CASE AUTH/2346/8/10

MERZ/DIRECTOR v ALLERGAN

Breach of undertaking

In Case AUTH/2335/7/10, Merz alleged that a presentation given by Allergan at a meeting had breached the undertaking given in Case AUTH/2183/11/08 by implying that Botox/Vistabel (botulinum toxin) was more potent than Merz's product Xeomin/Bocouture (also botulinum toxin). Merz submitted further evidence to support its allegation which, because it related to a different meeting, was taken up as a separate case, Case AUTH/2346/8/10.

As the complaint involved an alleged breach of undertaking, it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

Merz referred to a meeting in July 2010 at which Merz and Allergan had been invited to present to a group of health professionals who were trying to decide which botulinum to purchase. Merz noted that the invitation asked for five topics to be covered in the presentation ie product information; evidence base for licence usage; equivalence; head-to-head studies and stability.

Merz stated that the presentation given by Allergan's employees consisted of, amongst other topics, the data from Hunt and Clarke (2009) that was the subject of Case AUTH/2183/11/08 and the subsequent allegation of breach of undertaking in Case AUTH/2335/7/10. Merz submitted that some of the audience had asked if Allergan's data was accurate as Allergan had emphasised the supposed relative lack of potency of Xeomin. Merz was unaware of whether this was in the context of clinical head-to-head studies as requested by the organisers.

Merz noted that the meeting took place after Allergan knew about Merz's allegation of a breach of undertaking and as the meeting was clearly promotional, further demonstrated the lack of respect Allergan had for its undertakings to either Merz or the PMCPA and therefore continued to breach the Code including Clause 2.

The detailed response from Allergan is given below.

The Panel noted 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 that Allergan had been invited to a Botulinum Toxin Information Day to present information about Botox to a selected group of health professionals and managers. The invitation defined the scope and content of the presentation. The Panel considered that it was difficult to view Allergan's presentation as anything other than promotional given its delivery by a senior employee.

The Panel further noted Allergan's submission that its presentation should be viewed together with the presentation from Merz so that the Allergan presentation could be fairly assessed for balance. In the Panel's view, each presentation had to stand alone under the Code; neither could rely on the other for balance.

The Panel noted that slide 19 of the presentation referred to Hunt and Clarke and stated that in an Allergan saline based LD_{50} assay Botox and Xeomin were found to have different potencies with the potency of three Xeomin 100U vials ranging from 69U/vial to 78U/vial. No comparable data for Botox was reported. It was stated that the saline-based assay reflected 'real world' clinical usage. Immediately below the Hunt and Clarke data was data from Dressler *et al* in which, using a Merz non saline-based LD_{50} assay, Botox and Xeomin were found to be equipotent. The mean potency of Botox was reported as 101.7U/vial whereas that for Xeomin was 103U/vial. Beneath the two tables of data from Hunt and Clarke and Dressler *et al* was the claim 'By using stabilizing agents for the bioassay, it was shown that 100 unit vials of Botox (Allergan, Irving, CA) containing complexing proteins, and 100 unit vials of Xeomin, a preparation free from complexing proteins, show equipotency in the mouse LD_{50} bioassay' referenced to Mander (2009).

The Panel noted that the summary slide (slide 34) did not refer to the comparative potencies of Botox and Xeomin. Slide 13 referred to the non-interchangeability of units of Xeomin, Dysport and Allergan (Vistabel) by reference to the products' SPCs.

The Panel noted that in Case AUTH/2183/11/08, Allergan had been ruled in breach of the Code; the Panel referred to its ruling in that case.

Case AUTH/2183/11/08

In the Panel's view the data presented in a product monograph and an objection handler which derived from Hunt *et al* implied that there was a difference in potencies between Xeomin and Botox in favour of Botox. This was inconsistent with the summaries of product characteristics (SPCs) which showed similar dosing regimens for the two

products. The Panel accepted that there was some animal data that possibly showed a difference. However, the supplementary information to the Code was clear that animal data should not be extrapolated to the clinical situation unless there was data to show that it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the comparison could not be substantiated and did not reflect all of the evidence. Breaches of the Code were ruled.

Case AUTH/2346/8/10

The Panel considered that the comparative data shown in the presentation was sufficiently different to the material considered in Case AUTH/2183/11/08 for it not to be caught by the undertaking given in that case. The previous material had not referred to Dressler *et al* or the Mander data. The Panel did not consider that the presentation was in breach of the undertaking given in Case AUTH/2183/11/08 and so in that regard high standards had been maintained. No breach of the Code was ruled.

The Panel considered that as there had been no breach of the undertaking there could be no breach of Clause 2. No breach of that clause was ruled.

Upon appeal by Merz the Appeal Board noted that slide 19 of the presentation referred to Hunt and Clarke and stated that in an Allergan *saline-based* LD_{50} assay Botox and Xeomin were found to have different potencies. An adjacent table of data showed the potency of three Xeomin 100U vials, as tested in 2006, ranging from 69U/vial to 78U/vial. The same three lots were tested again in 2007, with recorded potencies of 61-67U/vial (Hunt and Clarke). The 2007 potency data was linked to a statement 'Avg potency of 2 batches tested just before/after expiry'. The Appeal Board questioned the relevance of testing the potency just after expiry of the product. Text to the right of the data from Hunt and Clarke stated '- Allergan 100U BOTOX Reference Standard (regulatory release)' and '- Saline-based assay reflects "real world" clinical usage.'

Below the Hunt and Clarke data was data from Dressler *et al* in which, using a Merz non saline-based LD_{50} assay, Botox and Xeomin were found to be equipotent. The mean potency of Botox was reported as 101.7U/vial whereas that for Xeomin was 103U/vial. Beneath the two tables of data from Hunt and Clarke and Dressler *et al* was the claim 'By using stabilizing agents for the bioassay, it was shown that 100 unit vials of Botox (Allergan, Irving, CA) containing complexing proteins, and 100 unit vials of Xeomin, a preparation free from complexing proteins, show equipotency in the mouse LD_{50} bioassay' referenced to Mander *et al*.

The Appeal Board considered that presenting the Hunt and Clarke data at the top of the slide gave it more prominence than the Dressler *et al* data below. Further, the use of phrases 'Reference Standard (regulatory release)' and 'real world' implied that the Hunt and Clarke results were more robust than those of Dressler *et al*. The Xeomin assay, as used by Dressler *et al* was referred to as 'non saline-based'. The Appeal Board considered that by emphasising *'non saline-based'* implied that it was not as good. Both assays had been accepted by the regulators for the respective botulinum toxins.

The Appeal Board noted that the summary slide (slide 34) did not refer to the comparative potencies of Botox and Xeomin.

The Appeal Board noted that none of the slides referred to the statement in the Bocouture SPC that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [ie Botox] are of equal potency'. Both the Bocouture SPC and the data on file to support this SPC statement were available to Allergan when the presentation was delivered but were nonetheless not included.

Slide 19 was in a section headed 'Non interchangeability of Botulinium Toxins' which also included slide 13 headed, 'Regulatory agencies recognize non-interchangeability' that gave details of non interchangeability statements in the SPCs for Xeomin, Dysport and Vistabel. Slide 18, headed 'What Clinical Data Exist for Xeomin?', gave limited information about some of the clinical data for Xeomin.

The Appeal Board did not accept Allergan's submission that slide 19 was a balanced slide on the Hunt and Clarke data. Nor did it accept Allergan's submission that the presentation was substantially different to the materials at issue in Case AUTH/2193/11/08. The Appeal Board considered that the use of Hunt and Clarke data implied that Botox was more potent than Xeomin which was inconsistent with the product SPCs and the available clinical data. This was sufficiently similar to the point at issue in Case AUTH/2183/11/08 to be caught by the undertaking in that case. The Appeal Board ruled a breach of the Code. In that regard high standards had not been maintained. The Appeal Board ruled a breach of the Code. The appeal on both points was successful.

The Appeal Board noted that an undertaking was an important document. The Appeal Board considered that failing to comply with the undertaking and assurance in this instance had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled a breach of Clause 2. The appeal on this point was successful.

In Case AUTH/2335/7/10 Merz had alleged that a presentation given by Allergan at a meeting had breached the undertaking given in Case AUTH/2183/11/08 by implying that Botox/Vistabel (botulinum toxin) was more potent than Merz's

product Xeomin/Bocouture (also botulinum toxin). Merz submitted further evidence to support its allegation which, because it related to a different meeting, was taken up as a separate case, Case AUTH/2346/8/10.

As the complaint involved an alleged breach of undertaking, it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

COMPLAINT

Merz referred to a meeting in July 2010 at which Merz and Allergan had been invited to present to a group of consultants, registrars and pharmacists who were trying to decide which botulinum to purchase. Merz noted that the invitation clearly stated that five topics were to be covered in the presentation ie product information; evidence base for licence usage; equivalence; head-to-head studies and stability.

The Allergan presentation, given by commercial employees, immediately followed the Merz presentation. The meeting was clearly promotional as it was intended to convince the audience to prescribe, buy and administer the medicines that were the subject of the presentation and therefore clearly fell into the definition given in Clause 1.2 of the Code.

Merz stated that the presentation given by Allergan employees consisted of, amongst other topics, the data from Hunt and Clarke (2009) that was the subject of Case AUTH/2183/11/08 and the subsequent allegation of breach of undertaking in Case AUTH/2335/7/10. Merz submitted it had been asked by members of the audience if the data presented by Allergan was accurate as Allergan had emphasised the supposed relative lack of potency of Xeomin. Merz was unaware of whether this was in the context of clinical head-to-head studies as requested by the organisers.

Merz noted that the meeting took place after Allergan knew about Merz's allegation of a breach of undertaking and as the meeting was clearly promotional, further demonstrated the lack of respect Allergan had for its undertakings to either Merz or the PMCPA and therefore continued to breach Clauses 25, 9.1 and 2 of the Code.

RESPONSE

Allergan stated that it, along with Merz, was invited to present at a Botulinum Toxin Information Day. Allergan submitted that its presentation was given by a senior medical employee, not a commercial employee, in response to an NHS foundation trust's request for scientific information. As outlined by Merz, both companies were asked to provide information on the five topics listed in the invitation.

Allergan did not agree that the meeting was promotional. It had reviewed, approved and certified its presentation as non-promotional ie as a scientifically accurate and balanced presentation, provided on request and addressing the topics stated in the invitation.

Commercial representatives attended in case the focus of the meeting evolved such as to require the provision of commercial information as it was not clear from the invitation as to the interests of the pharmacists or managers who would be present.

Allergan noted that Merz was specifically concerned about the use of the data by Hunt and Clarke. Allergan disagreed with Merz's allegation that Allergan's use of this data was in breach of the undertaking given in Case AUTH/2183/11/08.

Allergan and Merz were asked to address the topic of equivalence. Allergan covered this in the section of its presentation entitled 'Non-interchangeability of botulinum toxins'. This title was important as Allergan did not believe that the products were equivalent or that equivalence should be claimed.

The summary of product characteristics (SPCs) for the two botulinum toxin type A preparations stated that 'doses are specific to each preparation and are not interchangeable with other preparations of the toxin.'

Allergan noted that Merz had previously been found in breach of the Code for trying to establish equivalence (Cases AUTH/2119/4/08 and AUTH/2270/10/09). However, as established in Case AUTH/2270/10/09, and acknowledged by Merz, there was no data to support the equivalence of the two products and equivalence or equal potency could not be claimed from its non-inferiority studies. The two non-inferiority studies (Benecke *et al* 2005 and Roggenkämper *et al* 2006) demonstrated similar efficacy and safety profiles, not equivalence. Clearly lack of equivalence and non-interchangeability were linked.

Only slide 19 in the 34 slide presentation discussed Hunt and Clark. Allergan considered that these data were relevant in the context of a non-promotional presentation as they supported the fact that the botulinum toxin units were not interchangeable due to differences in LD_{50} assay techniques between different manufacturers.

The data were balanced by the inclusion of data from Dressler *et al* (2008) which demonstrated similar number of potency units for Botox and Xeomin when tested using the Merz reference LD_{50} assay. Hunt and Clarke showed that in the Allergan LD_{50} assay, with Botox set as the reference standard, Xeomin units were not equivalent to Botox units. In its presentation, Allergan used this data to support the fact that unit doses of the botulinum toxins were not interchangeable. This data was not used, as suggested by Merz, to demonstrate a lack of potency, only to confirm, as stated in the product SPCs, and established by case precedent, that botulinum toxin A units were not interchangeable.

Allergan suggested that Merz provided its presentation to the PMCPA for context. It was only when both presentations were viewed together that the Allergan presentation could be fairly assessed for balance.

Allergan considered that the use of one balanced slide on Hunt and Clarke was relevant in the context of a non-promotional scientific presentation. The data supported the fact that the botulinum toxin units were not interchangeable due to differences in LD_{50} assay techniques between different manufacturers. Therefore, these data were relevant to the clinical situation and its use in a non-promotional setting did not go against the ruling of Case AUTH/2183/11/08.

Allergan denied breaches of Clauses 25, 9.1 and 2 of the Code.

PANEL RULING

The Panel noted 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 considered that given the Authority's responsibility in ensuring compliance with undertakings, inter-company dialogue as set out in Paragraph 5.2 of the Constitution and Procedure was not required in this regard before a complaint could be accepted.

The Panel noted that Allergan had been invited to a Botulinum Toxin Information Day to present information about Botox to a selected group of consultants, clinicians, pharmacists and managers. The invitation defined the scope and content of the presentation. The speaker from Allergan was a senior medical employee. The Panel considered that it was difficult to view the presentation as anything other than promotional given its delivery by an Allergan employee.

It appeared that, because the presentation had been given in response to a request for information, Allergan considered that it was non-promotional. The Panel noted, however, that the exemption in Clause 1.2 to the term promotion, was for replies 'made in response to *individual* enquiries'. Such requests had to be unsolicited. The Panel was not certain that this was so or that each member of the audience had individually asked for the information. The Panel decided that the presentation could not take the benefit of this exemption to the definition of promotion.

The Panel further noted Allergan's submission that its presentation should be viewed together with the presentation from Merz so that the Allergan presentation could be fairly assessed for balance. In the Panel's view, each presentation had to stand alone under the Code; neither could rely on the other for balance.

The Panel noted that slide 19 of the presentation referred to Hunt and Clarke and stated that in an Allergan saline based LD_{50} assay Botox and Xeomin were found to have different potencies with the potency of three Xeomin 100U vials ranging from 69U/vial to 78U/vial. No comparable data for Botox was reported. It was stated that the saline-based assay reflected 'real world' clinical usage. Immediately below the Hunt and Clarke data was data from Dressler *et al* in which, using a Merz non saline-based LD_{50} assay, Botox and Xeomin were found to be equipotent. The mean potency of Botox was reported as 101.7U/vial whereas that for Xeomin was 103U/vial. Beneath the two tables of data from Hunt and Clarke and Dressler *et al* was the claim 'By using stabilizing agents for the bioassay, it was shown that 100 unit vials of Botox (Allergan, Irving, CA) containing complexing proteins, and 100 unit vials of Xeomin, a preparation free from complexing proteins, show equipotency in the mouse LD_{50} bioassay' referenced to Mander (2009).

The Panel noted that the summary slide (slide 34) did not refer to the comparative potencies of Botox and Xeomin. Slide 13 referred to the non-interchangeability of units of Xeomin, Dysport and Allergan (Vistabel) by reference to the products' SPCs.

The Panel noted that in Case AUTH/2183/11/08, Allergan had been ruled in breach of the Code; the Panel referred to its ruling in that case.

Case AUTH/2183/11/08

In the Panel's view the data presented in a product monograph and an objection handler which derived from Hunt *et al* implied that there was a difference in potencies between Xeomin and Botox in favour of Botox. This was inconsistent with the summaries of product characteristics (SPCs) which showed similar dosing regimens for the two products. The Panel accepted that there was some animal data that possibly showed a difference. However, the supplementary information to the Code was clear that animal data should not be extrapolated to the clinical situation unless there was data to show that it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the comparison could not be substantiated and did not reflect all of the evidence. Breaches of, *inter alia*, Clauses 7.2, 7.3 and 7.10 of the Code were ruled.

Case AUTH/2346/8/10

The Panel considered that the comparative data shown in the presentation was sufficiently different to the material considered in Case AUTH/2183/11/08 for it not to be caught by the undertaking given in that case. The previous material had not referred to Dressler *et al* or the Mander data. The Panel did not consider that the presentation was in breach of the undertaking given in Case AUTH/2183/11/08 and so

it ruled no breach of Clause 25. In that regard high standards had been maintained. No breach of Clause 9.1 was ruled.

The Panel considered that as there had been no breach of the undertaking there could be no breach of Clause 2. No breach of that clause was ruled.

APPEAL BY MERZ

Merz alleged that Allergan breached the undertaking given in Case AUTH/2183/11/08 by seeking to convince medical practitioners that Xeomin was less potent than Botox using the same data. This claim was inconsistent with the respective product SPCs and head-to-head clinical comparisons.

Merz alleged that the presentation at issue was clearly promotional as it was delivered as part of a commercial tendering process in order to convince the audience to purchase the product for the NHS. The invitation to present made this position clear. The fact that a commercial employee of Allergan was there clearly reinforced that the presentation was promotional and therefore subject to the Code.

The head-to-head comparisons of Xeomin vs Botox requested were addressed on slide 18 headed 'What Clinical Data Exists for Xeomin?'. Merz alleged that this title was derogatory since the audience would normally expect a review of a company's own product rather than its competitor's product, it was also misleading as it suggested that the slide contained the complete clinical dataset for Xeomin which it did not. This slide clearly discredited Xeomin. Whilst this slide did refer to the fact that Xeomin was demonstrated to be non-inferior to Botox in two studies, it did not mention the 1:1 dosing ratio used in Benecke *et al* and Roggenkämper *et al*. Dosing ratios were important as they had a direct impact on the relative cost of a medicine and were directly linked to product potency.

Merz alleged that slide 19 undermined the previous data and cast the potency of Xeomin in doubt. It presented the 'saline based', non-comparative assessment of Xeomin by Hunt and Clarke as the 'Allergan 100U Botox reference standard', approved by the regulator and 'real world' in design. This slide presented the assay as appropriate and approved by the regulator as a comparator assay for Xeomin, and carrying more weight than the 'Merz non-saline based' comparative assay by Dressler *et al*. The fact that the 'Merz non-saline based' assay performed by Dressler *et al* was the Xeomin 100 unit reference standard and the approved 'regulatory release' assay for Xeomin was deliberately omitted. Allergan therefore clearly intended to make the audience believe that its assay was the only 'reference standard' and credible evaluation tool; this misled the audience and discredited Xeomin. Further, the way the study was described as the 100U Botox reference standard, led the audience to believe that this was a comparative assay comparing Xeomin with Botox which it was not. There was only one comparative assay reported and that was by Dressler *et al*.

Merz alleged that the letter by Mander *et al* was not written in support of the publication by Hunt and Clarke but to refute it. Allergan failed to mention that this letter concluded that 'the differences observed by Hunt and Clarke are clearly artefacts created by the assay conditions used'. The reason for this was that the Allergan assay diluted Xeomin many times more than the maximum dilution specified in the SPC and therefore clearly did not reflect the 'real world' as suggested. There were clear reasons why the Allergan standard was not 'real world'. This standard diluted the toxin in saline up to 100ml, which was well beyond the dilutions specified in the respective Xeomin and Botox SPCs. Merz knew of no clinical situation where either 100 units of Botox or 100 units of Xeomin were diluted to a volume greater than 10ml. Xeomin 100 unit vials contained enough human serum albumin (HSA) to prevent the naked (150kD) toxin from being absorbed into the vial or syringe surface for dilutions up to 10ml. Dilutions substantially greater than this would overly dilute the HSA leading to absorption of the toxin into the vessel. This absorption was less for the complexed toxin. Thus it was clear that Botox could be expected to have an apparently higher potency than Xeomin if diluted to 100ml with saline but this was purely an artefact of the assay conditions used, as concluded by Mander *et al*. The use of stabilising agents in the Merz assay was appropriate for Xeomin and led to an outcome which was consistent with all the published clinical data and the appropriate product SPCs. Indeed, if information of the 1:1 dosing ratio used in the clinical evaluation of the products had been included in slide 18, it would have directly contradicted the message from the non-clinical evaluation of slide 19, that Xeomin was less potent than Botox.

Merz alleged that this position was directly supported by a very large clinical data set involving two regulatory, phase III clinical trials containing 763 patients that unequivocally showed that Xeomin was non-inferior, clinically no less effective, than Botox (Benecke *et al* and Roggenkämper *et al*). This data was accepted by the European regulators and was the basis upon which they gave Xeomin the identical dosing regimen to Botox as mentioned in the ruling in Case AUTH/2183/11/08.

Merz alleged that therefore it was clear that the animal data generated by Hunt and Clarke, which was an artefact of the assay conditions, was directly refuted by clinical data. The slide presented by Allergan was therefore incapable of substantiation, did not reflect all the data and would not lead to rational use of the medicine, the same ruling as in Case AUTH/2183/11/08. The fact that Allergan presented other data which it then attempted to discredit did not detract from this.

Allergan stated that it deliberately placed the clinical

evaluation of Botox and Xeomin in a section entitled 'Non-interchangeability of Botulinum Toxins', as it did not believe the products to be equivalent. This was not accurate as Allergan had clearly moved into clinical efficacy in the presentation of Xeomin clinical data in slide 18. Allergan also argued that clearly lack of equivalence and non-interchangeability were linked. Merz alleged that Allergan had sought to distort the purpose of a SPC product statement to its advantage providing a platform to cast doubt on the potency of Xeomin.

Merz alleged that for Allergan to have a clear position that the two products were not equivalent, there must have been a study designed to show equivalence that failed. This study had not been conducted and thus lack of equivalence, clinical or otherwise, could not be claimed or implied by Allergan. The saying 'lack of evidence was not evidence of lack' applied here and therefore Allergan's defence of lack of equivalence and lack of interchangeability being linked was equally incapable of substantiation.

Merz did not argue with the statement in the SPC about interchangeability of product units, quite the opposite. The non-interchangeability statement was one of caution to prescribers and pharmacists to ensure safe prescribing and administration of products that were not biochemically identical and to encourage brand prescribing. It did not, however, imply that two products could be of equal potency. This was made quite clear by the statement in the Bocouture SPC. Bocouture was exactly the same medicine as Xeomin but presented in a 50 unit vial. The Bocouture SPC contained the statement about lack of interchangeability of product units but also 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 comparator product was the Allergan 900kDa toxin.

Merz alleged that the majority of the clinical data submitted to obtain the marketing authorization for Bocouture was the phase III studies used to obtain the marketing authorization for Xeomin (Roggenkämper *et al* and Mander *et al* [sic]). For both statements to appear on the SPC of a product the regulators had stated that the assays for the two products were different but also that clinical data suggested that the conventional botulinum toxin (Botox) was equipotent to Bocouture (which was identical to Xeomin). Clearly Allergan's statement that the products were not interchangeable and that they were not equivalent was intended to reinforce Allergan's message that Xeomin was less potent than Botox, however, both of these statements were incapable of substantiation.

Merz alleged that the presentation of data showing lower potency could only be to convey the message of lower potency using the same data as was ruled on in Case AUTH/2183/11/08. As observed by the Panel in Case AUTH/2335/7/10 with regard to the presentation of the two sets of data on one slide; 'The Panel considered that the audience would inevitably compare the figures from the two tables and conclude that Xeomin was less potent than Botox'.

Merz alleged that this represented a breach of undertaking as:

- The Allergan representative sought to convince the audience in a clearly promotional presentation that Xeomin was less potent that Botox by presenting animal data which conflicted with all relevant clinical evaluations.
- The additional data presented on the slide was dismissed, by implication, as not being 'real world' leaving only data that showed a difference from which the audience were expected to draw the conclusion that Xeomin was less potent than Botox.
- The animal data from which the audience's conclusion would be drawn were exactly the same data subject to the undertaking in Case AUTH/2183/11/08.
- The presentation of the data went against the Panel's view in Case AUTH/2183/11/08 and it remained inconsistent with the identical dosing regimens in the SPC.
- The presentation of the data could not be substantiated, did not reflect all the evidence would not encourage the rational use of the medicine. This was the same ruling in Case AUTH/2183/11/08.

Merz questioned the value of undertakings if they allowed a company to present data ruled in breach of the Code in a slightly different way but draw the same misleading conclusion. Merz alleged that Allergan intended the presentation to circumvent the undertaking given following Case AUTH/2183/11/08 whilst ensuring that the same message was communicated. This eroded the purpose of undertakings. The presentation of the data in this way to draw these conclusions was clearly in breach of the undertaking given in Case AUTH/2183/11/08 and therefore in breach of Clauses 2, 9.1 and 25.

COMMENTS FROM ALLERGAN

Allergan disagreed that it had breached the undertaking given in Case AUTH/2183/11/08. Allergan was well aware of that case and the undertaking it had given and had fully taken into account its undertaking; it was confident that the presentation did not constitute a breach of undertaking.

Allergan strongly refuted the allegation by Merz that it used the data at issue in the undertaking (Hunt and Clarke 2006 – now available as a full publication) to convince medical practitioners that Xeomin was less potent than Botox. As below, this data was used in a balanced manner, reflected the available evidence, to illustrate that unit doses of botulinum toxin products were not interchangeable.

Merz's appeal rested on the assertion that Allergan breached the undertaking in respect of Case AUTH /2183/11/08, the key concluding section of the Panel's ruling in that case was (* asterisked clarification by Allergan):

'The Panel considered that given the comparative potency information in the product monograph and objection handler (*derived from Hunt and Clarke (2006) – now available as a full publication) it was not unrealistic that representatives might have used this information when promoting Botox to health professionals. There was no instruction about how to use the information comparing the potency of Xeomin and Botox. The Panel considered on the balance of probabilities the Allergan representative had claimed there was a difference in potency for the products. This was inconsistent with the summaries of product characteristics (SPCs) which showed similar dosing regimens for the two products. The Panel accepted that there was some animal data that possibly showed a difference. However, the supplementary information to Clause 7.2 was clear that animal data should not be extrapolated to the clinical situation unless there was data to show that it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the product monograph and objection handler were misleading with regard to the information about potency. The comparison could not be substantiated and did not reflect all of the evidence. The material would not encourage the rational use of a medicine. Thus the Panel ruled breaches of Clauses 7.2, 7.3 and 7.10.'

Allergan submitted that it would be clear from the evidence below that it had taken into account the requirement for balance, reflection of all the available data and the care required when presenting and extrapolating animal data. Allergan had not breached the undertaking or attempted to circumvent the undertaking as alleged by Merz. Allergan submitted that it had complied with both the letter and spirit of the Code.

The Allergan presentation was given by a senior member of its scientific support team, not a 'commercial employee', in response to a scientific information request from an NHS foundation trust. Given this written request Allergan did not believe the presentation was promotional. Allergan had taken the Panel's view on board and would ensure that future presentations of this type were reviewed as promotional items. That said, the presentation was reviewed, approved and certified as a scientifically accurate and balanced presentation, provided on request and addressing the topics as stated in the invitation.

The first issue raised by Merz in its appeal was that slide 18 headed 'What Clinical Data Exists for Xeomin' was derogatory and discredited Xeomin. Allergan disagreed. Allergan was specifically asked to cover which head-to-head studies existed. This was a fair summary of the data and clearly stated that non-inferiority was established for efficacy variables in the two studies cited by Merz (Benecke *et al* and Roggenkämper *et al*). This information was provided for balance. If further detail on, for example, dose ratios selected in the trials, was requested by the audience, this would have been covered by the speaker. However, as indicated by Merz, Allergan's presentation focussed primarily on the data regarding Botox not Xeomin.

Merz then focussed on slide 19 which included the Hunt and Clarke data at issue. This slide was one of 16 contained in a section entitled non-interchangeability of botulinum toxins. Allergan (and Merz) had been specifically asked to address the topic of equivalence. The title of this section was important as Allergan did not believe the products were equivalent or that equivalence should be claimed.

As stated in the SPC for Botox:

> 'Botulinum toxin units <u>are not interchangeable from one product to another.</u>'
>
> 'Doses recommended for BOTOX are not interchangeable with other preparations of botulinum toxin.'

Similar statements were in the Xeomin SPC:

> 'Due to differences in the LD_{50} assay, these units are specific to Xeomin and are not interchangeable with other Botulinum toxin preparations.'
>
> 'Unit doses recommended for Xeomin are not interchangeable with those for other preparations of Botulinum toxin.'

Allergan submitted that Merz had previously been found in breach of the Code for trying to establish equivalence between Botox and Xeomin (Case AUTH/2119/4/08 and Case AUTH/2270/10/09). However, as established, most recently in Case AUTH/2270/10/09, and acknowledged by Merz, there was no data to support the equivalence of the two products and equivalence or equal potency could not be claimed from their non-inferiority studies The two non-inferiority studies (Benecke *et al*; Roggenkämper *et al*) demonstrated similar efficacy and safety profiles. They did not demonstrate equivalence.

Only slide 19 in the presentation discussed the Hunt and Clark data. Allergan submitted that these data were relevant in the context of this presentation, as they supported the fact that the botulinum toxin units were not interchangeable due to differences in LD_{50} assay techniques between different manufacturers. The data were balanced by the inclusion of Dressler *et al* which demonstrated similar number of potency units for Botox and Xeomin when tested using the Merz reference LD_{50} assay. Hunt and Clarke showed that in the Allergan LD_{50} assay, with Botox set as the reference standard, Xeomin units were not equivalent to Botox units.

The speaker used this data to support the fact that unit doses of the botulinum toxins were not interchangeable. This data was not used as Merz suggested to demonstrate a lack of potency, only to confirm, as stated in the SPCs, and established by case precedent, that botulinum toxin A units were not interchangeable. The data was further balanced by reference to correspondence from Mander *et al* which provided the counter view to that of Allergan with respect to the Hunt and Clarke data as discussed by Merz. However, Merz failed to mention that Hunt and Clarke stated in their response to Mander *et al* (Hunt and Clarke, Editorial Response Letter to Mander *et al*, 2009) that the assay used in their study was not selected to show differences but was used because it was the standard assay used to release Botox as approved and recognised by the international regulatory authorities. The assay was therefore suitable and appropriate for comparison.

The fact that different neurotoxins reacted differently in potency assays because the medicines differed substantiated that these medicines were not the same ie that units were not interchangeable.

Clearly Merz and Allergan disagreed as to the relevance of the diluents used in the assay. Allergan substantiated that because saline was used as a diluent, it was a clinically more relevant assay. Additives such as gelatine could alter and confound the results of potency assays and were not used in the clinical setting. This debate would continue but Allergan submitted that it had presented a balanced view of the evidence.

Allergan submitted that slides 18 and 19 were complementary. One summarised the clinical data available, including the European non-inferiority studies (Benecke *et al* and Roggenkämper *et al*) which established that Xeomin was not inferior to Botox, the European spasticity trials and the studies conducted in the US which were used to support the recent US registration of Xeomin (Grafe and Hanschmann, 2010). The other slide confirmed that units of the products were not interchangeable.

Allergan robustly defended the right to make clear, as stated in the SPCs, that unit doses of botulinum toxins were not interchangeable and that Botox and Xeomin were not equivalent.

Allergan submitted that the use of one balanced slide on the Hunt and Clarke data was relevant. The data supported the fact that the botulinum toxin units were not interchangeable due to differences in LD_{50} assay techniques between different manufacturers. The slide was within a section containing 16 slides which included clinical data. Therefore, these data were relevant to the clinical situation and their use did not go against the ruling in Case AUTH/2183/11/08.

In conclusion, Allergan noted that, as stated in the Panel's ruling, the comparative data at issue was sufficiently different to the material at issue in Case AUTH/2183/11/08. Balance was provided by Dressler *et al* and Mander *et al*, along with the summary slide of clinical data. Therefore, Allergan refuted the alleged breaches of Clauses 25, 9.1 and 2 of the Code.

FINAL COMMENTS BY MERZ

Merz submitted that Allergan's misrepresentation of previous Panel and Appeal Board cases needed to be addressed.

- In Case AUTH/2119/4/08 Merz was ruled in breach of Clause 3.2 for not including the statement about the lack of interchangeability of unit doses from the SPC. The complaint was not about any lack of demonstrated equivalency.
- In Case AUTH/2270/10/09 Merz was ruled in breach for using the statement 'at least as effective as' which Merz believed accurately described the outcome of a non-inferiority study. Whilst Merz accepted that there was no clinical data that demonstrated equivalence of Xeomin to Botox, this was not the claim at issue.

Allergan continued to suggest that this presentation was non-promotional. However the presence of commercial staff at a meeting where Allergan presented to an audience which was to decide on the purchase of botulinum toxin was clearly promotional, as accepted by the Panel.

With regard to Allergan's suggestion that the choice of diluents was a matter of debate, Merz submitted that the gelatine based assay had been accepted by regulatory authorities in Europe, Mexico, Argentina, Canada and the US for the assessment of Xeomin. It appropriateness for this use was thus not in doubt.

Merz noted that the Hunt and Clarke data was presented and it alleged that it did not comply with the requirements of the supplementary information to Clause 7.2 of the Code as the large clinical studies clearly showed that Xeomin was non-inferior to Botox. The Hunt and Clarke data therefore, however it was presented, should not be extrapolated to the clinical situation as the clinical data directly contradicted it. This was the basis for the ruling in Case AUTH 2183/11/08 and was still true. The invitation did not ask for potency data and therefore its inclusion and context (including the dismissal of the Merz assay) in the presentation could only have been to extrapolate it to the clinical situation to suggest that Xeomin was less potent than Botox. This was the basis of the ruling in Case AUTH/2183/11/08 and therefore the presentation now at issue represented a breach of undertaking.

APPEAL BOARD RULING

The Appeal Board noted that slide 19 of the presentation referred to Hunt and Clarke and stated that in an Allergan **saline-based** LD_{50} assay Botox and Xeomin were found to have different potencies. An adjacent table of data showed the potency of three Xeomin 100U vials, as tested in 2006, ranging from 69U/vial to 78U/vial. The same three lots were

tested again in 2007, with recorded potencies of 61-67U/vial (Hunt and Clarke). The 2007 potency data was linked to a statement 'Avg potency of 2 batches tested just before/after expiry'. The Appeal Board questioned the relevance of testing the potency just after expiry of the product. Text to the right of the data from Hunt and Clarke stated '- Allergan 100U BOTOX Reference Standard (regulatory release)' and '- Saline-based assay reflects "real world" clinical usage.'

Below the Hunt and Clarke data was data from Dressler *et al* in which, using a Merz non saline-based LD_{50} assay, Botox and Xeomin were found to be equipotent. The mean potency of Botox was reported as 101.7U/vial whereas that for Xeomin was 103U/vial. Beneath the two tables of data from Hunt and Clarke and Dressler *et al* was the claim 'By using stabilizing agents for the bioassay, it was shown that 100 unit vials of Botox (Allergan, Irving, CA) containing complexing proteins, and 100 unit vials of Xeomin, a preparation free from complexing proteins, show equipotency in the mouse LD_{50} bioassay' referenced to Mander *et al*.

The Appeal Board considered that presenting the Hunt and Clarke data at the top of the slide gave it more prominence than the Dressler *et al* data below. Further, the use of phrases 'Reference Standard (regulatory release)' and 'real world' implied that the Hunt and Clarke results were more robust than those of Dressler *et al*. The Xeomin assay, as used by Dressler *et al* was referred to as 'non saline-based'. The Appeal Board considered that by emphasising **'non saline-based'** implied that it was not as good. Both assays had been accepted by the regulators for the respective botulinum toxins.

The Appeal Board noted that the summary slide (slide 34) did not refer to the comparative potencies of Botox and Xeomin.

The Appeal Board noted that none of the slides referred to the statement in the Bocouture SPC that 'Comparative clinical study results suggest that Bocouture and the comparator product containing conventional Botulinum toxin type A complex (900 kD) [ie Botox] are of equal potency'. Both the Bocouture SPC and the data on file to support this SPC statement were available to Allergan when the presentation was delivered but were nonetheless not included.

Slide 19 was in a section headed 'Non interchangeability of Botulinium Toxins' which also included slide 13 headed, 'Regulatory agencies recognize non-interchangeability' that gave details of non interchangeability statements in the SPCs for Xeomin, Dysport and Vistabel. Slide 18, headed 'What Clinical Data Exist for Xeomin?', gave limited information about some of the clinical data for Xeomin.

The Appeal Board did not accept Allergan's submission that slide 19 was a balanced slide on the Hunt and Clarke data. Nor did it accept Allergan's submission that the presentation was substantially different to the materials at issue in Case AUTH/2193/11/08. The Appeal Board considered that the use of Hunt and Clarke data implied that Botox was more potent than Xeomin which was inconsistent with the product SPCs and the available clinical data. This was sufficiently similar to the point at issue in Case AUTH/2183/11/08 to be caught by the undertaking in that case. The Appeal Board ruled a breach of Clause 25. In that regard high standards had not been maintained. The Appeal Board ruled a breach of Clause 9.1. The appeal on both points was successful.

The Appeal Board noted that an undertaking was an important document. The Appeal Board considered that failing to comply with the undertaking and assurance in this instance had brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board ruled a breach of Clause 2. The appeal on this point was successful.

The Appeal Board noted that Allergan had initially considered that the presentation was not promotional and had approved it in that context. That the presentation was non-promotional had been rejected by the Panel. The Appeal Board was concerned that Allergan's initial view regarding the status of the presentation showed a lack of understanding although at the appeal hearing the company made it clear that it now accepted that the presentation was promotional.

Complaint received **12 August 2010**

Case completed **6 December 2010**