CASE AUTH/2496/4/12

ALLERGAN/DIRECTOR v MERZ

Promotion of Xeomin and Bocouture and breach of undertaking

Allergan complained about three advertisements for Xeomin/Bocouture (botulinum neurotoxin type A) issued by Merz. As the complaint involved an alleged breach of undertaking, that part of it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings. Allergan marketed Vistabel/Botox (botulinum neurotoxin type A).

Allergan noted that Merz had used the claims 'Equipotent', 'Equal Potency' and '1:1 Clinical Conversion Ratio' alongside a visual of either a Xeomin or Bocouture vial standing next to a Botox or Vistabel vial. The visual was clearly designed to emphasise a direct 1:1 equivalence/conversion of the two medicines. Some of the material included the phrase 'Clinical studies suggest …'. In addition, less prominently and usually in smaller font, was the Summary of Product Characteristics (SPC) statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'.

Allergan alleged that the claims, along with the supporting visuals, were misleading and presented only part of the information in the Bocouture or Xeomin SPC. The overall message was that the products were equally potent and could be converted 1:1.

Allergan noted that the Bocouture SPC 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.'**

The Xeomin (50U) SPC 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.'**

Whilst, the Xeomin (100 units) SPC stated:

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

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 considered that, in line with the science behind botulinum toxins and over twenty years of regulatory experience, the most prominent and significant statement in the SPCs was that unit doses of the medicines were not interchangeable. This statement was imposed by the Pharmacovigilance Working Party (PhVWP) and in Allergan's view was not 'superseded' by a contradictory statement based upon non-inferiority clinical studies. Non-inferiority studies could not demonstrate equivalence and in that regard Allergan noted the ruling in Case AUTH/2270/10/09 together with Merz's submission in that case that it had no data to support a claim that Xeomin was equivalent to Botox.

Allergan noted that botulinum toxin potency was a laboratory measure and each manufacturer's assay was unique to its own medicine. When Hunt *et al* (2010) assessed the relative potencies of Bocouture and Vistabel using the Allergan assay, the potency of Merz's Bocouture 50U was found to be, on average, 34 units per vial whereas the average potency of Allergan's Vistabel/Botox 50U was as labelled. Conversely, Dressler *et al* (2008), using the Merz assay determined that the potencies of Merz's Xeomin and Allergan's Botox were not statistically different. Allergan submitted that as different products were likely to behave differently in different assays these findings were not contradictory since each company used its own proprietary assay.

Allergan submitted that these observed differences in potency and enzymatic activity supported the non-interchangeability of unit doses of botulinum toxins. The optimum dosage and number of injection sites in the treated muscle should be determined individually for each patient. A titration of the dose should be performed. Physicians should consult the appropriate SPC to obtain product-specific dosage recommendations.

Allergan alleged that the current Merz campaign and claims at issue were inaccurate, misleading, could not be substantiated and were not based on an up-to-date evaluation of all the available evidence. In particular, significant new data (Moers-Carpi *et al*, 2011) was omitted. These new data from a randomised, double blind, equivalence study (n=220) directly challenged the hypothesis that the products were interchangeable at a 1:1 dose ratio. The basis for this study was the investigators' experience of the relative clinical effectiveness of the different

medicines, the differences seen in the different reference LD50 assays and the different available dose ranging data. Allergan considered that this new data, while not inconsistent with the findings of the Merz non-inferiority studies, clearly challenged the basis for claims of equivalence and a 1:1 conversion ratio.

Allergan alleged that the claims by Merz for 'Equipotency' and '1:1 Conversion' between Xeomin/Bocouture and Vistabel/Botox was a source of significant concern. No 'dosing conversion' occurred or should be implied from the non-inferiority studies conducted by Merz. The direct medical impact was that a significant patient safety risk existed with prescribers encouraged to transfer information from one product to another.

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. Merz's own submission in that case was that it had no data to support a claim that Xeomin was equivalent to Botox which Allergan believed this was still so. Therefore, Allergan alleged that the claims for 'Equipotency' and '1:1 Conversion' between Xeomin/Bocouture and Vistabel/Botox (ie equivalence) were in breach of the undertaking in Case AUTH/2270/10/09.

The detailed response from Merz is given below.

The Panel considered each advertisement separately. With regard to one Bocouture advertisement, inter-company dialogue had been successful and so the Director decided that only the alleged breach of undertaking would be considered.

The Panel noted that the other Bocouture advertisement featured a photograph of vials of Bocouture and 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 SPC. The claim for a 1:1 clinical conversion ratio was referenced to Sattler *et al* (2010).

The Panel noted that in Section 4.2 of the Bocouture SPC, Posology and method of administration, the first statement in bold type read 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxins'. A similar bold statement also appeared in the Xeomin SPC. The Panel noted the prominence of these statements in the SPCs and considered that although the Bocouture SPC statement had been included in the advertisement at issue, it was given significantly less prominence than the other claims. Given its position below the thick blue line, it appeared to be separate from the main part of the advertisement. The prominence given to this statement in the SPC had not been reflected in the advertisement. The Panel considered that the advertisement was misleading in that regard. A breach of the Code was ruled. This ruling was not appealed.

The Panel noted that the claim '…clinical studies suggest… Equal Potency…' was referenced to the Bocouture SPC. The relevant statement in the SPC 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'. The second part of the claim in the advertisement '1:1 Clinical Conversion Ratio', was referenced to Sattler *et al*, a non-inferiority study which had demonstrated the non-inferiority of 24 units each of Bocouture/Xeomin to Vistabel/Botox in the treatment of glabellar frown lines. The Panel noted that it had previously been established that non-inferiority studies could not be used to imply equivalence.

The Panel considered that the overall impression from the advertisement was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, the advertisement encouraged prescribers to consider that the unit doses of Bocouture and Botox were interchangeable. The Panel considered that the advertisement was misleading in that regard. The Panel considered that the impression given by the advertisement could not be substantiated. Breaches of the Code were ruled. These rulings were not appealed.

The Xeomin advertisement featured a photograph of vial of Xeomin and Botox side-by-side with a colon (:) between them. The headline claim read 'Clinical studies suggest Xeomin and Botox are equipotent, with a conversation ratio of 1:1 Xeomin SPC'. Below the photograph of the vials on the left-hand side was the statement 'Always prescribe by brand, unit doses are not interchangeable'. This was referenced to the Xeomin 50U SPC. The headline claim and the statement were in a similar prominent white font on a black background.

The Panel noted that Section 4.2 of the Xeomin 50U SPC stated the following:

> **'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 Panel noted the prominence given to the first statement in the SPC and that the order of the two statements in the SPC had been reversed in the advertisement, which resulted in the claim 'Clinical studies suggest…' being used as the headline to the

advertisement. The Panel considered that the relative emphasis on the two SPC statements had not been reflected in the advertisement. In the Panel's view, the advertisement encouraged prescribers to consider the unit doses of Bocouture and Botox were interchangeable. The Panel considered that the advertisement was misleading in this regard. The Panel considered that the impression given by the advertisement could not be substantiated. Breaches of the Code were ruled. These rulings were not appealed.

With regard to the alleged breach of undertaking, the Panel noted that inter-company dialogue was not a pre-requisite and it thus considered that that aspect of the complaint would be considered in relation to all three advertisements at issue.

The Panel noted that in Case AUTH/2270/10/09, Merz had been ruled 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. A breach of the Code was ruled which was upheld on appeal.

Turning to the advertisements at issue, the Panel noted that they referred to Xeomin/Bocouture being 'equipotent' or having 'Equal Potency' to Botox/Vistabel. There was no suggestion that Xeomin/Bocouture might be more potent than Botox/Vistabel. In that regard the Panel did not consider that the advertisements breached the undertaking given in Case AUTH/2270/10/09. No breaches of the Code were ruled including Clause 2.

Upon appeal, 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 alleged breach of undertaking, the subject of the appeal, related only to claims of equivalence.

The Appeal Board noted that 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 which featured the 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 of a vial of each of the medicines side-by-side, implied 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 the Code. The appeal on this point was successful.

Similarly the Appeal Board considered that the Xeomin advertisement which featured the claim 'Clinical studies suggest Xeomin and Botox are equipotent, with a conversion ratio of 1:1 Xeomin SmPC' together with a visual of a vial of each medicine side-by-side with a colon between them, also implied that the medicines were clinically equivalent and that unit for unit they were interchangeable. The Appeal Board noted its comments above and thus ruled a breach of the Code. 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 had thus brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled breaches of the Code including Clause 2. The appeal on this point was successful.

Allergan Limited complained about the promotion of Xeomin/Bocouture (botulinum neurotoxin type A) by Merz Pharma UK Ltd. The materials at issue were two Bocouture advertisements (refs 1070/MER/AUG/2011/JH and 1075/BOC/DEC/2011/JH) and a Xeomin advertisement (ref 1281/XEO/OCT/2011/JL). As the complaint involved an alleged breach of undertaking, that part of it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Allergan marketed Vistabel/Botox (botulinum neurotoxin type A).

COMPLAINT

Allergan alleged that the advertisements and overall campaign led prescribers to conclude that Xeomin/Bocouture and Vistabel/Botox were interchangeable in terms of potency units and delivered equivalent clinical results. Allergan considered that this marketing strategy fundamentally contradicted the intent of the Pharmacovigilance Working Party (PhVWP) which, in 2006, mandated that all botulinum toxin summaries

of product characteristics (SPCs) included wording to highlight the non-interchangeability of unit doses between products in order to ensure their safe and appropriate use. Allergan strongly disagreed with Merz's view that the claims were supported by the clinical data, consistent with the SPC and not inconsistent with the findings of the PhVWP, and it thus alleged that the materials were in breach of the Code.

Allergan noted that the claims 'Equipotent', 'Equal Potency' and '1:1 Clinical Conversion Ratio' were used alongside a visual of vials of Xeomin/Bocouture and Botox/Vistabel standing side-by-side. The visual was clearly designed to emphasise a direct 1:1 equivalence/conversion of the two medicines. In some of the promotional materials the phrase 'Clinical studies suggest …' was added. In addition, less prominently and usually in smaller font, was the SPC statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of botulinum toxin'.

Allergan alleged that the claims, along with the supporting visuals, were misleading and presented only part of the information in the Bocouture or Xeomin SPC. The overall message given to health professionals was that the products were equally potent and could be converted 1:1.

Allergan noted that the Bocouture SPC 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.'

The Xeomin (50U) SPC 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.'

Whilst, the Xeomin (100U) SPC stated:

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

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 considered that, in line with the science behind botulinum toxins and over twenty years of regulatory experience, the most prominent and most significant statement on the SPCs for all the botulinum toxins was that unit doses of the medicines were not interchangeable. As noted above, this statement of non-interchangeability was imposed on all botulinum toxin manufacturers by the PhVWP; in Allergan's view it was not 'superseded' by a contradictory statement based upon clinical studies of a non inferiority design. Non-inferiority studies could not demonstrate equivalence. 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 and Merz's submission in that case that it had no data to support a claim that Xeomin was equivalent to Botox.

Allergan noted that assessment of potency was a laboratory measure and not a recognised clinical endpoint. Potency was measured in the laboratory using an LD50 assay. Each botulinum toxin manufacturer had its own unique and proprietary potency assay methodology. Data sets from Merz and Allergan in relation to the potency of the competitor products gave contradictory results for reasons which could be explained by the differences in the toxins and the assay methods.

Allergan submitted that Hunt *et al* (2010) assessed the relative potencies of Bocouture 50U and Vistabel 50U using the Allergan standardised potency bioassay (approved and used for quantifying the biological activity of formulated ~900 kD Botox) and evaluated enzymatic activity through LCA-HPLC. The average potency of Bocouture 50U dose was found to be 34 units (31-36 95% CI) per vial vs 50 units (46-56 95% CI) per vial for Vistabel/Botox (ie as labelled). Potency was verified by running four separate test sessions for both medicines. These results were further corroborated with a lower than expected light chain activity for Bocouture and were consistent with previous findings for Xeomin 100U. Conversely Dressler *et al* (2008) determined the biological potencies of five commercially available unexpired batches of Xeomin and Botox using the LD50 bioassay for batch release of Xeomin and concluded that the potencies of the Xeomin and Botox batches were not statistically different.

The assays used by Allergan and Merz, which were both approved for batch release, were not the same and different products were likely to behave differently in different assays. Thus these findings were not contradictory since each company used its own proprietary assay.

Allergan submitted that these observed differences in potency and enzymatic activity supported the non-interchangeability of unit doses of botulinum toxin type A products. The optimum dosage and number of injection sites in the treated muscle should be determined individually for each patient. A titration of the dose should be performed. Physicians should consult the appropriate SPC to obtain product-specific dosage recommendations.

Allergan alleged that the current Merz campaign and claims at issue were misleading and did not reflect the balance of evidence. In particular, significant new data (Moers-Carpi *et al*, 2011) was omitted. These new data from a large (n=220) randomised, double blind, equivalence study directly challenged the hypothesis that the products were interchangeable at a 1:1 dose ratio. The basis for this study was the investigators' experience of the relative clinical effectiveness of the different medicines, the differences seen in the different reference LD50 assays and the different available dose ranging data. Allergan considered that this new data, while not inconsistent with the findings of the Merz non-inferiority studies, clearly challenged the basis for claims of equivalence and a 1:1 conversion ratio.

Allergan alleged that the claims by Merz for 'Equipotency' and '1:1 Conversion' between Xeomin/Bocouture and Vistabel/Botox was a source of significant concern. No 'dosing conversion' occurred or should be implied from the non-inferiority studies conducted by Merz. The direct medical impact was that a significant patient safety risk existed with prescribers encouraged to transfer information from one product to another.

Allergan alleged that the advertisements and Merz's campaign based around these core claims were inaccurate, misleading, could not be substantiated and were not based on an up-to-date evaluation of all the available evidence. Breaches of Clauses 7.2, 7.3 and 7.4 were alleged.

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. Merz's own submission in that case was that it had no data to support a claim that Xeomin was equivalent to Botox and Allergan believed that this was still so; Merz had not published any new clinical data that supported a claim of equivalence. Therefore, Allergan believed the claims for 'Equipotency' and '1:1 Conversion' between Xeomin/Bocouture and Vistabel/Botox (ie equivalence) were in breach of the undertaking in Case AUTH/2270/10/09 and in breach of Clause 25.

When writing to Merz the Authority asked it to respond to Clauses 2 and 9.1 in addition to the clauses cited by Allergan.

RESPONSE

Merz submitted it was important to clarify the background and inter-company dialogue between the companies.

In January 2012 Allergan complained about two Bocouture leavepieces (refs 1059/BOC/May/2011/JH and 1059/BOC/MAY/2011/JH), a Bocouture advertisement (ref 1070/MER/AUG/2011/JH) and a Xeomin advertisement (ref 1281/XEO/OCT/2011/JL). As a consequence Merz promptly withdrew one of the leavepieces (ref 1059/BOC/MAY2011/JH) and upon review of all other current promotional material identified an advertisement (ref 1075/BOC/DEC/2011/JH) which was exactly the same as the leavepiece and so it too was withdrawn at the same time as a direct consequence of the inter-company dialogue. Merz stated that it had provided copies of both withdrawal certificates.

Merz stated that it had not received a complaint from Allergan about this advertisement either before or after its withdrawal. The fact that the Bocouture advertisement (ref 1075/BOC/DEC/2011/JH) was now the subject of Allergan's complaint with no prior inter-company dialogue represented an unusual circumstance which in Merz's view might not be consistent with the Constitution and Procedure.

Merz noted that in Case AUTH/2270/10/09 Allergan complained about the claim 'At least as effective as Botox with a similar safety profile'. The Panel ruled that it was misleading as it implied 'possible superiority'. Merz consequently undertook not to use the claim and noted that neither it nor any suggestion of superiority of Xeomin/Bocouture over Vistabel/Botox appeared in the advertisements now at issue. Merz did not consider that there was a breach of undertaking and as such Clause 25 could not be applied to the materials at issue.

Merz noted Allergan's submission that Case AUTH/2270/10/09 ruled that non-inferiority studies could not be used to claim 'equivalence'. It should be noted that the material considered in both Case AUTH/2270/10/09 and the current case (Case AUTH/2496/4/12) did not contain a claim of 'equivalence'. This was because equivalence was a specific statistical term used to describe a specific statistical test.

Merz considered that Allergan had sought to leverage the protected status of the word 'equivalence', conferred on it by its specific meaning, and make it all encompassing to cover any term which related to comparability or similarity. This point arose in Case AUTH/2357/9/10 in relation to the promotion of Pradaxa. In that case the Panel ruled that an image of a set of scales accompanied by the claim '…efficacy and safety equivalent to …' was not supported by the non-inferiority studies cited. The Panel also ruled, however, that the claim '… efficacy and safety comparable to…' was substantiated by the non-inferiority studies cited. Upon appeal the Appeal Board further reinforced that 'comparable' did not imply 'equivalence'. Merz did not consider that the terms used in the advertisements were interchangeable with or implied equivalence, which, as established in previous cases, was not a general term but had a very specific meaning.

Merz submitted that the claims at issue were specifically chosen as they were the Medicines and Healthcare products Regulatory Agency's (MHRA's) approved descriptors of relative potency, as expressed in the Bocouture and Xeomin SPCs as outlined below.

Section 4.2 Xeomin 50U SPC:

> '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.'

Section 4.2 Bocouture 50U SPC:

> '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 the use of the statements 'clinical studies suggest … equipotent' or 'equal potency' were very different to the implication of 'At least as effective as Botox with a similar safety profile'. They did not imply superiority and they were consistent with the MHRA's position. Further to this, while not the subject of the undertaking, none of the advertisements used the term 'equivalent' to describe the outcomes of clinical comparisons. Merz thus denied a breach of Clauses 2 and 25.

Merz submitted that Allergan had falsely stated that the campaign would lead prescribers to conclude that units of potency were interchangeable between brands and that Xeomin/Bocouture and Vistabel/Botox were equivalent. This assertion was undermined by the fact that all of the material at issue stated that units of potency were not interchangeable and none of the materials included a claim of equivalence.

Allergan had sought to confuse the objectives of the PhVWP, to clarify that each particular brand had its own unit of potency, with the ability to compare the clinical efficacy of products when used in patients. Merz considered that the two statements positioned one after the other in the relevant SPCs of Xeomin and Bocouture, and reviewed below, were supplementary in nature, not contradictory. The first sentence in each SPC provided the prescriber with information that related to the assay. As Allergan had previously shown, by using the Allergan assay for Vistabel/Botox and Xeomin/Bocouture an apparent difference in unit doses measured was seen (Hunt *et al*). Because of this both manufacturers used their own specific product assays. The second sentence in each SPC informed prescribers that in the clinical setting, ie that which was most relevant to health professionals, the two products demonstrated similar results (an equal potency of the product appeared to have been demonstrated) when a dosing conversion ratio of 1:1 was used. These statements co-existed on the SPCs because they were both factually correct and were related to different situations. They were not contradictory.

Section 4.2 Xeomin 50U SPC:

> 'Due to 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) [Botox] are of equal potency when used with a dosing conversion ratio of 1:1.'

Section 4.2 Bocouture 50U SPC

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

Merz submitted that the advertisements were faithful and unambiguous representations of the respective product SPCs, which were founded on head-to-head matched dose non-inferiority studies using a 1:1 dosing ratio designed with the scientific advice of the European Medicines Agency and accepted by the regulators in 28 countries. They did not imply superiority nor did they state that the product unit doses were equivalent or had been tested for equivalence.

Merz submitted that the statements allowed prescribers to make a considered comparison between products. The quotations in the advertisement were deliberately taken from the SPCs because they were the MHRA endorsed position. The accompanying visual did not mislead as to the comparison, denigrate or distort the relationship between the brands and supported the SPC statements on relative potency. The lasting impression was that clinical studies suggested 1 unit of Vistabel/Botox was comparable to 1 unit of Xeomin/Bocouture.

Merz submitted that the fully referenced advertisements reflected the clinical registration data represented by the SPC. They did not omit published, peer reviewed, controlled, comparative, non-inferiority studies. Whilst the advertisements did not specifically refer to the Allergan sponsored Hunt and Clarke pre-clinical data (the subject of Cases AUTH/2346/8/10 and AUTH/2335/7/10), nor the Allergan sponsored non-controlled Moers-Carpi *et al* (the subject of Cases AUTH/2489/3/12 and AUTH/2487/3/12), Merz did not believe that this made the advertisements based on the product registration data misleading or inaccurate. This was because the Hunt and Clarke data did not address the clinical situation which was paramount and Moers-Carpi *et al* did not directly compare the relative product potencies as the doses were not matched.

Based upon these arguments Merz did not consider that the advertisements were in breach of Clauses 7.2 or 7.3. Additionally the claims could be substantiated and were the unambiguous view of the regulator which, Merz assumed, took in to account the PhVWP (2006) opinion when it granted the product licence. The advertisements therefore were not in breach of Clause 7.4.

Finally, Merz submitted that the advertisements in question were consistent with the standards for the advertising of medicines. They included straightforward images of the products and unambiguously supported the relative potency statements in the product SPCs. As such Merz considered that high standards had been maintained and it thus denied a breach of Clause 9.1.

PANEL RULING

The Panel noted that the advertisements at issue were all different to one another and so in that regard each one was considered separately.

- Bocouture advertisement (ref 1070/MER/AUG/2011/JH)

In that regard, it appeared that inter-company dialogue had been successful and so the Director decided that only the alleged breach of undertaking would be considered.

- Bocouture advertisement (ref 1075/BOC/DEC/2011/JH)

The Director noted Merz's submission that this advertisement had not specifically been the subject of inter-company dialogue. However, the advertisement featured some of the claims at issue and so in that regard the Director considered that it was another example of the material which the two companies had discussed and was thus covered by the inter-company dialogue. The Director further noted Merz's submission that the advertisement had been withdrawn as a result of inter-company dialogue about a leavepiece. However, the evidence of withdrawal provided, dated 20 January 2012, related to the Bocouture advertisement (ref 1070/MER/AUG/2011/JH) above. The Director considered that on the evidence before her the advertisement (ref 1075/BOC/DEC/2011/JH) had not been withdrawn and as it featured claims which had been the subject of inter-company dialogue, the complaint about it could proceed.

The Panel noted that 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 SPC. The claim for a 1:1 clinical conversion ratio was referenced to Sattler *et al* (2010).

The Panel noted that in Section 4.2 of the Bocouture SPC, Posology and method of administration, the first statement in bold type read 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxins'. A similar bold statement also appeared in the Xeomin SPC. The Panel noted the prominence of these statements in the SPCs and considered that although the statement from the Bocouture SPC had been included in the advertisement at issue, it was given significantly less prominence than the other claims. Given its position below the thick blue line, it appeared to be separate from the main part of the advertisement. The prominence given to this statement in the SPC had not been reflected in the advertisement. The Panel considered that the advertisement was misleading in that regard. A breach of Clause 7.2 was ruled.

The Panel noted that the claim '…clinical studies suggest… Equal Potency…' was referenced to the Bocouture SPC. The relevant statement in the SPC 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'. The second part of the claim in the advertisement '1:1 Clinical Conversion Ratio', was referenced to Sattler *et al*, a non-inferiority study which had demonstrated the non-inferiority of 24 units each of Bocouture/Xeomin (n=277) to Vistabel/Botox (n=93) in the treatment of glabellar frown lines. The Panel noted that it had previously been established that non-inferiority studies could not be used to imply equivalence.

The Panel considered that the overall impression from the advertisement was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, the advertisement encouraged prescribers to consider that the unit doses of Bocouture and Botox were interchangeable. The Panel considered that the advertisement was misleading in that regard and a breach of Clauses 7.2 and 7.3 was ruled. The Panel considered that the impression given by the advertisement could not be substantiated. A breach of Clause 7.4 was ruled.

- Xeomin advertisement (ref 1281/XEO/OCT/2011/JL)

This advertisement featured a photograph of a vial of Xeomin and a vial of Botox side-by-side with a colon (:) between them. The photograph was surrounded by what appeared to be a line drawing of an ornate picture frame. The headline claim read 'Clinical studies suggest Xeomin and Botox are equipotent, with a conversation ratio of 1:1 Xeomin SPC'. Below the photograph of the vials, ie beneath the 'picture frame', on the left-hand side was the statement 'Always prescribe by brand, unit doses are not interchangeable'. This was referenced to the Xeomin 50U SPC. The headline claim and the statement below the 'picture frame' were in a similar prominent white font on a black background.

The Panel noted that Section 4.2 of the Xeomin 50U SPC stated the following:

> '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 Panel noted the prominence given to the first statement in the SPC and that the order of the two statements in the SPC had effectively been reversed

in the advertisement, which resulted in the claim 'Clinical studies suggest…' being used as the headline to the advertisement. The Panel considered that the relative emphasis on the two statements in the SPC had not been reflected in the advertisement. In the Panel's view, the advertisement encouraged prescribers to consider the unit doses of Bocouture and Botox were interchangeable. The Panel considered that the advertisement was misleading in this regard. A breach of Clauses 7.2 and 7.3 was ruled. The Panel considered that the impression given by the advertisement could not be substantiated. A breach of Clause 7.4 was ruled.

- Alleged breach of undertaking

The Panel noted its comments above about the Bocouture advertisement (ref 1070/MER/AUG/2011/JH) and inter-company dialogue and the alleged breaches of Clauses 7.2, 7.3 and 7.4. The Panel noted that inter-company dialogue was not required in relation to an alleged breach of undertaking (Clauses 2, 9.1 and 25) and thus considered that that aspect of the complaint would be considered in relation to all three advertisements at issue.

The Panel noted that in Case AUTH/2270/10/09, Merz had been ruled 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. A breach of the Code was ruled which was upheld on appeal.

Turning to the case now before it, the Panel noted that the advertisements at issue referred to Xeomin/Bocouture being 'equipotent' or having 'Equal Potency' to Botox/Vistabel. There was no suggestion that Xeomin/Bocouture might be more potent than Botox/Vistabel. In that regard the Panel did not consider that the advertisements were in breach of the undertaking given in Case AUTH/2270/10/09. No breach of Clause 25 was ruled. The Panel subsequently ruled no breach of Clauses 2 and 9.1.

APPEAL BY ALLERGAN

Allergan appealed the Panel's ruling of no breach of Clause 25. As the Panel's rulings of no breach of Clauses 2 and 9.1 (cited by the Authority in this case) were as a direct consequence of its ruling of no breach of Clause 25, Allergan's appeal was also taken as an appeal of those clauses.

Allergan noted that the claims 'Equal Potency' or 'Equipotent' and '1:1 Clinical Conversion ratio' or 'Conversion ratio of 1:1' appeared alongside a visual of either Bocouture/Xeomin or Vistabel/Botox vials standing side-by-side. Allergan alleged that the visual clearly emphasised a direct 1:1 equivalence/conversion of the two medicines. In some of the promotional materials the phrase 'clinical studies suggest' was added. In addition, less prominently and usually in smaller font, was the SPC statement 'Unit doses recommended for Bocouture are not interchangeable with those for other preparations of Botulinum toxin'.

- Bocouture advertisement (ref 1075/BOC/DEC/2011/JH)

Allergan noted the Panel's ruling that the advertisement was misleading in breach of Clauses 7.2, 7.3 and 7.4. Specifically, 'The Panel considered that the overall impression from the advertisement was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, the advertisement encouraged prescribers to consider that the unit doses of Bocouture and Botox were interchangeable' (emphasis added). The impression given by the advertisement could not be substantiated. The Panel noted that in Case AUTH/2270/10/09 it had been established that non-inferiority studies could not be used to imply equivalence.

- Xeomin advertisement (ref 1281/XEO/OCT/2011/JL)

Allergan noted that the Panel had considered this advertisement misleading in breach of Clauses 7.2, 7.3, and 7.4 in that it encouraged prescribers to consider that unit doses of Bocouture and Botox were interchangeable. The impression given by the advertisement could not be substantiated.

- Breach of undertaking

Allergan noted that, as stated by the Panel and established in Case AUTH/2270/10/09, non-inferiority studies could not be used to claim equivalence. Merz's submission in Case AUTH/2270/10/09 was that it had no data to support a claim that Xeomin/Bocouture was equivalent to Botox/Vistabel and this was still so; Merz had not published any new clinical data to support a claim of equivalence.

In this case the Panel considered that the overall impression from the Bocouture advertisement (1075/BOC/DEC/2011/JH) was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, both advertisements had encouraged prescribers to consider that the unit doses of Xeomin/Botox and Bocouture were interchangeable. The Panel considered that the advertisements were misleading in this regard.

In Allergan's view these misleading claims were caught by the undertaking given in Case AUTH/2270/10/09. Whilst the claim at issue in that case was 'At least as effective as' the Panel's ruling clearly also addressed equivalence.

Allergan noted the following from the Appeal Board's ruling in Case AUTH/2270/10/09: 'The Appeal Board noted Merz's submission at appeal that it had no data upon which to make the claim that Xeomin was equivalent to Botox. In the Appeal Board's view the claim "At least as effective" not only implied equivalence but also possible superiority which was misleading'.

Therefore, Allergan alleged that any claim which implied clinical equivalence and interchangeability must be in breach of the undertaking given in Case

AUTH/2270/10/09. Allergan therefore appealed the Panel's ruling of no breach of Clause 25.

COMMENTS FROM MERZ

Merz noted that in Case AUTH/2270/10/09 Allergan complained about the use of the claim 'At least as effective as Botox with a similar side effect profile' on an exhibition panel for Xeomin. The Panel ruled that this was misleading as it implied 'possible superiority' of Xeomin vs Botox which was not supported by the available data. The breach was upheld upon appeal and Merz undertook not to use the claim again. The claim or any suggestion of superiority of Xeomin/Bocouture over Botox/Vistabel, did not appear in the advertisements now at issue.

Merz submitted that, as comparative claims between Xeomin and Botox had been the subject of much discussion and dispute, it had taken significant care to ensure that comparisons of the two products were appropriate, could be substantiated, were consistent with the regulator's view and did not breach previous undertakings. Merz was very disappointed that the advertisements now at issue implied that was not intended. However, the advertisements were substantially different from the exhibition panel used in 2009 and at issue in Case AUTH/2270/10/09. As ruled by the Panel, they did not breach the undertaking for Case AUTH/2270/10/09.

Merz submitted that following the Panel's ruling in Case AUTH/2270/10/09 there had been substantial changes to the product lines and available data. Examples of this were that the MHRA approved the 50U Xeomin vial and the licence of Bocouture. Within these documents specific guidance on comparative potency was included in the respective SPCs. Merz considered that the regulatory approved guidance was the most up-to-date perspective on the matter and the language therein the most appropriate way to compare Xeomin with Botox and Bocouture with Vistabel. The SPCs did not refer to superiority and neither did the advertisements.

The claims at issue were:

- Xeomin advertisement (ref 1281/XEO/OCT/2011/JL):

  'Clinical studies suggest Xeomin and Botox are equipotent, with a conversion ratio of 1:1 Xeomin SmPC'.

Section 4.2 of the revised Xeomin 50U SPC stated 'Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [Botox] are of equal potency when used with a dosing conversion ratio of 1:1'.

Merz submitted that the claim used was a contracted but faithful representation of the SPC. The claim was presented as a headline above a visual of the Xeomin and Botox vials and was balanced by the prominent statement below: 'Always prescribe by brand, unit doses are not interchangable' (emphasis added).

Merz noted that the Panel considered that the reversal of the order of the statements taken from the SPC had resulted in the impression that unit doses were interchangeable. Based upon this impression the advertisement was ruled to be in breach of Clauses 7.2, 7.3 and 7.4. There was no indication of an implied superiority in the advertisement or referred to by the Panel ruling.

- Bocouture advertisements (refs 1075/BOC/DEC/2011/JH, 1070/MER/AUG/2011/JH)

  'In glabellar frown lines, clinical studies suggest

  Bocouture vs Botox:
  Equal Potency
  1:1 Clinical Conversion Ratio'.

Section 4.2 of the new Bocouture 50U SPC stated 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [Botox] are of equal potency'.

Merz noted that the statement 'Unit doses recommended for Bocouture are <u>not</u> interchangeable with those for other preparations of botulinum toxin' (emphasis added) was also clearly stated. The Panel concluded that the impression was given that Bocouture had been unequivocally demonstrated clinically equivalent to Vistabel and that prescribers were encouraged to consider the two products' units interchangeable. The advertisements were ruled to be in breach of Clauses 7.2, 7.3 and 7.4. There was no indication of an implied superiority in the advertisements or referred to by the Panel which deemed that they gave the impression of 'equivalent'.

Merz submitted that since the completion of Case AUTH/2270/10/09 in 2010, there had been substantial further data and opinion published which confirmed comparable efficacy for Xeomin/Bocouture and Botox/Vistabel at a 1:1 dose conversion ratio. This was reinforced by a recent meta-analysis of 8 core studies and a further 11 identified studies across a range of indications which concluded 'consequently 50 or 100 units of each product should be considered of equal potency until such time as compelling clinical evidence to the contrary becomes available' (Jandhyala 2012 and Prager *et al*, 2012).

Merz submitted that it had intended to communicate that Xeomin/Bocouture had been demonstrated 'clinically comparable' to Botox/Vistabel which could be substantiated by the growing published data and opinion as well as the respective product SPCs. Indeed, it was fair to question if the claim in Case AUTH/2270/10/09 had been 'As effective as Botox with a similar side effect profile' (rather than 'At least as'), whether it would have been found in breach in the first instance, for implying comparable rather than superior efficacy. The current advertisements did not imply superiority.

In developing the advertisements Merz submitted that it was deliberately cautious and used the language of the SPC (and the registration study) to convey comparable efficacy at a 1:1 clinical conversion ratio reflecting the dosing in the non-inferiority registration trials. Although Merz had not

intended to imply unequivocal equivalence or unit interchangeability which could not be substantiated, with hindsight it accepted the Panel's view on this matter and chose not to appeal. Merz noted that in the Panel ruling it was the 'overall impression' that was given rather than a literal statement of fact; the terms 'equivalent' or 'interchangeable' had not featured in any of the material reviewed in this or Merz's prior cases. If the impression given by the advertisements at issue was that the products were indeed 'interchangeable' and 'equivalent unit for unit' despite saying 'not interchangeable', how could the advertisements have also conveyed a message of superiority, proposing that one product was better than the other?

In summary, Merz supported the Panel's view that the claim 'At least as effective as', which implied superiority, was significantly different from the claims at issue which related to 'equal potency'. The Panel ruled that the advertisements at issue implied that the products were so similar that they were interchangeable, despite clearly stating 'not interchangeable'. If the impression was they were the same/similar, how could they also be found in breach of an undertaking that was based on leaving the impression of superiority?

Merz regretted that despite faithfully using the SPC guidance on potency, the Panel considered that the overall impression was one of unequivocal equivalence and interchangeability. Accepting that misjudgement, Merz submitted that the point at issue was sufficiently different from the prior case not to represent a breach of undertaking. Therefore Merz denied a breach of Clause 25.

Furthermore, Merz submitted that its efforts to stay within the explicit guidance of the product SPCs in developing the advertisements did not represent a failure to maintain high standards nor did it bring discredit upon, or a loss of confidence in, the pharmaceutical industry. Merz thus also denied breaches of Clauses 2 and 9.1.

FINAL COMMENTS FROM ALLERGAN

Allergan agreed with the Panel's rulings that the advertisement at issue were in breach of Clauses 7.2, 7.3 and 7.4. Specifically, 'The Panel considered that the overall impression from the advertisement was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so. In the Panel's view, the advertisement encouraged, prescribers to consider that the unit doses of Bocouture and Botox were interchangeable. …the impression given by the advertisement could not be substantiated.' (emphasis added).

Allergan noted that Merz had not appealed these rulings.

Allergan alleged the claims of 'Equal Potency' or 'Equipotent' and '1:1 Clinical Conversion ratio' or 'Conversion ratio of 1:1' also breached Merz's undertaking given in Case AUTH/2270/10/09.

Allergan noted that the rulings in Case AUTH/2270/10/09 by the Panel and the Appeal Board were not only about an implied claim of 'superiority' as Merz seemed to believe but also in relation to 'comparability' and 'equivalence'. Indeed Merz accepted that there was no evidence to support claims of equivalence. The summary of the case made the ruling very clear:

> 'The Panel considered that there was a difference between showing non-inferiority to showing comparability. The Panel considered on the basis of the data the claim that Xeomin was 'At least as effective as Botox' did not reflect the available evidence. It implied possible superiority of Xeomin as alleged and was misleading. Breaches of the Code were ruled.
>
> Upon appeal by Merz the Appeal Board noted that both parties agreed that Benecke et al and Roggenkamper et al were non-inferiority studies that showed that Xeomin was no worse than Botox by a pre-specified margin (delta) that was clinically acceptable.
>
> The Appeal Board noted Merz's submission that it had no data upon which to make the claim that Xeomin was equivalent to Botox. In the Appeal Board's view the claim 'At least as effective' 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. The Appeal Board upheld the Panel's ruling of breaches of the Code.'

Allergan submitted that as stated by the Panel in this case, and established in Case AUTH/2270/10/09, non-inferiority studies could not be used to claim equivalence and the Panel also noted there was a difference between demonstrating 'non-inferiority' and 'comparability'. Merz had submitted in Case AUTH/2270/10/09 that it had no data to support a claim that Xeomin/Bocouture was equivalent to Botox/Vistabel. This was still so; Merz had not published any new clinical data to support a claim of equivalence.

Allergan submitted that, in its response to the appeal, Merz erroneously referred to the 'new' and 'revised' SPCs for Xeomin and Bocouture when in fact referring to statements in Section 4.2 of its previous SPC, claiming 'equal potency' which had been removed at the regulator's request. (Current Merz Xeomin and Bocouture SPCs effective March 2012).

Allergan noted Merz's claim that it was deliberately cautious and used language to convey comparable efficacy at a 1:1 clinical conversion ratio which in itself was contrary to the Panel ruling in Case AUTH/2270/10/09. Thus Allergan submitted Merz's intent was in breach of the undertaking.

Allergan also noted Merz's reference to substantial further data and opinion confirming comparable efficacy and its reference to a meta-analysis of 8 studies (Jandhyala). Merz also cited, but did not discuss, a retrospective analysis of daily practice in treatment of the upper face (Prager *et al*).

Allergan noted that in Jandhyala mixed treatment comparisons meta-analysis, only 8 clinical studies were identified in the literature search three of which compared Dysport with placebo and were not relevant for inclusion in the analysis. Of the five applicable studies, four compared Botox (20U) with placebo. No Xeomin vs placebo studies were included in the analysis. The fifth study (Sattler *et al*) involved a Xeomin treatment arm but differed significantly from the Botox vs placebo studies included as evidence for the Botox effect size:

a) it was a non-inferiority study and not placebo controlled
b) the investigators were not blinded
c) the dose of Botox (24U) differed from the dose applied in the Botox placebo controlled trials (20U)
d) the endpoint cited was a responder definition of a 1 point change on the facial wrinkle scale in contrast to the change to 'none or mild' used in the four Botox placebo controlled trials.

With only one head-to-head study included and no other studies that included Xeomin to add to the evidence of the head-to-head, there seemed no justification for the claim of substantial further data based on this analysis funded by Merz.

Jandhyala appeared to acknowledge the limited data input in the results section where it was stated that at a dose of 24 units each, there was a 94% likelihood of Xeomin producing a better outcome than Botox. This implied that the only analysis performed was comparing the effect sizes of each product in Sattler *et al*, a non-inferiority study.

Allergan submitted that in this case the Panel considered that the overall impression from the Bocouture advertisement (ref 1075/BOC/DEC/2011/JH) was that, unit for unit, it had been unequivocally demonstrated that Bocouture and Vistabel were clinically equivalent which was not so (emphasis added).

In the Panel's view, both advertisements encouraged prescribers to consider that the unit doses of Xeomin/Botox and Bocouture/Vistabel were interchangeable. The Panel considered that the advertisements were misleading in this regard.

Allergan submitted that these misleading claims were covered by the undertaking given in Case AUTH/2270/10/09. Whilst the claim at issue in that case was 'At least as effective as', the ruling clearly also addressed equivalence.

Allergan noted the following section from the Appeal Board's ruling in Case AUTH/2270/10/09.

'The Appeal Board noted Merz's submission at appeal that it had no data upon which to make the claim that Xeomin was equivalent to Botox. In the Appeal Board's view the claim 'At least as effective as' not only implied equivalence but also possible superiority which was misleading.'

Therefore, Allergan submitted that the claims found in breach which implied clinical equivalence and interchangeability were in breach of the undertaking given in Case AUTH/2270/10/09.

APPEAL BOARD RULING

The Appeal Board noted its ruling in Case AUTH/2270/10/09 stated that:

> 'The Appeal Board noted Merz's submission at the appeal that it had no data upon which to make the claim that Xeomin was equivalent to Botox. In the Appeal Board's 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. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3.'

The Appeal Board noted that the undertaking in that case 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) which featured the 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.

Similarly the Appeal Board considered that the Xeomin advertisement (ref 1281/XEO/OCT/2011/JL) which featured the claim 'Clinical studies suggest Xeomin and Botox are equipotent, with a conversion ratio of 1:1 Xeomin SmPC' together with a visual beneath of a vial of each medicine side-by-side with a colon between them, again implied to prescribers that the medicines were clinically equivalent and that unit for unit they were interchangeable. The Appeal Board noted its comments above and 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.

Complaint received **5 April 2012**

Case completed **9 August 2012**