CASE AUTH/2177/10/08

ALLERGAN v MERZ PHARMA

Xeomin leavepiece

Allergan complained about a leavepiece for Xeomin (Botulinum neurotoxin type A) issued by Merz Pharma. Allergan supplied Botox (Botulinum neurotoxin type A). Merz's product, unlike Allergan's, was free from complexing proteins.

As the complaint implied that Merz had breached its undertaking given in Case AUTH/2119/4/08 that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The detailed response from Merz is given below.

The claim 'The first Botulinum neurotoxin free from complexing proteins' was the title of the leavepiece and appeared in association with the image of a horse chestnut emerging from its spiky shell.

Allergan noted that the claim was placed above the image of a horse chestnut (the neurotoxin) emerging from a spiky shell (the complexing proteins). Allergan alleged this statement, when associated with the image, implied some special merit for Xeomin associated with the removal of the complexing proteins, versus other neurotoxins on the market.

Allergan believed that the special merit which was implied must relate to a benefit gained from the removal of the complexing proteins. The back page of the leavepiece inferred some potential benefit from the lack of complexing proteins with the claim 'Low foreign protein load suggests low potential for neutralising antibody formation'. However this suggestion had not been demonstrated clinically. In fact, in a journal advertisement (the subject of Case AUTH/2119/4/08) the above claim was qualified with the statement 'These observations have not been confirmed in the clinical setting'.

In addition, as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate. It was thought that the accessory proteins might confer an advantage in persistency in the target muscle versus naked neurotoxin. This issue had not been resolved in favour of one generally accepted viewpoint. Allergan alleged that the claim with the associated visual implied an advantage for Xeomin versus other Botulinum toxin products with complexing proteins and some special merit for Xeomin above other Botulinum toxins on the market.

Therefore, Allergan alleged that the claim 'The first Botulinum neurotoxin free from complexing proteins' when associated with the image of the horse chestnut and spiky shell was misleading and implied a special merit for Xeomin which could not be substantiated.

The Panel noted that in Case AUTH/2119/4/08, it had considered the claim 'Neurotoxin you need – complexing proteins you don't' in association with the picture of a horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum toxin type A products associated with complexing proteins for which there was no supporting data. This impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of the Code had been ruled.

The Panel noted that the claim now at issue, 'The first Botulinum neurotoxin free from complexing proteins' was different to that at issue in Case AUTH/2119/4/08 although, as before, it appeared above the image of the horse chestnut emerging from its spiky shell. The claim itself was a statement of fact and was substantiated by the cited reference (Benecke *et al* 2005) and by the summary of product characteristics (SPC). Nonetheless the Panel considered that even when a claim was true, the context in which it was used was very important. The front page of the leavepiece at issue consisted almost solely of the claim, the horse chestnut visual and the product logo which also incorporated the strapline '*Free* from complexing proteins'. Given the spiky shell of the horse chestnut, the Panel considered that the front page of the leavepiece implied that there was something injurious about complexing proteins, that they were deemed an unnecessary 'hazard' and that there was some special merit or clinical advantage if a Botulinum neurotoxin was free of such proteins. The claim would be assumed to be of clinical consequence. The Panel considered that the claim was misleading as alleged. Breaches of the Code were ruled.

Upon appeal by Merz, the Appeal Board considered that regardless of the fact that the claim was true, in the context of the image of the horse chestnut it implied a special merit or clinical advantage for Xeomin. There was no evidence that removing the complexing proteins from the Botulinum neurotoxin conferred any clinical advantage. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Allergan alleged that the image itself was misleading since it was clearly intended to represent the neurotoxin as a smooth and attractive nut and the complexing protein as a

prickly and potentially injurious outer casing.

As stated above, and as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate; it was thought that they might confer an advantage in persistency in the target muscle versus naked neurotoxin.

The Panel noted its comments above. The Panel further noted that the specific role of complexing proteins was the subject of scientific debate as acknowledged by Merz. The Panel considered that associating Xeomin with the horse chestnut visual implied that Xeomin was free of some superfluous, unwanted and possibly injurious element that was otherwise associated with other Botulinum neurotoxins. The Panel considered that the horse chestnut image, and the messages it implied, was misleading. A breach of the Code was ruled.

Upon appeal by Merz, the Appeal Board considered that the image and the messages it portrayed were misleading and upheld the Panel's ruling of a breach of the Code.

Allergan alleged that the claim 'Low foreign protein load suggests low potential for neutralising antibody formation' was misleading as this observation had not been confirmed in a clinical setting. In a recent Xeomin journal advertisement this claim was qualified with the statement 'These observations have not been confirmed in the clinical setting'. A study in rabbits had shown that Xeomin was not associated with any biologically relevant immunogenicity. However, the clinical relevance of this data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost *et al* and Bluemel *et al*).

The two references cited by Merz to support the claim (Jost *et al* and Benecke *et al*) stated that clinical studies were required to confirm this observation in an animal model and that 'this issue should be assessed in long-term safety studies with antibody testing' (Benecke *et al*).

The Panel noted that it was an established principle under the Code that all claims related to the clinical situation unless otherwise stated. The supplementary information stated that care must be taken with the use of data derived from *in vitro* studies, studies in healthy volunteers and in animals so as to not mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

The Panel noted that the claim at issue was referenced to Jost *et al* which was a review of the pre-clinical and clinical development of Xeomin. A pre-clinical antigenicity study in rabbits suggested that it would be unlikely that therapy would fail due to antibody formation over long-term use (Bluemel *et al*). Jankovic *et al* had compared the antibody levels produced following the clinical use of two Botulinum neurotoxin type A preparations, one with 25ng protein/100u and the other with 5ng protein/100u. It appeared that extrapolation of those results had led Jost *et al* to state that [Xeomin] was likely to be associated with fewer neutralising antibodies and reduced numbers of secondary non-responders. At the end of their 'discussion' section, Jost *et al* stated that future studies should focus on the administration of Xeomin in Botulinum-A-naive patients, with the aim of investigating its antigenic properties, and determining long-term efficacy and safety profiles.

The Panel noted that although the claim 'Low foreign protein load *suggests* low potential for neutralising antibody formation' (emphasis added) did not directly refer to Xeomin, it was an integral part of the Xeomin leavepiece and was a claim for the product. The Panel did not accept the implication that it would be read as a general scientific proposition. The Panel noted that clinically, the antigenic potential of Xeomin had still to be established. The Panel thus considered that in that regard the claim was misleading as alleged. The use of the word 'suggests' did not negate the impression that a low potential for neutralising antibody formation with Xeomin had been proven. A breach of the Code was ruled.

Upon appeal by Merz, the Appeal Board noted that although the claim did not directly refer to Xeomin, it was an integral part of the Xeomin leavepiece and was a claim for the product. The Appeal Board noted that clinically the antigenic potential of Xeomin had still to be established. The Appeal Board considered that the claim was misleading and it upheld the Panel's ruling of a breach of the Code.

The alleged breach of undertaking was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The Panel noted that in the previous case, Case AUTH/2119/4/08, Allergan had complained about the claim 'Neurotoxin you need – complexing protein you don't'. The Panel had considered the claim in association with the image of the horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum neurotoxin type A products associated with complexing proteins for which there was no supporting data. The impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of the Code was ruled.

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that

companies complied with undertakings.

The Panel noted its comments and ruling above and considered that the messages conveyed in the leavepiece now at issue were closely similar to those considered in Case AUTH/2119/4/08 and were covered by the undertaking given in that case. Given that the leavepiece implied a clinical disadvantage for Botulinum neurotoxins with complexing proteins, the Panel considered that Merz had not complied with its undertaking. A breach of the Code was ruled. High standards had not been maintained and a further breach was ruled. The Panel considered that in breaching its undertaking Merz had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Upon appeal by Merz the Appeal Board considered that the claim at issue 'The first Botulinum neurotoxin free from complexing proteins' was different to the claim at issue in Case AUTH/2119/4/08 'Neurotoxin you need – complexing protein you don't'. The Appeal Board noted that the image of the horse chestnut accompanying both claims was the same. There had been no ruling specifically related to the image in Case AUTH/2119/4/08. The Appeal Board noted that Merz had taken steps to comply with its undertaking given in Case AUTH/2119/4/08. The Appeal Board did not consider that the current material meant that Merz had breached its undertaking and no breach of the Code was ruled.

Allergan Ltd complained about a leavepiece (ref 1056/XEO/MAY/2008/SM) for Xeomin (Botulinum neurotoxin type A) issued by Merz Pharma UK Ltd. Allergan supplied Botox (Botulinum neurotoxin type A). Merz's product, unlike Allergan's, was free from complexing proteins.

Inter-company correspondence had failed to satisfy Allergan's concerns.

As the complaint implied that Merz had breached its undertaking given in Case AUTH/2119/4/08 that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. Merz was accordingly asked to comment in relation to Clauses 2, 9.1 and 25 of the Code in addition to the clauses cited by Allergan.

1 Claim 'The first Botulinum neurotoxin free from complexing proteins'

This was the title of the leavepiece and appeared in association with the image of a horse chestnut emerging from its spiky shell.

COMPLAINT

Allergan noted that the claim was placed above the image of a horse chestnut (the neurotoxin) emerging from a spiky shell (the complexing proteins). Allergan alleged this statement, when associated with the image, implied some special merit for Xeomin associated with the removal of the complexing proteins, versus other neurotoxins on the market.

Allergan believed that the special merit which was implied must relate to a benefit gained from the removal of the complexing proteins. The back page of the leavepiece inferred some potential benefit from the lack of complexing proteins with the claim 'Low foreign protein load suggests low potential for neutralising antibody formation'. However this suggestion had not been demonstrated clinically. In fact, in the Xeomin advertisement in the BMJ, 15 March 2008, (ref 1012a/XEO/NOV/2007 – the subject of Case AUTH/2119/4/08) the above claim was qualified with the statement 'These observations have not been confirmed in the clinical setting'. A study in rabbits had shown that Xeomin was not associated with any biologically relevant immunogenicity. However, as Merz's advertisement stated, the clinical relevance of these data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost *et al* 2007 and Bluemel *et al* 2006).

In addition, as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate. It was thought that the accessory proteins might confer an advantage in persistency in the target muscle versus naked neurotoxin. Certainly, this issue of the role of complexing proteins had not been resolved in favour of one generally accepted viewpoint. Allergan alleged that the claim with the associated visual implied an advantage for Xeomin versus other Botulinum toxin products with complexing proteins and some special merit for Xeomin above other Botulinum toxins on the market.

In its response Merz stated that this implication was 'incomprehensible' but did not further address Allergan's concerns. Whilst the special merit or advantage being claimed might not be clear to the reader and might be left to their imagination, Allergan strongly believed that the claim and visual implied an unsubstantiated advantage.

Therefore, Allergan alleged that the claim 'The first Botulinum neurotoxin free from complexing proteins' when associated with the image of the horse chestnut and spiky shell was in breach of Clauses 7.2 and 7.10 as it was misleading and implied a special merit for Xeomin which could not be substantiated.

RESPONSE

Merz noted that the Xeomin summary of product characteristics (SPC) clearly stated that Xeomin was free from complexing proteins. No other commercially available Botulinum neurotoxin was free from complexing proteins. Based on this, the claim was true, accurate and unambiguous.

The claim was supported with an image of a horse chestnut emerging from its shell. Merz believed that the image was an appropriate metaphor to support the claim '... free from complexing proteins'. The metaphor was chosen as it captured the role of the complexing proteins in an accessible and meaningful way.

In nature the highly active neurotoxin was protected by an outer casing of complexing proteins including haemagglutinins and non-toxic, non-haemagglutinin proteins. It was generally accepted that the primary role of the complexing proteins was to protect the neurotoxin from the harsh acid conditions of the stomach when the toxin was ingested. Studies of the 900kD neurotoxin complex had demonstrated that once the complex passed from an acidic pH environment to one of a physiological pH there was a rapid disassociation of the neurotoxin and the protective protein complex with the complex breaking into a number of fragments. This disassociation occurred in minutes compared with the onset of therapeutic effect which was measured in days (Eisele and Taylor 2008).

The horse chestnut represented a clear metaphor of this process with the outer casing of the shell providing robust protection of the fragile nut as it was delivered from the tree to its site of action, the soil. Once in place the nut was released from its protective shell and was able to perform its functional role, becoming a new tree.

Merz believed that this was a clear and unambiguous metaphor which reinforced the accurate claim that Xeomin was the first neurotoxin free from complexing proteins and as such denied that the image and copy were a breach of Clause 7.2.

Allergan asserted that the metaphor implied special merit for Xeomin which it supported with reference to the claim found later in the leavepiece, that a 'Low foreign protein load suggests low potential for the neutralising antibody formation'. As this paragraph was not associated with an allegation of a breach of the Code it would be dealt with later.

Merz challenged the assertion that the claim 'The first Botulinum neurotoxin free from complexing proteins' and the use of an unambiguous image/metaphor to support it exaggerated the properties or implied some special merit of Xeomin. Xeomin was free from complexing proteins, a fact stated in its SPC, and as such Merz refuted the assertion that the claim and supporting image were in breach of Clause 7.10.

PANEL RULING

The Panel noted that in Case AUTH/2119/4/08, it had considered the claim 'Neurotoxin you need – complexing proteins you don't' in association with the picture of a horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum toxin type A products associated with complexing proteins for which there was no supporting data. This impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that the claim now at issue, 'The first Botulinum neurotoxin free from complexing proteins' was different to that at issue in Case AUTH/2119/4/08 although, as before, it appeared above the image of the horse chestnut emerging from its spiky shell. The claim itself was a statement of fact and was substantiated by the cited reference (Benecke *et al* 2005) and by the SPC. Nonetheless the Panel considered that even when a claim was true, the context in which it was used was very important. The front page of the leavepiece at issue consisted almost solely of the claim, the horse chestnut visual and the product logo which also incorporated the strapline '*Free* from complexing proteins'. Given the spiky shell of the horse chestnut, the Panel considered that the front page of the leavepiece implied that there was something injurious about complexing proteins, that they were deemed an unnecessary 'hazard' and that there was some special merit or clinical advantage if a Botulinum neurotoxin was free of such proteins. The claim would be assumed to be of clinical consequence. The Panel considered that the claim was misleading as alleged. Breaches of Clauses 7.2 and 7.10 were ruled.

APPEAL BY MERZ

Merz noted that this leavepiece was developed for use with specialist neurologists who were experienced users of Botulinum toxin and familiar with the medicine class and therapeutic area.

Merz noted that the Panel had acknowledged that this claim was a truthful, substantiated statement of fact and that the property was stated explicitly in the SPC and therefore in itself was not misleading.

Merz noted that the Panel had considered that the association of the visual with the claim led to an impression of merit of clinical consequence being formed which was not substantiated and was therefore misleading. Merz submitted that it was not justifiable to rule a statement of fact, which was not misleading, in breach of the Code based upon a visual which was subject to a separate charge. This would preclude the use of a clear statement of fact, as it appeared in the SPC, as a future claim. Merz therefore challenged the validity of the judgement.

However, in defence of the impression created by the claim in association with the visual, Merz submitted that there was merit in removing complexing proteins from Botulinum toxin, that this merit could be substantiated and was of clinical consequence.

Merz submitted that Botulinum toxins occurred in nature and were produced by *Clostridium botulinum* bacteria. The bacteria encased the toxins within complexing proteins to provide protection from protein denaturation by stomach acid prior to absorption through the gastrointestinal tract. On reaching physiological pH the protein complex rapidly dissociated, in less than a minute, into a number of fragments releasing the toxin from its protective coat (Eisele and Taylor). The presence of such proteins allowed the neurotoxin to reach its target and have its effect. This effect was therefore a protective one much like the shell around a horse chestnut.

Merz submitted that in the clinical setting the neurotoxin was not required to pass through the gastrointestinal tract and was injected directly into the target site. Given this, complexing proteins might, in principle, be considered unnecessary for therapeutic efficacy.

Studies into the pharmacodynamics of Xeomin demonstrated that removal of the complexing proteins did not hamper therapeutic efficacy (Xeomin Assessment Report). This had been confirmed in the pivotal phase II and phase III clinical trials for Xeomin which clearly showed that Xeomin had the same clinical efficacy as Botox on a 1:1 dosing ratio, without the need for complexing proteins (Wohlfarth *et al* 2007, Benecke *et al*, Roggenkamper *et al* 2006). This robust clinical evidence remained uncontested.

The safety of Xeomin had been investigated and compared to Botulinum toxins containing complexing proteins in all phases of clinical development. Xeomin had been demonstrated to have equivalent diffusion properties (Wohlfarth *et al*) and safety (Benecke *et al*, Roggenkamper *et al*) to conventional Botulinum toxins. This was recognized by BfArM, the regulatory assessor of the Reference Member State, and was reflected in the conclusion of its medicine safety assessment with the statement:

> 'In summary the overall safety profile of Xeomin is in accordance with the known safety profile of other BoNT/A containing preparations. There were no new safety concerns regarding the safety and tolerability of Xeomin based on the presented clinical studies'.

Merz submitted that the proposition championed by Allergan that there was a current scientific debate on the clinical necessity of complexing proteins was founded on a discussion paper on the cellular origin of neurotoxin and two reviews co-authored by Allergan employees, one of which was published in an Allergan sponsored supplement and contained significant inaccuracies relating to Xeomin (Aoki *et al* 2006).

Johnson and Bradshaw (2001) provided no data on the benefits of complexing proteins (only supposition) but did discuss data on immunogenicity (see below).

Merz submitted that the Allergan paper by Foster *et al* (2006) suggested that the difference in diffusion of toxin complexes in rats was due to differences in the complexing proteins. A similar position was suggested by Aoki *et al*. This data was in rats and the only data in humans contradicted this (Wohlfarth *et al*) leading to the conclusion that the animal data was not of direct relevance to the clinical situation, as required by the Code.

Merz submitted that thus, based upon the efficacy, safety and tolerability profile of Xeomin, a neurotoxin free from complexing proteins, it had been demonstrated that complexing proteins were not required, and therefore could be considered unnecessary, for comparable therapeutic efficacy, safety and tolerability to be achieved.

The confidential assessment report for Xeomin issued by the German regulatory authority, BfArM, clearly identified the merit of removing complexing proteins:

> 'Xeomin (NT 201) is a freeze-dried formulation of botulinum neurotoxin type A (BoNT/A) free of complexing proteins obtained from a well characterised strain of *Clostridium botulinum*. This highly purified nature is therefore thought to represent a clinical advance compared to existing preparations of BoNT/A which contain haemagglutinins.'
>
> 'BoNT/A is obtained from specific strains of *Clostridium botulinum*, and is produced as part of a high molecular weight complex, which is formed by several haemagglutinins and other non toxic proteins. The currently marketed preparations are not free of complexing proteins. They contain other proteins of clostridial origin, which are potentially immunogenic and may lead to the development of antibodies and secondary non-response to treatment.
>
> Immunogenicity is highly relevant to the treatment of focal dystonias as these conditions are chronic and require regular, usually life-long therapy. The proportion of secondary nonresponders to BoNT/A is reported to be around 10%, with a further 40% of treated patients developing titers of non-neutralising antibodies against the haemagglutinins.
>
> Xeomin (NT 201) contains BoNT/A free of complexing proteins, which undergoes a biological manufacturing process to remove accompanying haemagglutinins. In animal models, Xeomin has shown no detectable immunogenicity. This is anticipated to translate into less neutralising antibodies in patients and fewer secondary non-responders upon longterm therapy.'

The assessor went on to further strengthen the merit of removing the natural bacterial defence provided

by the complexing proteins resulting in 'obviously lower toxicity when given by the oral route'.

Merz submitted that the potential for immunogenicity was further expounded in Johnson and Bradshaw provided by Allergan which stated that one of the major drawbacks of the clinical use of Botulinum toxins was the formation of antibodies but provided no data on the positive role of complexing proteins.

Thus complexing proteins could be characterised as potentially immunogenic with the potential to promote antibody formation and secondary non-response. The development of antibodies to a formulation of neurotoxin containing complexing proteins (Botox) and not Xeomin was demonstrated in an animal study (Bluemel *et al*). In the study no neutralising antibodies were produced by Xeomin treated rabbits (0/20) in contrast 20% (4/20) of Botox treated rabbits developed neutralising antibodies.

Merz submitted that in order to confirm the direct relevance of this data to humans the opinion of a World expert in the field was sought. On reviewing the rabbit data Professor Dr H Schellekens, Professor of Immunology, University of Utrech concluded:

> 'Because the microbial product is a foreign protein both for rabbits as well as patients, the reduced immunogenicity seen in rabbits may be extrapolated to patients as has been shown with other microbial products such as asparaginase, adenosinedeamidase (ADA) and staphylokinase. All these products showed both reduction of immunogenicity in animals as well as patients.'

He concluded:

> 'Moreover the magnitude of reduction of immunogenicity seen in rabbits will surely be reflected in reduced immunogenicity in patients.'

Merz submitted that this position, and the authority of Professor Schellekens on the subject, was endorsed by Professor Giovannoni, Neuroscience Centre Lead & Professor of Neurology at Barts and The London School of Medicine and Dentistry, who was a respected UK expert in the field.

Merz submitted that the data clearly showed that complexing proteins increased the potential for neutralizing antibody formation and provided no incremental clinical efficacy, tolerability or safety benefits. Based on this finding it could be concluded that the inclusion of complexing proteins in formulations of Botulinum neurotoxin represented an unnecessary hazard, to which, until now, there had been no alternative.

The low potential for developing neutralising antibodies described above was a direct reflection of the lack of complexing proteins and therefore might be considered a special merit of clinical significance.

Xeomin was a freeze-dried, purified form of Botulinum neurotoxin. Its constituent parts were the pure 150kDa neurotoxin, human albumin and sucrose. Through a process of purification, and the removal of complexing proteins, Merz had developed an inherently stable neurotoxin which had been demonstrated stable at ambient temperature and had a licensed indication for storage at temperatures ≤25°C for up to 3 years from manufacture. By comparison conventional unpurified forms of neurotoxin complexes (Botox and Dysport) required refrigeration (SPC). The special merit resulting from this characteristic, namely reducing the possibility of treatment failure due to failure in the cold chain, was acknowledged in Case AUTH/2119/4/08 and could be considered a merit of clinical significance.

In summary Merz submitted that the claim 'The first Botulinum neurotoxin free from complexing proteins' was a truthful substantiated statement of fact. The associated visual was an appropriate metaphor. The impression created by the visual was not misleading in that complexing proteins had been demonstrated unnecessary and might be considered potentially hazardous. Special merit and clinical advantage for a Botulinum neurotoxin free of such proteins could be substantiated and this view was consistent with the view of the licensing authority.

Further, it was not justifiable to rule a statement of fact, which was not misleading, in breach of the Code based upon a visual which was subject to a separate charge. To pursue a charge which would control the use of an unambiguous and factually accurate statement directly quoted from the SPC represented a position which was not supportable by the letter or the spirit of the Code.

Merz submitted that the evidence demonstrated that there was merit in being free from complexing proteins and therefore the impression created by the claim and associated visual was not misleading and could not be in breach of Clause 7.2. As this impression was accurate it did not exaggerate the properties of Xeomin and could not be in breach of Clause 7.10. In light of this evidence the Panel's ruling of a breach of Clauses 7.2 and 7.10 must be overruled.

COMMENTS FROM ALLERGAN

Allergan noted that Merz now appeared to agree that the claim 'The first Botulinum neurotoxin free from complexing proteins'; when placed above the image of a horse chestnut (the neurotoxin) emerging from a spiky shell (the complexing proteins), implied a special merit for Xeomin vs other toxins on the market. In Merz's response to the complaint it defended the use of the claim as a statement of fact and the horse chestnut image as a clear and unambiguous metaphor to reinforce an accurate claim. Merz had challenged Allergan's assertion that the claim and the image/metaphor

exaggerated the properties or implied some special merit of Xeomin. However, as well as defending the claim as a statement of fact, Merz now appeared to agree that there was both an implied, and indeed an actual special merit in removal of complexing proteins.

Allergan alleged that Merz confirmed that the claim and associated visual were in breach of Clauses 7.2 and 7.10.

Allergan strongly disagreed with the suggestion that there was a special merit of clinical consequence gained for the removal of complexing proteins or that complexing proteins represented an 'unnecessary hazard'.

Allergan agreed that the claim 'The first Botulinum neurotoxin free from complexing proteins' was a statement of fact supported by the Xeomin SPC. However, when associated with the horse chestnut visual this claim was misleading and implied a special merit for Xeomin (the nut) versus Botulinum toxins with complexing proteins (the spiky shell).

Merz clearly believed this to be the case as it defended this impression created by the claim in association with the visual.

Allergan alleged that the clinical evidence presented by Merz did not support its suggestion that complexing proteins represented an 'unnecessary hazard'. The two 16 week non-inferiority studies (Benecke *et al*; Roggenkamper *et al*) cited by Merz had established non-inferiority vs Botox, not clinical equivalence. These studies concluded that both products had comparable safety profiles, with similar adverse event patterns in terms of type and frequency. However, neither supported the supposition that complexing proteins were unnecessary or indeed hazardous. Both studies discussed the potential benefit from a lack of complexing proteins but went on to confirm that this possible benefit had not been demonstrated in a clinical setting. Specifically, Benecke *et al* stated:

> 'Based on its physiochemical properties and toxicologic evidence NT201 [Xeomin] is expected to lead to a reduced incidence of non-responders after long term treatment as described for other marketed BTX-A products. This issue should be assessed in long-term safety studies with antibody testing.'

Similarly, Roggenkamper stated:

> 'There is good nonclinical evidence that NT201 will be less immunogenic than BOTOX, owing to the high purified preparation and absence of immunologenic proteins. Thus NT201 may specifically be of therapeutic value in the long-term treatment of blepharospasm. Firm proof, however, warrants long-term clinical studies in conjunction with antibody tests'.

Allergan noted the phase 2 study in 32 volunteers (Wohlfarth *et al*) demonstrated that both Botox and Xeomin were effective and well tolerated in healthy male subjects. In this model the desired paretic effect was observed for both products with no diffusion into adjacent muscles. However, this study did not support the supposition that complexing proteins were 'unnecessary' or 'hazardous'. There were a significant number of non-clinical publications discussing the role of complexing proteins. Indeed, as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate (Aoki *et al*; Foster *et al*; Johnson and Bradshaw). Certainly, the issue of the role of complexing proteins had not been resolved in favour of one generally accepted viewpoint.

Allergan noted that Merz had presented a section from the assessment report for Xeomin issued by the BfArM to support its argument that complexing proteins were an unnecessary hazard. The section stated that in animal models Xeomin had shown no detectable immunogenicity and that this was anticipated to translate into less neutralizing antibodies (emphasis added). To date, the only available data on immunogenicity was in rabbits which had shown that Xeomin was not associated with any biologically relevant immunogenicity in this model (Bluemel, *et al*). Although, to be accurate, one rabbit developed ELISA detectable antibodies after Xeomin treatment (Jost, *et al*). The clinical relevance of the rabbit data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost, *et al*).

In contrast, there was a wealth of long-term clinical data regarding antibody formation following injections of Botox. Overall, neutralizing antibody formation was rare with the current preparation of Botox (Brin *et al* 2008; Mejia *et al* 2005; Yablon *et al* 2007).

The expert statement and implication of potential benefit to patients from reduced immunogenicity in rabbits, did not, in Allergan's view, warrant the conclusion of Merz that the inclusion of complexing proteins in formulations of Botulinum neurotoxin represented an unnecessary hazard.

Allergan did not agree that a lack of complexing proteins was a special merit of clinical significance. The ability to store Xeomin at room temperature (prior to reconstitution) did not provide a special merit of clinical significance. In Case AUTH/2119/4/08 the above property was considered to have important practical implications for the customer. It was disingenuous to now suggest that the claim at issue, in association with the visual was used to support the special merit that no refrigeration was required prior to reconstitution. The special merit of clinical significance being implied was a low foreign protein load suggesting a low potential for neutralizing antibody formation which had not yet

been demonstrated in clinical practice.

In addition, Allergan was not aware of any data to support the suggestion that the removal of complexing proteins accounted for the ability to store Xeomin at room temperature. Indeed, it was likely that the addition of more human serum albumin (a known stabilising agent) to Xeomin (1g in Xeomin vs 0.5g in Botox) provided sufficient stabilization to enable storage at room temperature. Thus, the ability to store Xeomin at room temperature (prior to reconstitution) was likely to be a function of formulation.

In summary, Allergan submitted that the claim 'The first Botulinum neurotoxin free from complexing proteins' when associated with the image of the horse chestnut and spiky shell was in breach of Clauses 7.2 and Clause 7.10; it was misleading and implied a special merit for Xeomin which could not be substantiated.

Allergan did not agree with the view presented by Merz that a statement of fact could not be ruled as misleading. In this case, with the context of the associated visual, the statement was indeed misleading.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'The first Botulinum neurotoxin free from complexing proteins' was a statement of fact taken from the Xeomin SPC. It would encourage readers to consider the clinical benefits that arose from Xeomin being free from complexing proteins. The Appeal Board considered that the image of the horse chestnut implied that the nut (Xeomin), which represented the purified neurotoxin protein, was the necessary element and that the spiky shell (complexing proteins), which were absent in Xeomin but present in other Botulinum neurotoxins, were an unnecessary hazard.

The Appeal Board considered that regardless of the fact that the claim was true, in the context of the image of the horse chestnut it implied a special merit or clinical advantage for Xeomin. There was no evidence that removing the complexing proteins from the Botulinum neurotoxin conferred any clinical advantage. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

2 The horse chestnut visual

COMPLAINT

Allergan believed that the image itself was misleading since it was clearly intended to represent the neurotoxin as a smooth and attractive nut and the complexing protein as a prickly and potentially injurious outer casing.

As stated above, and as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate; it was thought that they might confer an advantage in persistency in the target muscle versus naked neurotoxin (Aoki *et al*; Foster *et al* and Johnson and Bradshaw).

Allergan did not agree with Merz's view that the horse chestnut seed and shell was an accurate metaphor in relation to Botulinums. In fact its argument that 'the horse chestnut seed does not need the spiky shell to provide its end effect' was at odds with the conclusions of Case AUTH/2119/4/08. The 'shell' (or complexing proteins) might influence where the 'nut' (or neurotoxin) acted in the target muscle and hence might influence its clinical effect.

Allergan alleged that the image was in breach of Clause 7.8.

RESPONSE

Merz stated that, as discussed in point 1 above the horse chestnut metaphor was chosen as it captured the role of the complexing proteins in an accessible and meaningful way.

As previously stated, in nature the highly active neurotoxin was protected by an outer casing of complexing proteins including haemagglutinins and non-toxic, non-haemagglutinin proteins. It was generally accepted that the primary role of the complexing proteins was to protect the neurotoxin from the harsh acid conditions of the stomach when the toxin was ingested. Studies of the 900kD neurotoxin complex had demonstrated that once the complex passed from an acidic pH environment to one of a physiological pH there was a rapid disassociation of the neurotoxin and the protective protein complex with the complex breaking into a number of fragments. This disassociation could be measured in minutes compared with the onset of therapeutic effect which was measured in days (Eisele and Taylor).

The horse chestnut represented a clear metaphor of this process with the outer casing of the shell providing robust protection of the fragile nut as it was delivered from the tree to its site of action, the soil. Once in place the nut was released from its protective shell and was able to perform its functional role, becoming a new tree.

Allergan asserted that the image was misleading in representing the neurotoxin as smooth and attractive and the complexing proteins as prickly and injurious. The complexing proteins which surrounded it, made up of haemagglutinins and non-toxic, non-haemagglutinin proteins, provided stability and protection for the neurotoxin. Presenting Botulinum as a fragile nut surrounded by the robust protection of its shell was consistent with the function and form of Botulinum

neurotoxin *in vivo* and as such was neither misleading nor inappropriate. Merz denied a breach of Clause 7.8.

Allergan also asserted that this metaphor did not allow for potential benefits afforded by the presence of complexing proteins. Merz accepted that the specific role of complexing proteins might be the subject of scientific debate but disputed the assertion that the metaphor was redundant based on an as yet unproven clinical hypothesis regarding the persistency of the neurotoxin in the target muscle.

The two largest clinical trials investigating the use of toxins in the symptomatic treatment of cervical dystonia (Benecke *et al*) and blepharospasm (Roggenkamper *et al*) demonstrated equal efficacy and tolerability between Xeomin, which was free from complexing proteins, and Botulinum neurotoxin complex type A (Botox) which was not. A further clinical study had demonstrated no difference in persistence between Xeomin and Botox (Wohlfarth *et al*). No conflicting clinical data challenging equal efficacy, tolerability or persistence had been published to date. Based on this Merz believed that to incorporate non-clinical scientific arguments which were based on a review of data in mice (Aoki *et al*), a preclinical discussion paper (Foster *et al*) and a genetic study of the clostridium bacterium (Johnson and Bradshaw), was misleading and did not present a fair, balanced and clinically relevant view of the matter.

Secondly Allergan stated that Case AUTH/2119/4/08 made comment upon the point that the seed of the horse chestnut did not need its spikey shell to have its effect. This was inaccurate. The case referred to the visual in the context of the claim then at issue 'Neurotoxin you need - complexing proteins you don't' stating that the visual strengthened the impression given by the claim that complexing proteins were unnecessary. As the claim did not appear in any current materials Merz believed that, within the context of this complaint, this ruling was not relevant.

In summary Merz believed that the visual effectively and appropriately supported the headline with which it was associated, namely that Xeomin was 'The first Botulinum neurotoxin free from complexing proteins'. No claim was made or inferred that complexing proteins were not required by, or added value to, other products in the field. Based upon these arguments Merz believed that this was a clear and unambiguous metaphor which reinforced the accurate claim that Xeomin was the first neurotoxin free from complexing proteins and as such contested that the image, with or without the associated text, breached Clause 7.8.

PANEL RULING

The Panel noted its comments above at point 1.

The Panel further noted that the specific role of complexing proteins was the subject of scientific debate as acknowledged by Merz. The Panel considered that associating Xeomin with the horse chestnut visual implied that Xeomin was free of some superfluous, unwanted and possibly injurious element that was otherwise associated with other Botulinum neurotoxins. The Panel considered that the horse chestnut image, and the messages it implied, was misleading. A breach of Clause 7.8 was ruled.

APPEAL BY MERZ

Merz submitted that given the data presented in point 1 above, the visual of the horse chestnut was not in breach of Clause 7.8. The artwork did not mislead as to the nature of the medicine and the image of a chestnut being released from its shell was an appropriate metaphor for the release of Botulinum neurotoxin from its complexing proteins.

Merz did not accept that the visual depicted complexing proteins as 'injurious' (as the spikes on the horse chestnut were soft not hard) but accepted that it might be concluded that complexing proteins were unnecessary and a benefit of clinical significance might be achieved with their removal. Complexing proteins had been demonstrated unnecessary for clinical efficacy and safety to be achieved. They might however impact on product stability and increase the risk for the formation of neutralising antibodies leading to primary or secondary treatment failure. Their removal conferred a clinical advantage of significance. Based on this the visual could be considered a fair and balanced metaphor which did not mislead either directly or indirectly and therefore was not in breach of Clause 7.8.

COMMENTS FROM ALLERGAN

Allergan alleged the image itself was misleading since it was clearly intended to represent the neurotoxin as a smooth and attractive nut and the complexing proteins as a prickly and potentially injurious (rather than soft) outer casing.

As stated above, and as concluded in Case AUTH/2119/4/08, the role of complexing proteins was still the subject of scientific debate. It was thought that the accessory protein might confer an advantage in persistency in the target muscle vs naked neurotoxin (Aoki *et al*; Foster *et al* Johnson and Bradshaw).

Allergan did not agree that the horse chestnut seed and shell was an accurate metaphor for Botulinum toxins. The 'shell' (or complexing proteins) might influence where the 'nut '(or neurotoxin) acted in the target muscle and hence might influence its clinical effect. Merz now stated that the visual might lead the reader to conclude that complexing

proteins were unnecessary and a benefit of clinical significance might be achieved from their removal. Therefore, Allergan alleged that the image was in breach of Clause 7.8.

APPEAL BOARD RULING

The Appeal Board noted its ruling above at point 1. The role of complexing proteins was unclear and the subject of scientific debate. The image implied that the complexing proteins as present in other Botulinum neurotoxins were an unnecessary hazard. The Appeal Board considered that the image and the messages it portrayed were misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8. The appeal on this point was unsuccessful.

3 Claim 'Low foreign protein load suggests low potential for neutralising antibody formation'

COMPLAINT

Allergan alleged that the claim was misleading and in breach of Clause 7.2 as this observation had not been confirmed in a clinical setting.

As stated above, in a recent Xeomin advertisement in the BMJ, 15 March 2008 (ref 1012a/XEO/NOV/2007), this claim was qualified with the statement 'These observations have not been confirmed in the clinical setting'. A study in rabbits had shown that Xeomin was not associated with any biologically relevant immunogenicity. However, the clinical relevance of this data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost *et al* and Bluemel *et al*).

The two references cited by Merz to support the claim (Jost *et al* and Benecke *et al*) both referred to the animal study undertaken by Merz but also confirmed that clinical studies were required to confirm this observation in an animal model and that 'this issue should be assessed in long-term safety studies with antibody testing' (Benecke *et al*).

Allergan alleged that the claim was misleading, in breach of Clause 7.2.

RESPONSE

Merz noted the allegation that the claim was in breach of Clause 7.2 as it had not been confirmed in a clinical setting. There was no requirement for claims to be purely clinical in Clause 7.2. Clearly the use of rabbit data was of direct relevance to the clinical setting as rabbits had humoral immunity in much the same way as humans. Indeed Allergan's use of animal data to justify its position on complexing proteins above was evidence that it did not hold this view either. Furthermore, although this claim was in the material at issue in Case AUTH/2119/4/08, Allergan did not consider that clinical justification was needed then and did not make this part of its complaint.

Foreign protein, in this case of bacterial origin, injected into humans would produce an immunological effect. This was the basis of human defence from invasion by other biological organisms. Given this fact, the lower the amount of foreign protein the lower the potential for antibody formation.

Xeomin had a very low protein content at 0.6ng/100u (compared with Allergan's Botulinum neurotoxin type A with 5ng/100u for example). Thus with such a low protein load the potential for antibody formation was also low. This had been confirmed with the rabbit study cited in the leavepiece which demonstrated the formation of neutralizing antibodies against Botox treated rabbits (20% of sample) but not against Xeomin treated rabbits (0% of sample) (Bluemel *et al*).

In a clinical setting Jankovic *et al* (2003) directly compared the antibody levels of patients who had been treated with a toxin of 25ng protein/100u with the antibody levels of those on 5ng protein/100u and concluded 'the low risk of antibody formation after current [Botulinum neurotoxin] type A treatment is related to lower protein load' ($p<0.004$). This study was in two preparations of Allergan's Botulinum neurotoxin, but the conclusion was clear.

Unlike the unresolved discussion of the role of complexing proteins in neurotoxin use, the proposition that a low foreign protein load suggested a low potential for neutralizing antibody formation was a matter of scientific consensus and Merz was unaware of any current arguments against this.

Based upon these facts Merz denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that it was an established principle under the Code that all claims related to the clinical situation unless otherwise stated. The supplementary information to Clause 7.2 stated that care must be taken with the use of data derived from *in vitro* studies, studies in healthy volunteers and in animals so as to not mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance.

The Panel noted that the claim at issue was referenced to Jost *et al* which was a review of the pre-clinical and clinical development of Xeomin. A pre-clinical antigenicity study in rabbits suggested that it would be unlikely that therapy would fail

due to antibody formation over long-term use (Bluemel *et al*). Jankovic *et al* had compared the antibody levels produced following the clinical use of two Botulinum neurotoxin type A preparations, one with 25ng protein/100u and the other with 5ng protein/100u. It appeared that extrapolation of those results had led Jost *et al* to state that [Xeomin] was likely to be associated with fewer neutralising antibodies and reduced numbers of secondary non-responders. At the end of their 'discussion' section, Jost *et al* stated that future studies should focus on the administration of Xeomin in Botulinum-A-naive patients, with the aim of investigating its antigenic properties, and determining long-term efficacy and safety profiles.

The Panel noted that although the claim 'Low foreign protein load *suggests* low potential for neutralising antibody formation' (emphasis added) did not directly refer to Xeomin, it was an integral part of the Xeomin leavepiece and was a claim for the product. The Panel did not accept the implication that it would be read as a general scientific proposition. The Panel noted that clinically, the antigenic potential of Xeomin had still to be established. The Panel thus considered that in that regard the claim was misleading as alleged. The use of the word 'suggests' did not negate the impression that a low potential for neutralising antibody formation with Xeomin had been proven. A breach of Clause 7.2 was ruled.

APPEAL BY MERZ

Merz submitted that Schellekens stated that the rabbit data were of direct relevance and significance to the clinical situation (as in point 1). This was also the position taken by the German regulator, BfArM, in the assessment report which stated:

> 'Xeomin (NT 201) contains BoNT/A free of complexing proteins, which undergoes a biological manufacturing process to remove accompanying haemagglutinins. In animal models, Xeomin has shown no detectable immunogenicity. This is anticipated to translate into less neutralising antibodies in patients and fewer secondary non-responders upon longterm therapy.'

Merz submitted that this clearly demonstrated the lower potential of Xeomin to produce neutralising antibodies than either Botox or Dysport. Given this the claim was not misleading and therefore not in breach of Clause 7.2.

COMMENTS FROM ALLERGAN

Allergan alleged that the claim 'Low foreign protein load suggests low potential for neutralising antibody formation' was misleading and in breach of Clause 7.2 as this observation had not been confirmed in a clinical setting. A study in rabbits had shown that Xeomin was not associated with any biologically relevant immunogenicity in this model. However, the clinical relevance of this data had yet to be confirmed and long-term use of Xeomin had yet to be investigated (Jost, *et al*; Bluemel, *et al*).

The statement by Schellekens only supported the argument that there might be a lower potential for Xeomin to produce neutralizing antibodies. He specifically stated that the removal of complexing proteins was 'anticipated' to translate into less neutralizing antibodies.

Therefore, Allergan alleged that this claim was misleading and in breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted the principle that the greater the amount of foreign protein antigen introduced, the greater the host's antibody response. However, the Appeal Board noted from Allergan that there was evidence that antibodies to the complexing proteins did not affect the efficacy of Botox. The only antibodies that had a neutralising effect were those directed to the core Botulinum neurotoxin itself and more specifically the active site of the molecule. Thus a greater antibody response did not necessarily mean that there would be an increase in neutralizing antibodies.

The Appeal Board noted that although the claim 'Low foreign protein load *suggests* low potential for neutralising antibody formation' (emphasis added) did not directly refer to Xeomin, it was an integral part of the Xeomin leavepiece and was a claim for the product. The Appeal Board noted that rabbit data from Bluemel *et al* had suggested that Xeomin use was not associated with the formation of neutralising antibodies. The assessment report for Xeomin prepared by the German regulator, BfArM, referred to anticipated less neutralising antibodies. The expert opinion provided by Merz stated that the reduced immunogenicity in rabbits might be extrapolated to patients. There was no mention of neutralising antibodies nor was it clear whether the expert had introduced an element of caution with regard to extrapolation to patients or had, in effect, given permission to extrapolate (as interpreted by Merz). However, the Appeal Board noted that clinically the antigenic potential of Xeomin had still to be established. The Appeal Board considered that the claim was misleading and it upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

4 Implied breach of undertaking

As stated above, this aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

RESPONSE

Merz noted that the claim found in breach in Case AUTH/2119/4/08 was 'Neurotoxin you need - complexing proteins you don't'. The Panel ruling stated 'The Panel considered that the claim was misleading'. The claim had been withdrawn and had not been used again. The visual was only mentioned in the sense that it strengthened the claim. The visual was not the subject of the complaint and therefore was not ruled upon by the Panel.

Merz had complied fully with the undertaking and had not reused the claim at issue. Merz denied that it had breached Clauses 2, 9.1 and 25.

PANEL RULING

The Panel noted that in the previous case, Case AUTH/2119/4/08, Allergan had complained about the claim 'Neurotoxin you need – complexing protein you don't'. The Panel had considered the claim in association with the image of the horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum neurotoxin type A products associated with complexing proteins for which there was no supporting data. The impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted its comments and ruling in point 1 above and considered that the messages conveyed in the leavepiece now at issue were closely similar to those considered in Case AUTH/2119/4/08 and were covered by the undertaking given in that case. Given that the leavepiece implied a clinical disadvantage for Botulinum neurotoxins with complexing proteins, the Panel considered that Merz had not complied with its undertaking. A breach of Clause 25 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel considered that in breaching its undertaking Merz had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

APPEAL BY MERZ

Merz submitted that in the ruling in point 1 the Panel stated that the claim was different to that at issue in Case AUTH/2119/4/08 and went on to state that the claim was a statement of fact, which the original claim was not. The claim now at issue was different, had a different meaning, and was factual. The Panel's statement that it was 'different' and 'closely similar' were contradictory. The original claim was withdrawn and not reused.

Merz submitted that 'free from complexing proteins' was an SPC statement, chosen for its unambiguity and it was a regulatory approved referenced statement. Totally different from the prior case it was not from opinion or peer reviewed literature that was identified in the prior ruling as being 'still for scientific debate'.

Merz submitted that the Panel asserted that the claim should be assessed within the context of the associated visual. The visual of the horse chestnut emerging from its shell had not been the subject of the previous complaint and ruling, and had been integral to the campaign since its launch.

Merz noted that in Cases AUTH/1588/5/04 and AUTH/1589/5/04 Bristol-Myers Squibb and Sanofi-Synthelabo were found not to have breached an undertaking. The claim at issue was: 'Imagine you've had a heart attack, stroke or have PAD, Imagine you've been prescribed aspirin, imagine improving on that. Plavix delivers significant protection above and beyond aspirin'. It was found in breach of Clauses 7.2 and 7.4 as 'the implied claim for benefit compared to aspirin could not be substantiated' as 'the study was not powered to evaluate efficacy in individual subgroups'. The two companies were also asked to answer the allegation of a breach of undertaking issued after Case AUTH/889/6/99. The advertisement claimed that: 'compared to aspirin, Plavix was significantly more effective at reducing MI, reducing stroke and reducing vascular death'. In this case the claim was found to be misleading and breach was ruled. The associated breach of undertaking was ruled by the Panel to be 'not so' as 'the study was powered to detect a realistic treatment effect in the whole study cohort and not each of the three clinical subgroups'. The Panel's view was that there was no breach of undertaking despite the almost identical wording of the claims and identical Panel rulings.

Merz submitted that there was clear inconsistency in the rulings of the Panel if the Xeomin claim, which was acknowledged by the Panel to be different to that at issue in Case AUTH/2119/4/8 and a statement of fact, was found in breach of undertaking when a claim that was almost identical had historically not been found in breach.

Merz submitted that the claim was sufficiently different not to be a breach of undertaking as it was acknowledged as different by the Panel and finding this in breach would create a contradiction in the Panel's rulings.

Merz submitted that the ruling that the claim was in breach of undertaking was clearly incorrect and ran against precedent set by the Panel. There had

been no breach of undertaking and Merz had continued to maintain high standards and not engage in promotional activity likely to bring discredit upon the industry. The ruling of breaches of Clauses 25, 9.1 and 2 must be overturned.

COMMENTS FROM ALLERGAN

Allergan had not complained about a possible breach of undertaking and thus it did not have the right to comment on Merz's appeal.

APPEAL BOARD RULING

The Appeal Board noted that in Case AUTH/2119/4/08 Allergan had complained about the claim 'Neurotoxin you need – complexing protein you don't'. The Panel had considered the claim in association with the image of the horse chestnut emerging from its spiky shell. The Panel, *inter alia*, considered that the claim implied a proven clinical disadvantage for those Botulinum neurotoxin type A products associated with complexing proteins for which there was no supporting data. The impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Appeal Board considered that the claim at issue 'The first Botulinum neurotoxin free from complexing proteins' was different to the claim at issue in Case AUTH/2119/4/08 'Neurotoxin you need – complexing protein you don't'. The Appeal Board noted that the image of the horse chestnut accompanying both claims was the same. There had been no ruling specifically related to the image in Case AUTH/2119/4/08. The Appeal Board noted that Merz had taken steps to comply with its undertaking given in Case AUTH/2119/4/08. The Appeal Board did not consider that the current material meant that Merz had breached its undertaking and no breach of Clause 25 was ruled. Consequently the Panel's rulings of breaches of Clauses 9.1 and 2 no longer stood. The appeal on this point was successful.

Complaint received **20 October 2008**

Case completed **16 February 2009**