In both instances directly relevant and significant, new clinical data were presented, which Allergan believed substantially changed the scientific landscape and understanding of non-interchangeability of potency units of botulinum toxins. These data supported Allergan's assertion (as stated in the SPCs for all botulinum toxin products and throughout the presentation) that units doses were not interchangeable from one product to another.

At the heart of these issues were the two companies' understanding of the SPCs and how the information should be interpreted and presented in a balanced way to health professionals.

For clarity Allergan reproduced the various SPC statements:

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'**

The SPC for Vistabel stated:

> 'Considering that botulinum toxin units are different depending on the medicinal products, doses of botulinum toxin are not interchangeable from one product to another.'

The SPC for Xeomin (50 units) stated:

> **'Due to unit differences in the LD50 assay, Xeomin units are specific to Xeomin. Therefore unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.**
>
> Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1.'

The SPC for Xeomin (100 units) stated:

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

The SPC for Bocouture stated:

> **'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.**
>
> Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency.'

Allergan considered that the most prominent and significant statement in all of the botulinum toxin SPCs was that unit doses of products were not interchangeable. This statement of non-interchangeability was imposed on all botulinum toxin manufacturers by the Pharmacovigilance Working Party (PhVWP) which, following a class review in 2006, mandated that all botulinum toxin SPCs included wording to highlight the non-interchangeability of unit doses between products, in order to ensure the safe and appropriate use of botulinum toxins. In the two events at issue where Merz had alleged a breach of undertaking, Allergan submitted that it had clearly communicated the non-interchangeability of unit doses, supported by new clinical data, not that Merz's toxin was less potent than Allergan's. This was the message that Allergan had always wanted to convey. Allergan fully accepted and understood the rulings in the previous cases. However, at these two events no undertaking had been breached as no animal data had been used, despite the availability of substantial new clinical data from an appropriately powered (n=220), randomised, double-blind, peer reviewed equivalence study. It had not been stated or implied that Merz's products were less potent, only that they were not the same and that unit doses were not interchangeable. Allergan had been required to make this explicitly clear to customers in part because of Merz's marketing strategy of promoting a 1:1 conversion ratio as demonstrated in a recent advertisement (a copy was provided) and indeed in Merz's complaint itself. Allergan considered that this strategy fundamentally contradicted the intent of the PhVWP when it mandated that all botulinum toxin SPCs included wording (in bold) to highlight the non-interchangeability of unit doses between products to ensure the safe and appropriate use of botulinum toxins.

Assessment of potency was a laboratory measure, using an LD50 assay, and was not a recognised endpoint in clinical studies. Each botulinum toxin manufacturer had its own unique and proprietary potency assay methodology. Consequently, the PhVWP's mandated statement that unit doses of the botulinum toxin containing products were not interchangeable be included in all SPCs including that of Xeomin and Bocouture. Allergan did not believe that this requirement was superseded by a contradictory statement based upon clinical studies of a non inferiority design. Non-inferiority studies could not demonstrate equivalence. Allergan noted that in Case AUTH/2270/10/09, the Appeal Board's view was that the results of a non-inferiority study could not be used to claim equivalence. It was noted that the expression 'suggest … are of equal potency' (emphasis added) had been used in the Bocouture SPC.

The suggestion by Merz of 'a dosing conversion ratio of 1:1' between Xeomin/Bocouture and Botox/ Vistabel was of significant concern. No 'dosing conversion' occurred or should be implied from the non-inferiority studies conducted by Merz with its toxin.

Allergan considered 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.

1 Meeting presentation

COMPLAINT

Merz alleged that in November 2011 a scientific support manager from Allergan gave a presentation on botulinum toxins at a practitioners meeting. Merz believed that the presentation was promotional and thus fell within the scope of the Code.

The presentation was prefaced with the metaphor that although all beer was made from water, malt, hops and yeast, different beer strengths could be created from the same ingredients. The presentation went on to make claims about the relative potency of Vistabel vs Bocouture – a comparison which was previously the subject of Case AUTH/2346/8/10 – and built the case that the units of potency of the products were not interchangeable and that

Bocouture was less potent than Vistabel. The presentation specifically did not include or reflect the position of the European regulator which opposed this view and was included in section 4.2 of the Bocouture SPC which stated:

> 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency'.

Merz submitted that in Case AUTH/2346/8/10 the Appeal Board stated that 'both the Bocouture SPC and data on file that support the SPC statement were available to Allergan when the presentation was delivered but were nonetheless not included'. Allergan had again presented a discussion about product potency excluding not only the regulator's view but now also that of the Appeal Board. No new independent data to change the up-to-date understanding of relative potencies had been published and as such the scientific landscape remained unchanged. In fact since the Appeal Board's ruling the regulator had made its view even more clear, specifying a 1:1 conversion ratio between Botox (Vistabel) and Xeomin (Bocouture) with the publication of the Xeomin 50 unit SPC in May 2011 which stated in section 4.2:

> 'Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used with a dosing conversion ratio of 1:1.'

Merz alleged that the Allergan presentation referred to non-interchangeability of unit doses directly quoted from the product SPCs yet it again failed to mention the regulatory view of the relative potencies. Merz noted that the botulinum toxin in both Vistabel and Bocouture came from the same (Hall strain) clostridium botulinum and as such would not be expected to demonstrate different clinical effect.

The Allergan speaker then presented data from a recent non-peer reviewed poster authored by two Allergan employees together with a third author (Moers-Carpi *et al* 2011) to further develop the impression that Bocouture was less potent than Vistabel. Merz submitted that the design of this study was open to significant question as there was no control arm and unmatched doses of each product were used, making a potency comparison difficult.

Merz stated that prior to the publication of this recent data it had been established, and reflected in both product SPCs, that the correct starting dose for Vistabel and Bocouture in the treatment of moderate to severe glabellar frown lines was 20 units. This starting dose had been further investigated by Carruthers *et al* (2005) who compared 4 doses (10U, 20U, 30U and 40U) of Botox in eighty females with moderate to severe glabellar frown lines. The study demonstrated that Botox 20U and 30U showed no measurable clinical difference and the authors concluded that there 'were no statistically significant differences among the three higher-dose groups'. It was postulated that in most patients a 20U dose was sufficient to saturate the local nerve endings so that additional dosing had little or no incremental clinical effect.

The new Allergan study compared 30U of Bocouture with 20U of Vistabel in moderate to severe glabellar frown lines. Merz alleged that the crafting of this presentation, the selective use of data, and what could only be a deliberate omission of the very clearly established regulatory position to leave the impression of reduced potency of Bocouture to Vistabel was both cynical and clearly in breach of previous multiple undertakings made by Allergan.

RESPONSE

Allergan provided a copy of the presentation at issue with a document from the speaker, a scientific services manager, outlining his/her recollection of what was said. No materials had been provided to the delegates.

Allergan noted that the presentation did not refer to the Hunt and Clarke (2006 or 2009) data and this data was not discussed during the presentation. Slides 9-14, 19, 21 and 48 covered the topic of non-interchangeability and potency was referred to in some of these but specifically in the context of potency units being specific to each product. There was no statement, suggestion or inference that one product was less potent than another, just that each botulinum toxin was unique. The speaker provided a summary of how the 'beer' analogy and slide had been discussed.

Allergan noted that the presentation did not specifically include the statement in the Bocouture SPC that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency'. However, as stated in his/her summary the speaker clearly referred to Sattler *et al* (2010), the non-inferiority study upon which the SPC statement was based. The speaker would have included slides on the study itself if the presentation time had not been significantly reduced at short notice by the meeting organisers.

Allergan considered the issue of non-interchangeably was addressed appropriately prior to the introduction of significant new clinical data (Moers-Carpi *et al*).

In contradiction of Merz's allegations, these data had been peer reviewed by the scientific committees of European Masters in Anti-Aging Medicine (EMAA) and further information from this study had also been peer reviewed and accepted for a poster presentation at the American Society for Dermatologic Surgery (ASDS).

Allergan submitted that this new peer-reviewed equivalence study (Moers-Carpi *et al*) had been published since the rulings in the cases cited above and indeed since the update to the SPC labelling

of Bocouture and Xeomin 50 units in the UK. These new data from a large (n=220) randomised, double blind, equivalence study directly challenged the hypothesis that the products were indeed interchangeable at a 1:1 dose ratio and had provoked significant interest in the scientific and clinical community, which was, at the same time, seeing contradictory weekly advertisements from Merz in the BMJ quoting a 1:1 ratio.

Allergan was surprised to note that Merz had erroneously referenced Botox dose ranging data in relation use in glabellar lines, stating that this meant the dose ranging for Bocouture would be similar. The Botox dose ranging publication (Carruthers *et al*) stated, 'It should be noted that the results reported in this study refer to the Allergan (Irvine, CA, USA) formulation of botulinum toxin type A (Botox, Botox Cosmetic, Vistabel) and cannot be generalized to other formulations or serotypes of botulinum toxin'. Furthermore, Merz had conducted its own dose-ranging clinical study of Bocouture (data from which was presented publicly at the European Academy of Dermatology and Venerology conference in 2009 and subsequently sent to Allergan in July 2010 following an information request, as it did not believe these data had been published in a peer reviewed journal). This dose-ranging study by Merz stated that there was indeed a dose response for Bocouture between 10, 20 and 30 units when used in glabellar lines (Merz - Data on File; a copy was provided by Allergan). Allergan submitted that the differences seen for Botox and Bocouture in clinical dose ranging studies further supported the non-interchangeability of potency units in a clinical setting. This was also supported by regulatory agency assessments of the products, as there were differences between the labels for Vistabel and Bocouture, where a single dose of 20 units was indicated for Vistabel as compared to 20-30 units for Bocouture.

Allergan was deeply concerned that the UK label for Bocouture contained an inaccurate, contradictory and hence misleading statement:

> **'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin.**
>
> Comparative clinical study results suggest that Bocouture and the comparator product containing Botulinum toxin type A complex (900kD) are of equal potency.'

Allergan had been in confidential correspondence with the PhVWP about its concerns and understood that a label change had subsequently been requested by Germany (reference member state for Xeomin and Bocouture) following discussions at the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

Allergan strongly denied that the presentation had breached an undertaking. There was no statement, suggestion or inference that one product was less potent than another, only that each botulinum toxin was unique. The animal data at issue in the previous cases was not presented. The new clinical data presented was used to support Allergan's assertion (as stated in the SPCs for all botulinum toxin products) that units doses were not interchangeable from one product to another.

Allergan stated that the slide deck used at the meeting in November had been reviewed and it regretted to inform the PMCPA that it had not been reviewed or approved for use at the meeting. Allergan acknowledged that this was a clear breach of the Clause 14.1. The failure to seek appropriate review and approval of the presentation meant that the employee and therefore Allergan had failed to maintain high standards in breach of Clause 9.1.

The employee had been told that failure to get the presentation approved was a very serious matter, in breach of Clause 14.1 and of Allergan policy and procedures. As a consequence a full internal investigation had been instigated and would result in appropriate disciplinary action for the employee.

Allergan took this matter extremely seriously and, apart from actions being undertaken with the employee, it would reinforce the requirement for approval of all presentations with all relevant personnel. Any repeat of such failures would result in disciplinary action including dismissal of individuals responsible for such breach.

In response to a request for further information Allergan stated there was a verbal invitation for the scientific services manager to be an expert speaker at the meeting. This was followed up by an email.

The slide deck used by the manager built on a slide deck that had been approved as a core set of Medical Affairs slides. This core set could be selected from by the medical affairs team but any selection from the set required approval of the presentation prior to use in breach of Clause 14.1.

PANEL RULING

The Panel noted that in Case AUTH/2346/8/10, the Appeal Board considered that a presentation by Allergan had implied that Botox was more potent than Xeomin which was inconsistent with the product SPCs and the available clinical data. Although the material at issue in Case AUTH/2346/8/10 differed from that in Case AUTH/2183/11/08, the Appeal Board considered that the overall effect was sufficiently similar to the point at issue in Case AUTH/2183/11/08 for it to be caught by the undertaking in that case and so breaches of the Code were ruled including a breach of Clause 2.

Turning to the case now before it, Case AUTH/2460/11/11, the Panel noted that Bocouture/Xeomin contained the same active constituent as Botox/Vistabel, ie botulinum toxin type A (BONT/A). In all of the products the neurotoxin was derived from the identical Hall strain of Clostridium botulinum type A. Bocouture/Xeomin which was free from complexing proteins had a molecular weight of 150kD whilst Botox/Vistabel was associated with other proteins and had a higher

molecular weight (900kD). The SPCs for Botox/Vistabel stated that under physiological conditions it was presumed that the complex dissociated and released the pure neurotoxin.

The Panel noted that there appeared to be no standard assay method for the two BONT/A preparations. The SPCs for Botox/Vistabel referred to Allergan Units/vial and the Bocouture/Xeomin SPCs referred to LD50 units per vial. The Xeomin SPC stated that due to differences in the LD50 assay, these units were specific to Xeomin and were not interchangeable with other botulinum toxin preparations. All of the SPCs stated that as the botulinum toxin units differed from product to product, doses recommended for one product were not interchangeable with those for another. The Bocouture SPC, however, stated that comparative clinical study results suggested that Bocouture and the comparator product containing conventional botulinum toxin type A complex (900kD) [Botox/Vistabel] were of equal potency. The Xeomin 50 units SPC contained the equivalent statement but added 'when used with a dosing conversion ratio of 1:1'. In this regard the Panel noted that Sattler *et al* (2010) demonstrated the non-inferiority of 24 units each of Bocouture/Xeomin (n=277) to Botox/Vistabel (n=93) in the treatment of glabellar frown lines. The SPCs for Bocouture and Vistabel stated identical recommended unit doses for the treatment of moderate to severe glabellar frown lines, ie five injections each of 4 units. The Bocouture SPC stated that the dose might be increased to up to 30 units if required by the individual needs of the patient.

The Panel noted that the presentation at issue had been given at an aesthetic practitioners meeting. The title of the presentation was 'Botulinum Toxin Review and Update'. The second slide stated that the most potent of the seven botulinum neurotoxin serotypes was type A, the active constituent of Vistabel and Bocouture. It was also stated that unit doses of botulinum toxin were not interchangeable from one product to another. Slide 14 of the presentation depicted the SPCs for, *inter alia*, Bocouture and Vistabel and was headed 'Summary of product characteristics recognises the non-interchangeability of units of BONT-A products'. Although the relevant statement in the Bocouture SPC was highlighted, the subsequent statement that comparative clinical study results suggested that Bocouture and Botox/Vistabel were of equal potency was not and nor was this information given in any other slide.

The final section of the presentation headed 'Introduction to Clinical Trials' discussed non-inferiority studies in general and the last 19 slides in particular detailed the results of Moers-Carpi *et al* which compared the efficacy of Vistabel (20 units, n=105) vs Bocouture (30 units, n=104) in the treatment of patients with moderate/severe glabellar lines. There was no explanation as to why different doses of the two medicines had been chosen despite the doses (in numbers of units) recommended in the respective SPCs being identical. The slide which introduced the study stated that 20 units of Vistabel and 30 units of Bocouture both represented labelled doses. It did not appear, however, that information about the doses chosen in the study had been presented within the context of the SPC recommendations, ie that the starting dose for Bocouture was 20 units which could be increased to up to 30 units if required. The slide headed 'Study Conclusions' (the last slide in the presentation before the Vistabel prescribing information) stated that Vistabel (20 units) was as effective as Bocouture (30 units) in the treatment of glabellar lines and that the study reinforced the data previously reported by Hunt *et al* (2010). The Panel noted that there was no reference in the presentation to Sattler *et al* although the speaker submitted in an account of the meeting that he/she had talked about the data and that the study had shown that in the same therapy area 24 units of Bocouture was non-inferior to 24 units of Vistabel. The Panel queried how much time the speaker would have had to explain the Sattler *et al* data given that he/she had otherwise presented 50 slides in 30 minutes.

The Panel also noted that there was no reference in the presentation to Carruthers *et al*, the dose ranging study with Botox/Vistabel which had shown that in the treatment of frown lines doses of 30 or 40 units did not produce statistically significantly better results than a dose of 20 units and that the majority of patients responded well to 20 units with some needing a higher dose to achieve the same effect. There were 10 patients in each treatment group. Although this was a Botox/Vistabel study, the Panel considered that it demonstrated an important point which would have helped to provide context to the rest of the presentation. The Panel noted that Allergan had provided a copy of data on file from Merz which it stated demonstrated a dose response for Bocouture/Xeomin between 10 (n= 48), 20 (n=47), and 30 (n=48) units when used to treat glabellar lines. When determined by the investigator at day 30, the percentage of responders to 20 units and 30 units was 74.5 and 91.7 respectively. It was not stated in the information before the Panel whether this was a statistically significant difference.

Overall, the Panel considered that the presentation did not reflect the balance of evidence with regard to the relative potencies of Botox/Vistabel vs Bocouture/Xeomin and was concerned to note that, as acknowledged by Allergan, it had not been reviewed or approved for use at the meeting. In the Panel's view the presentation implied that Botox/Vistabel was more potent than Bocouture/Xeomin. In that regard the Panel considered that this was sufficiently similar to the point at issue in Case AUTH/2346/8/10 for it to be covered by the undertaking in that case. Thus the presentation now at issue breached undertakings given previously. A breach of Clause 25 was ruled. In that regard high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking was such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Panel ruled a breach of Clause 2.

2 Conduct of a representative

COMPLAINT

Merz stated that an Allergan sales representative visited a customer who used Bocouture. The representative used an A4 copy of the Moers-Carpi *et al* poster to support his assertion that the potency of Bocouture was inferior to that of Vistabel. A direct copy of the poster given to the customer was provided. The poster concluded:

> 'This clinical study found that 20 units of onabotulinumtoxinA [Vistabel] are as effective as 30 units of incobotulinumtoxinA [Bocouture] in reducing the severity of glabellar lines 28 days post injection, and demonstrated a trend in favour of onabotulinumtoxinA at days 84, 98 and 112. These results were obtained despite a 50% higher dose of incobotulinumtoxinA than onabotulinumtoxinA.'

The poster further added 'Results reinforce reported biological activity data (1,2) ...' and directly referred to the Hunt and Clark data that was the subject of the breach of undertaking in Case AUTH/2346/8/10. The customer was clearly left with the message that Bocouture did not possess the same clinical potency per unit as Vistabel.

RESPONSE

Allergan confirmed that requests from three of the representative's customers for copies of the Moers-Carpi *et al* poster had been forwarded to the medical information department. These responses were provided to the customers in line with Allergan's Medical Information and Healthcare Compliance procedures. Without knowing the identity of the doctor in question Allergan could not provide any further specific information to refute the allegations made by Merz or provide a comprehensive account of the representative's recollection of what was said. However, Allergan's records showed that its representative had responded appropriately to the three requests for copies of the Moers-Carpi *et al* poster.

Allergan confirmed that the representative had passed the ABPI Medical Representatives Examination.

Allergan denied that it had breached its undertakings in Case AUTH/2183/11/08, AUTH/2346/8/10 and AUTH/2335/7/10 and therefore denied any breach of Clauses 25, 9.1 or 2.

In response to a request for further information Allergan stated that it had one promotional item which referred to the Moers-Carpi *et al* poster. A copy was provided. The field force was not given copies of the Moers-Carpi *et al* poster or briefed to use it with customers. Any unsolicited requests for the poster were forwarded to medical information. Allergan provided part of its healthcare compliance training slide set which covered how Allergan briefed representatives to handle requests for reprints/clinical papers and posters. The Moers-Carpi *et al* poster was not on the approved list of materials which could be requested by the field force. A copy of the list of materials/reprints which could be requested was provided. Therefore, any requests for the poster were directed to medical information.

The representative had forwarded three unsolicited requests for the Moers-Carpi *et al* poster to the medical information department. The poster was sent direct to one customer and the representative delivered it to the other two in sealed envelopes which were left unopened with the customers.

PANEL RULING

The Panel noted that the Vistabel sales aid (ref UK/0775/2011) provided by Allergan as the only promotional item that referred to Moers-Carpi *et al* was entitled 'Not all toxins are Vistabel'. The front cover included the statement 'Vistabel unit doses are not interchangeable with other preparations of botulinum toxins'. One page in the sales aid was headed 'Head-to-head data review of glabellar lines' beneath which was boxed text with a very brief description of Sattler *et al* and a more detailed description of Moers-Carpi *et al*. Subsequent pages of the sales aid detailed the results of Moers-Carpi *et al* with the use of a bar chart and graph. The back page of the material included the claim 'A recently conducted equivalence study confirms that unit doses of Vistabel and Merz toxin are not interchangeable in clinical practice' which was referenced to Moers-Carpi *et al*. There was no reference on the back page to the Sattler *et al* non-inferiority study which showed that 24 units of Bocouture/Xeomin was non-inferior to 24 units of Botox/Vistabel in the treatment of glabellar lines. There was no mention of the statement in the Bocouture SPC that clinical data suggested equal potency.

There was no complaint about the sales aid. However, the Panel considered it was relevant to the allegation that the customer was left with the message that Bocouture did not possess the same clinical potency per unit as Vistabel.

The Panel noted that the Moers-Carpi *et al* poster was not available for representatives to distribute; if customers asked for a copy the representatives had to ask medical information to send a copy or receive a copy themselves in a sealed envelope for onward transmission to the customer. Allergan had acknowledged that three customers had asked the representative for a copy of the poster. In that regard the Panel noted Allergan's submission that the requests were unsolicited. In the Panel's view, the emphasis on the Moers-Carpi *et al* data within the sales aid meant that any request for a copy of the poster which was prompted by a representative's discussion of that data was a solicited request for the poster.

The Panel noted that it was impossible to know what the representative had said to any of the three customers about the poster or whether the representative had used the sales aid. However, the Panel considered that, given the content of the sales aid, on the balance of probabilities, the representative had used the Moers-Carpi *et al* poster to inform the

health professional that in order to achieve the same clinical outcome in the treatment of glabellar lines 20 units of Vistabel was needed vs 30 units of Bocouture ie unit for unit, Bocouture was less potent than Vistabel.

The Panel noted its comments in point 1 above with regard to the clinical data and the statement in the Bocouture SPC that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900kD) are of equal potency'. Noting the content of the sales aid the Panel considered that the arranged provision of the Moers-Carpi *et al* poster by the representative would, on the balance of probabilities, leave the health professional with the impression that Bocouture did not possess the same clinical potency as Vistabel as alleged. In the Panel's view this breached the undertakings previously given. A breach of Clause 25 was ruled. In that regard high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that an undertaking was an important document and that Allergan's successive breaches of undertaking was such as to bring discredit upon and reduce confidence in the pharmaceutical industry. The Panel ruled a breach of Clause 2.

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The Panel noted its rulings in this case that Allergan had again breached undertakings with regard to claims about the relative potency of its botulinum toxin vs that of the Merz product. Case AUTH/2346/8/10 had also been ruled in breach of Clauses 2, 9.1 and 25. In the Panel's view, the repeated and serious nature of such breaches of the Code raised concerns about the company's procedures and warranted consideration by the Appeal Board. In accordance with Paragraph 8.2 of the Constitution and Procedure, the Panel reported the company to the Appeal Board.

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COMMENTS FROM ALLERGAN ON THE REPORT

Allergan submitted that it understood the reasoning behind the breaches ruled. It took the Panel's rulings extremely seriously and assured the Appeal Board that it was committed at a senior management level and throughout the organisation to abide by the Code. There was no deliberate decision to ignore recommendations from previous cases or any 'systemic incompetence' or 'contempt' for the Code as suggested by Merz. Allergan provided detailed comments on the case and the actions it had taken. Allergan stated that it had taken on board all the learnings from this case and would fully address these moving forward.

At the consideration of the report Allergan acknowledged that failings had occurred but submitted that it had already partially implemented a number of actions to address the issues raised in this case including: brand team process for all materials; acceleration of a competency framework for copy reviewers; setting compliance goals and objectives; a review of all healthcare compliance training materials; increased impact of monthly Code updates; retraining of staff, a quality management system investigation and Corrective and Preventative action (CAPA) plan reviewed and monitored by the UK management team and compliance committee and finally a review and update of all relevant healthcare compliance and medical information SOPs. Allergan submitted that it would show its continued commitment through robust CAPAs.

APPEAL BOARD CONSIDERATION

The Appeal Board noted that Allergan had accepted the breaches of the Code and that it had already undertaken meaningful action to improve its culture and processes to avoid similar errors in the future. Further steps to improve compliance were planned. The Appeal Board considered that the breaches of undertaking were a company issue not solely the responsibility of one individual.

The Appeal Board considered that the company's comments on the report and presentation revealed a marked lack of insight and objectivity. Given that potency comparisons between Botox and Xeomin had previously resulted in two breaches of undertaking it was vital that Allergan briefed, trained and had systems in place such that its staff did not use material that could result in a further breach of undertaking or unapproved slides. The Appeal Board considered that an undertaking and assurance was an important document and it was extremely concerned that Allergan had now breached its undertaking and assurance on three separate occasions in a short space of time. This was completely unacceptable.

The Appeal Board decided that Allergan should be publicly reprimanded for successive breaches of its undertaking. The Appeal Board also decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require an audit of Allergan's procedures in relation to the Code to be carried out by the Authority. The audit should be conducted in April 2012. On receipt of the audit report the Appeal Board would consider whether further sanctions were necessary.

FURTHER APPEAL BOARD CONSIDERATION

On receipt of the April 2012 audit report the Appeal Board considered that Allergan's procedures were not satisfactory. The Appeal Board was extremely disappointed that there was insufficient responsibility taken across the company for Code compliance. Company culture did not appear to support compliance with the Code. The Appeal Board noted that it had already publicly reprimanded Allergan.

The Appeal Board decided that Allergan should be re-audited in three months' time at which point it expected there to be significant improvement. As part of the usual re-audit process Allergan would be asked to provide an update of its response to the first audit with actions and timelines. Upon receipt of the report for the re-audit, the Appeal Board would decide whether further sanctions were necessary.

The Appeal Board subsequently decided in Cases AUTH/2487/3/12 and AUTH/2489/3/12 to require an audit which would be conducted at the same time as the re-audit required in Case AUTH/2460/11/11.

Although the Appeal Board was disappointed, on receipt of the August 2012 audit report, at the lack of progress demonstrated, the company appeared to have taken action including setting time frames for the bulk of the processes and work to be completed by the end of 2012. The Appeal Board was concerned that the amendments to some of the standard operating procedures (SOPs) had not been finalized. The Appeal Board noted that there were plans to significantly change the company structure. The Appeal Board considered that Allergan should be re-audited in January 2013 at which point it expected there to be significant improvement.

Upon receipt of the January 2013 audit report, the Appeal Board noted that although Allergan had made progress, further improvement was necessary. The Appeal Board noted that one key change in senior personnel would take place shortly and another in due course. Given that further improvement was required, the Appeal Board considered that Allergan should be re-audited in September 2013. Upon receipt of the next audit report, the Appeal Board would decide whether further sanctions were necessary.

Upon receipt of the September audit report, the Appeal Board noted that Allergan had made progress since the re-audit in January. The company had undergone four audits since April 2012. It was important that the progress shown in the September 2013 audit was continued and maintained. Every opportunity should be taken for improvement. The Appeal Board noted that Allergan needed to ensure that it updated its processes in good time to reflect the 2014 Code and that relevant staff were trained on the new Code. Allergan provided details of its plans to implement the recommendations in the audit report. On the basis that this work was completed, the Appeal Board decided that no further action was required.

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Undertaking received	**26 January 2012**
Appeal Board Consideration	**23 February, 24 May, 11 October 2012, 6 March 2013**
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