CASE AUTH/3650/5/22

ELI LILLY v UCB

Eli Lilly v UCB – Bimzelx leavepiece

CASE SUMMARY

This case was in relation to three claims within a Bimzelx (bimekizumab) leavepiece issued by UCB Pharma Ltd which Eli Lilly alleged were unfair, unbalanced and misleading and could not be substantiated. The Panel ruled a breach of the following Clauses of the 2021 Code because it considered that within the context of the leavepiece:

- **the extrapolation of in vitro data to clinical significance implied by the claim 'Blocking IL-17A and IL-17F results in superior inhibition of inflammatory responses vs blocking IL-17A alone' was misleading and the implication of clinical superiority of IL-17A and IL-17F blockade over IL-17A alone had not been substantiated**
- **the clinical relevance and significance implied by the claim 'BIMZELX provides more complete inhibition of the IL-17A and IL-17F pathway compared with blocking IL-17A alone' was misleading; the extrapolation of such in vitro data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance**
- **the claim 'IL-17F levels are approximately 30-fold higher than IL-17A in psoriatic skin', misled as to the clinical significance of the relative concentrations of IL-17 protein levels as evidenced in the in-vitro data**

Breach of Clause 5.1 (unsuccessfully appealed)	**Failing to maintain high standards**
Breach of Clause 6.1 (unsuccessfully appealed)	**Making a misleading claim**
Breach of Clause 6.2 (unsuccessfully appealed)	**Making an unsubstantiated claim**

APPEAL

All the Panel's rulings of breaches of the 2021 Code were upheld on appeal by UCB.

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

COMPLAINT

Eli Lilly alleged that UCB's Bimzelx promotional leavepiece (ref IL-P-BK-PSD-2100004, date of preparation September 2021) aimed at dermatology health professionals, was a clear contravention of the Code. The leavepiece contained three claims that Eli Lilly alleged were unfair, unbalanced and misleading and could not be substantiated.

For background, Eli Lilly provided a list of IL-17 inhibitors approved for the treatment of moderate-to-severe psoriasis as follows:

Product name	Manufacturer	Mode of action
Bimzelx (bimekizumab)[+]	UCB	Anti-IL17A/F
Cosentyx (secukinumab)[#]	Novartis	Anti-IL17A
Kyntheum (brodalumab)[#]	Leo Pharma	Anti-IL17RA*
Taltz (ixekizumab)	Eli Lilly	Anti-IL17A

[+]Bimekizumab is the only approved biologic that inhibits both IL17A and IL17F
[#]secukinaumb and ixekizumab inhibit IL17A only
[*]R represents receptor and is different in its mode of action vs all other approved IL-17 inhibitors

1 Claim 'Blocking IL-17A and IL-17F results in superior inhibition of inflammatory response vs blocking IL-17A alone'

Eli Lilly stated that this claim was aimed at clinicians who managed patients with moderate-to-severe psoriasis and was referenced to Glatt *et al* 2018, the introduction of which stated:

> 'We tested this hypothesis in vitro using human joint and skin cells, and we also conducted a proof-of-concept trial in patients with PsA [psoriatic arthritis].'

Eli Lilly alleged this claim, derived from Glatt *et al,* misled to its significance as the data was taken from two studies:

> An *in vitro* study using joint and skin cells
>
> A Proof of concept (PoC) PsA trial (NCT02141763 - a Phase Ib study of psoriatic arthritis patients randomised to either bimekizumab (n=39) or placebo (n=14)) which was being used to extrapolate findings for this psoriasis leavepiece.

Eli Lilly noted that while bimekizumab had a licence for the treatment of moderate-to-severe psoriasis, it did not have a licence for psoriatic arthritis and yet psoriatic arthritis evidence was being used in the leavepiece. Furthermore, Glatt *et al* stated in the discussion:

> 'When evaluating these data, the size and duration of the PoC trial limits the interpretation of the safety dataset; furthermore, the small sample size warrants cautious interpretation of the observed therapeutic effect size.'

Eli Lilly did not accept the intimation taken from extrapolating these data to imply a promotional superiority claim. Moreover, Eli Lilly could not accept the suggested amended promotional claim proposed during inter-company dialogue:

> 'In vitro blockage of IL-17A and IL-17F results in superior inhibition of inflammatory responses vs blocking IL-17A alone.'

Eli Lilly alleged that UCB's intention to imply promotional superiority of bimekizumab, the only anti-IL17A/F targeting molecule, over anti-IL17A targeting molecules secukinumab and ixekizumab was misleading and could not be substantiated in breach of Clauses 6.1 and 6.2 of the Code as the claim misled as to its significance and could not be substantiated.

2 Claim 'BIMZELX provides more complete inhibition of the IL-17A and IL-17F pathway compared with blocking IL-17A alone'

Eli Lilly stated that this claim was referenced to Cole *et al* 2020 and the abstract of the publication stated:

> 'Using an *in vitro* skin cell activation assay, we demonstrate that dual neutralization of both IL-17A and IL-17F resulted in greater suppression of inflammatory proteins than inhibition of IL-17A alone.'

Eli Lilly alleged the claim was misleading in its significance based on the *in vitro* evidence used and in breach of Clause 6.1 of the Code.

3 Claim 'IL-17F levels are approximately 30-fold higher than IL-17A in psoriatic skin'

Eli Lilly alleged that this claim, referenced to Kolbinger *et al* 2017, misled, distorted and exaggerated the findings of the publication. The authors clearly stated:

> 'Although IL-17F protein levels in patients with psoriasis were much higher than IL-17A levels, they were not consistently upregulated in lesional versus nonlesional skin in all psoriasis plaques and did not correlate with psoriasis disease activity as measured by using PASI scores. One possible explanation for this discrepancy is that IL-17A is about 100-fold more potent than IL-17F for signaling through IL-17R.'

The discussion went on:

> 'We sought to validate this finding using a larger independent cohort of patients with psoriasis. In the validation set serum IL-17A levels continued to have a good correlation, whereas IL-17F levels had a weaker if not poor correlation with PASI scores… we conclude that IL-17A has a more dominant role in driving pathologic changes in psoriatic skin than IL-17F.'

On this basis, Eli Lilly remained firmly of the view that the claim was:

- **Misleading**: The claim implied clinical significance based on unproven evidence. The focus of the claim was, IL-17F levels were 30-fold higher than IL-17A levels. However, Kolbinger *et al* was clear in the conclusion, stating:

> 'we conclude that IL-17A has a more dominant role in driving pathologic changes in psoriatic skin than IL-17F.'

Therefore, Eli Lilly alleged that the emphasis of the claim, IL-17F levels were 30-fold higher was undue:

- **Insufficiently complete**: The promotional claim did not provide the clinical significance of the IL-17F and IL-17A levels, which was commented on by Kolbinger *et al* who stated:

  > 'Although IL-17F protein levels in patients with psoriasis were much higher than IL-17A levels, they were not consistently upregulated in lesional versus nonlesional skin in all psoriasis plaques and did not correlate with psoriasis disease activity as measured by using PASI scores.'

Furthermore:

> 'We sought to validate this finding using a larger independent cohort of patients with psoriasis. In the validation set serum IL-17A levels continued to have a good correlation, whereas IL-17F levels had a weaker if not poor correlation with PASI scores.'

Eli Lilly alleged that this was cherry-picking data to exaggerate the clinical significance of unproven benefits of the UCB product and this not being an objective representation of the study findings which could have easily misled busy health professionals to misinterpret the data and its clinical significance.

On this basis, Eli Lilly alleged a breach of Clause 6.1 of the Code as the claim misled, distorted and exaggerated the findings of the publication and could not be substantiated with respect to existing IL-17A inhibitors, including Eli Lilly's ixekizumab.

4 Alleged failure to maintain high standards

Eli Lilly alleged that it considered the three claims at issue represented a failure to maintain high standards and was a breach of Clause 9.1.

When writing to UCB, the Authority asked it to consider the requirements of Clauses 6.1, 6.2 and 9.1 of the Code.

RESPONSE

UCB stated that it was committed to compliance with the Code and took take the matters raised extremely seriously.

UCB stated that it had engaged with Eli Lilly in inter-company dialogue with respect to this promotional leavepiece from 11 January 2022 to 1 March 2022 and addressed Eli Lilly's claims in detail during this period (both in correspondence and a telephone discussion). UCB confirmed that the material provided by Eli Lilly in support of this matter was used at the annual British Dermatology Nursing Group (BDNG) congress in September 2021. UCB confirmed (as advised during inter-company dialogue) that this material was updated in November 2021 and the material supplied, subject to the complaint, was no longer in use. UCB provided a copy of

the revised material which was in use before this matter was raised to UCB in January 2022 and at the time of the complaint to the Authority (Nov 2021 IL-P-BK-PSO-2100004).

UCB stated that as could be seen from the inter-company dialogue, it did not agree that this material was misleading. UCB submitted that the material clearly called out that this related to an *in vitro* study and the reference in question, Glatt *et al.* (Ann Rheum Dis 2018;77:523–532), was being used to support the *in vitro* statement.

UCB addressed each of the claims as they appeared in the current material below.

1 In vitro blockage of IL-17A and IL-17F results in superior inhibition of inflammatory responses vs blocking IL-17A alone

UCB stated that it maintained its position, as outlined in its inter-company dialogue exchange with Eli Lilly, that the material in use was not misleading. The material clearly stated in the header that the statements at issue were based on *in vitro* data. Furthermore, this statement was clearly in line with Section 5.1 of the GB SPC for BIMZELX® which stated the following regarding the mechanism of action:

> 'Bimekizumab is a humanised IgG1/κ monoclonal antibody that selectively binds with high affinity to IL-17A, IL-17F and IL-17AF cytokines, blocking their interaction with the IL-17RA/IL-17RC receptor complex. Elevated concentrations of IL-17A and IL-17F have been implicated in the pathogenesis of several immune-mediated inflammatory diseases including plaque psoriasis. Bimekizumab inhibits these proinflammatory cytokines, resulting in the normalization of skin inflammation and as a consequence improvement in clinical symptoms associated with psoriasis. From in vitro models, bimekizumab was shown to inhibit psoriasis-related gene expression and cytokine production to a greater extent than inhibition of IL-17A alone.'

In reference to the Glatt *et al.* 2018 publication, where it did report the findings from a Proof of Concept (PoC) psoriatic arthritis trial as per the publication title; the manuscript also covered data from a number of preclinical experiments. These experiments assessed the role of IL-17A and IL-17F in tissue inflammation and included data from normal human dermal fibroblasts (skin cells) which were not specific to psoriatic arthritis. Of note, the IL-17A specific antibodies used in these experiments were created in-house by UCB, rather than marketed medicines, to ensure that antibody binding affinity was not a variable factor. Glatt *et al.* demonstrated that dual neutralisation of IL-17A and IL-17F demonstrated greater suppression of inflammation in both skin and joint cells. This was relevant to psoriasis and therefore UCB contested the view of Eli Lilly that it was misleading. In relation to the comments regarding the size and duration of the PoC trial limiting the interpretation of the safety dataset, this was in reference only to the PoC study. As described above, the manuscript contained data from other preclinical experiments, and it was data from these which had been used to substantiate the claim.

Further publications not referenced in the material also supported the scientific conclusions of Glatt *et al.* For example, Oliver *et al.* (Br J Dermatol (2022) 186, 652–663) observed that dual neutralisation of IL-17A and IL-17F was shown to inhibit psoriasis-related gene expression to a greater extent than inhibition of IL-17A alone.

To further evaluate the hypothesis that inhibition of both IL-17A and IL-17F would result in superior clinical response to IL-17A blockage alone, UCB conducted a Phase 3B head-to-head

study against the IL-17A inhibitor secukinumab in patients with moderate to severe plaque psoriasis (BE RADIANT study). In the BE RADIANT study, (Reich *et al*. N Engl J Med. 2021 Jul 8;385(2):142-152) dual inhibition of IL-17A and IL-17F with bimekizumab was shown to be clinically superior to inhibition of IL-17 A with secukinumab at both Weeks 16 and 48. Data from the BE RADIANT study was also included in the GB SPC on BIMZELX®. UCB disagreed that this material was misleading. The data was clearly identified as coming from an *in vitro* source, the conclusions could be supported by the GB SmPC on BIMZELX® and a phase 3 head-to-head clinical study. UCB stated that data from this study was shown within the same material.

2 BIMZELX provides more complete inhibition of the IL-17A and IL-17F pathway compared with blocking IL-17A alone

As per the response above, UCB maintained its position that the current statement was not misleading as the material from November 2021 clearly stated in the header that the statements at issue were based on *in vitro* data and it was clearly in line with the BIMZELX SPC. UCB confirmed that it intended to update the references on this material accordingly.

3 IL-17F levels are approximately 30-fold higher than IL-17A in psoriatic skin

UCB stated that it disagreed that this statement was misleading and exaggerated the authors' findings. In UCB's view, this statement accurately reflected the ratio of IL-17F vs IL-17A in psoriasis skin lesions from the publication Kolbinger *et al.* (J Allergy Clin Immunol 2017 Mar;139(3):923-932.e8.). This paper also showed that neither IL-17A or IL-17F could be detected in the skin of healthy subjects, demonstrating that both cytokines were upregulated in the skin of psoriasis patients.

Whilst UCB disagreed that this statement was in breach of the ABPI Code and believed this content was scientifically correct, as stated in the inter-company dialogue, UCB intended to amend this statement and remove the reference relating to the 30-fold higher expression of IL-17F in future materials.

Summary

In summary, the material provided by Eli Lilly was replaced in November 2021. UCB did not believe this material was misleading for the reasons set out above and trusted that the actions UCB had outlined in this letter concluded the matter.

PANEL RULING

The Panel noted that a Bimzelx leavepiece (Sept 2021 IL-P-BK-PSD-2100004) was the subject of the inter-company dialogue and subsequent complaint to the Authority. The Panel noted that this original leavepiece (September 2021) had been used in September 2021 and subsequently withdrawn before the commencement of inter-company dialogue in January 2022. An updated version (Nov 2021 IL-P-BK-PSO-2100004) was current when inter-company dialogue commenced and when the complaint was subsequently submitted. The updated version was referred to in inter-company dialogue in relation to first claim at issue. The Panel noted the parties' submissions about inter-company dialogue and that it had been unsuccessful and the matter referred to the Panel for consideration.

The Panel considered each of the three claims as raised by Eli Lilly and responded to by UCB.

1 'Blocking IL-17A and IL-17F results in superior inhibition of inflammatory responses vs blocking IL-17A alone'.

The Panel noted its general comments about inter-company dialogue above and the two versions of the leavepiece. The Panel noted that the claim at issue in the original leavepiece read 'Blocking IL-17A and IL-17F results in superior inhibition of inflammatory responses vs blocking IL-17A and IL-17F alone' and in the updated leavepiece read '*In vitro blockage of* IL-17A and IL-17F results in superior inhibition of inflammatory response*s* vs blocking IL-17A alone'. The page in question was otherwise identical. The Panel ruled upon the claim at issue and commented on the updated version in its ruling.

The Panel considered that context was important and, in this regard, noted that the front page of the leavepiece featured the strong claims 'Put psoriasis on high alert' and 'The next innovation in skin has arrived'. The reader would then see the claim at issue and *in vitro* data on page 2. This was immediately followed on the facing page, page 3, by clinical claims including the prominent heading 'An opportunity to challenge expectations:' which sat above efficacy claims including 'Superior efficacy in pivotal and head-to-head studies with Bimzelx'.

The Panel noted the claim in question was prominently placed at the top of the inside cover on page 2 of the leavepiece in bold light blue font with 'superior inhibition' in darker blue font, thus designed to catch the reader's eye. A very small footnote in black font at the bottom of the page stated 'Based on data derived from in vitro and human studies. The clinical significance of *in vitro* data is unknown'. The footnote was referenced to Glatt *et al* 2018 and Cole *et al* 2020.

The Panel considered that the location of the *in vitro* data on page 2 implied that there was evidence to show that it was of direct relevance and significance to the clinical data presented within the leavepiece. The Panel considered that the very small footnote at the bottom of the page was insufficient to negate the primary impression of clinical significance given by the claim in question.

The Panel noted UCB's submission that a Phase 3B head-to-head study against the IL-17A inhibitor secukinumab in patients with moderate to severe plaque psoriasis (BE RADIANT study), showed that dual inhibition of IL-17A and IL-17F with bimekizumab was clinically superior to inhibition of IL-17 A with secukinumab at both Weeks 16 and 48 and data from this study was included in the Bimzelx GB SPC and also shown within the same leavepiece but not referenced on the page on which the claims in question appeared.

The Panel noted Eli Lilly's comments about Glatt *et al* and that Bimzelx did not have a licence for psoriatic arthritis and yet psoriatic arthritis evidence was being used in the leavepiece. UCB referred to the PoC psoriatic arthritis trial which was part of Glatt *et al* noting that the study also included entirely separate data from preclinical experiments which included data in skin cells which were not specific to psoriatic arthritis. UCB noted that Glatt *et al* demonstrated that dual neutralisation of IL-17A and IL-17F demonstrated greater suppression of inflammation in both skin and joint cells and submitted that this was relevant to psoriasis. UCB also submitted that further publications not referenced in the materials supported the conclusions of Glatt *et al* and gave an example, Oliver *et al,* but did not provide that paper for the Panel to consider nor identify the other publications.

Eli Lilly alleged that UCB's intention to imply promotional superiority of bimekizumab, the only anti-IL17A/F targeting molecule, over anti-IL17A targeting molecules secukinumab and

ixekizumab was misleading and could not be substantiated and was in breach of Clauses 6.1 and 6.2 of the Code. The Panel considered that the claim in question was a comparative superiority claim, differentiating Bimzelx from anti-IL-17A targeting molecules approved for the treatment of moderate-severe psoriasis. The Panel noted that there was some data in relation to secukinumab and the BE RADIANT study which was reflected in the Bimzelx SPC and noted its comments above in this regard. The Panel noted that no comparative data had been submitted in relation to ixekizumab.

The Panel noted that Clause 6.1 and its supplementary information required that material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine and that 'data derived from *in vitro* studies, studies in healthy volunteers and in animals' stated that such data must not be used in such a way that misleads as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance. In this regard, the Panel considered the extrapolation of *in vitro* data to imply clinical significance was misleading as alleged. The Panel considered that the implication of clinical superiority of IL-17A and IL-17F blockade over IL-17A alone had not been substantiated. A **breach of Clauses 6.1 and 6.2 was ruled**.

The Panel did not consider the addition of the phrase '*in vitro*' to the page heading in the updated leavepiece changed the Panel's concerns about the clinical implication of the claim in question.

2 'BIMZELX provides more complete inhibition of the IL-17A and IL-17F pathway compared with blocking IL-17A alone'.

The Panel noted that this claim appeared as the third of four bullet points that appeared beneath the headline claim considered at point 1 above. Eli-Lilly alleged that this claim misled as to its clinical significance as the reference used was Cole *et al* 2020 which stated 'Using an *in vitro* skin cell activation assay, we demonstrate that dual neutralization of both IL-17A and IL-17F resulted in greater suppression of inflammatory proteins than inhibition of IL-17A alone'. In its response, UCB submitted that the updated page header clarified that this claim was in relation to *in vitro* data and that the references would be updated accordingly.

The Panel considered that its general comments above in relation to the first claim in question and the implied clinical relevance and significance of the *in vitro* data were relevant here.

The Panel considered that claims must be able to standalone without the need for additional qualification from footnotes and the like. The Panel noted that Cole *et al* 2020 stated that its investigations 'demonstrate *in vitro* dual inhibition of IL-17A and IL-17F is required to fully suppress IL-17 driven inflammation by activated MAIT [Mucosal associated invariant T] cells. Whether MAIT cells are drivers of pathogenesis during inflammation still requires investigation'. The Panel considered that the extrapolation of such *in vitro* data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance, noting the study authors' comments in Cole *et al* 2020 the Panel considered that the implied clinical relevance and significance was misleading as alleged and **ruled a breach of Clause 6.1 accordingly.**

The Panel did not consider the addition of the phrase *in vitro* to the page heading in the updated leavepiece changed the Panel's concerns about the clinical implication of the claim in question.

3 'IL-17F levels are approximately 30-fold higher than IL-17A in psoriatic skin'

The Panel noted that this claim appeared as the second of the four bullet points immediately above the claim at issue at point 2 above. The Panel noted the parties' submissions on inter-company dialogue on this point and considered that the position on inter-company dialogue was less straightforward on this point. Nonetheless, it appeared to the Panel that as the claim remained in use at the time of the complaint to the Authority, it was subject to consideration. In addition, the matter had been referred to the Panel for consideration.

The Panel noted that comments about the clinical significance of the *in vitro* data were, in effect, covered by its comments in relation to the first and second claims above. UCB submitted that the claim in question accurately reflected the ratio of IL-17F vs IL-17A in psoriasis skin lesions in Kolbinger *et al* 2017 and that the paper also showed that neither IL-17A or IL-17F could be detected in the skin of healthy subjects. The Panel noted that the same paper stated that 'Although IL-17F protein levels in patients with psoriasis were much higher than IL-17A levels, they … did not correlate with psoriasis disease activity as measured by using PASI scores'. Therefore, the Panel considered that this claim misled as to the clinical significance of the relative concentrations of IL-17 protein levels as evidenced in the *in-vitro* data and **ruled a breach of Clause 6.1 accordingly.**

Clause 9.1

The Panel noted that Eli Lilly cited Clauses from the 2021 Code including Clause 9.1 and, in this regard, had referred to maintaining high standards. The Panel noted that Clause 9.1 in the 2021 Code required 'All relevant personnel, including representatives, and members of staff, and others retained by way of contract, concerned in any way with the preparation or approval of material or activities covered by the Code must be fully conversant with the Code and the relevant laws and regulations'. Maintaining high standards, as referred to by Eli Lilly, fell under Clause 5.1 of the 2021 Code (Clause 9.1 of the 2019 Code). It thus appeared that Clause 9.1 of the 2021 Code had been cited in error. Given that Eli Lilly had clearly referred to the matter of high standards and UCB had the opportunity to respond to the matter raised, including during inter-company dialogue, the Panel considered the matter raised under Clause 5.1 of the 2021 Code.

The Panel noted its comments and rulings above, particularly in relation to the clinical significance of the claims at issue. The Panel was concerned that the claims at issue appeared prominently on the inside front cover, page 2, of the leavepiece. The front cover, page 1 of the leavepiece, described Bimzelx as the 'next innovation' and the page facing that in question contained clinical claims. In the Panel's view, there was an implication that the *in vitro* data supported the comparative nature of the clinical claims in relation to all relevant products. The Panel was concerned about the use of a footnote in very small font size at the bottom of the page in question as referred to in relation to the first and second claim above. Any qualification required to ensure that a claim complied with the Code should form part of the claim or be within the immediate visual field of the claim. The Panel considered that UCB had failed to maintain high standards and **ruled a breach of Clause 5.1.**

APPEAL BY UCB

UCB appealed the Panel's decision in relation to its findings of breaches of Clause 6.1 and, accordingly, Clauses 5.1 and 6.2 – as consequential breaches of the Code.

Breach of Clause 6.1

UCB submitted that whilst it recognised the need to comply with the requirement of Clause 6.1 of the Code – which was the central point of the complaint – UCB was very disappointed by the Panel's decision as it had mischaracterised the underlying data and the context in which such data were presented in the leavepiece.

UCB noted that Clause 6.1 of the Code stated:

> 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis.'

Clause 6.2 stated, amongst other things:

> 'Any information, claim or comparison must be capable of substantiation.'

UCB submitted that the Code did not limit the type of evidence that could be used to support comparative claims, provided that the methodological approach was valid. Nor did the Code exclude a prior assessment provided by a regulatory body responsible for granting a marketing authorisation or health technology appraisal as supportive evidence. As detailed below, UCB had relied upon the particulars set out in the approved summary of product characteristics ('SPC') and the health technology appraisal decision which respectively contained the direct and indirect evidence previously submitted by UCB as supportive of the relative clinical efficacy/effectiveness claims.

UCB noted that the PMCPA had ruled the following statements contained in the leavepiece in breach of Clause 6.1:

- Blocking IL-17A and IL-17F results in superior inhibition of inflammatory responses vs blocking IL-17A alone.

- BIMZELX provides more complete inhibition of the IL-17A and IL-17F pathway compared with blocking IL-17A alone.

- IL-17F levels are approximately 30-fold higher than IL-17A in psoriatic skin.

UCB noted that the Code was an integral part of the regulatory framework governing the advertising and promotion of medicinal products in the United Kingdom. It should, therefore, be read in conjunction with the requirements set out in the Human Medicines Regulations 2012 (SI 2012/1916) '("Medicines Regulations")[1] (1. As amended by The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019), which remained rooted in EU pharmaceutical law principally those provisions set out in Directive 2001/83/EC (the "Directive") governing the particulars set out in the SPC and advertising.)'.

Consistent with Medicines Regulations, an approved SPC set out the agreed position of the medicinal product as distilled during the course of the assessment process. The SPC was the basis of information for healthcare professionals on how to use the medicinal product

safely and effectively.

UCB submitted that according to Medicines Regulations and the Code, it should be the common ground that a pharmaceutical company was permitted to advertise and promote to healthcare professionals a prescription only medicine provided that all parts of the advertising of a medicinal product complied with the particulars listed in the approved SPC. The promotional material should encourage the rational use of the medicinal product by presenting it objectively and without exaggerating its properties. The advertising must not be misleading.

UCB submitted that the data referenced in the leavepiece were properly described therein to represent fairly and accurately the current state of knowledge of the unique pharmacological properties relating to Bimzelx, consistent with the prevailing rules and requirements. Most importantly, the data were presented in a manner that was compatible with the particulars set out in the approved SPC (provided). Together with the indirect evidence previously submitted to support a positive health technology appraisal in England, there was a proper evidentiary basis to support the contention that bimekizumab was clinically superior to secukinumab and ixekizumab.

Bimekizumab was a therapeutic monoclonal antibody specifically designed to selectively target both IL-17A and IL-17F to mediate clinically relevant therapeutic effects to treat patients with moderate to severe plaque psoriasis in adult patients who were candidates for systemic therapy or phototherapy. UCB submitted that the proper characterisation of the differential pharmacodynamic properties exhibited by bimekizumab compared to IL-17A inhibition in vitro and IL-17A with secukinumab in a Phase 3b study had been accepted by major regulatory authorities, including the Medicines and Healthcare products Regulatory Agency ('MHRA'), and crystallised in the approved SmPC (The SPC specifically states that bimekizumab is a humanised IgG1/K monoclonal antibody that selectively binds with high affinity to IL-17A, IL-17F and IL-17AF cytokines, blocking their interactions with the IL-17RA/ILRC receptor complex. Elevated concentrations of IL17A and IL-17F have been implicated in the pathogenesis of several immune-mediated inflammatory diseases including plaque psoriasis). The SPC specifically stated that bimekizumab was a humanised IgG1/K monoclonal antibody that selectively binds with high affinity to IL-17A, IL-17F and IL-17AF cytokines, blocking their interactions with the IL-17RA/ILRC receptor complex. Elevated concentrations of IL17A and IL-17F have been implicated in the pathogenesis of several immune-mediated inflammatory diseases including plaque psoriasis. See further below.

UCB noted that an SPC followed the same order described in Article 11 of the Directive as interpreted by the European Commission's guidance:

a) Name of the medicinal product.

b) Qualitative and quantitative composition.

c) Pharmaceutical form.

d) Clinical particulars (including therapeutic indications and posology).

e) Pharmacological properties.

f) Pharmaceutical particulars.

g) Marketing authorisation holder.

h) Marketing authorisation number(s).

i) Date of first authorisation/renewal of the authorisation.

UCB submitted that of relevance to this appeal, the approved SPC for Bimzelx described in Section 4.1 the therapeutic indications for the treatment of moderate to severe plaque psoriasis in adults who were candidates for systemic therapy. In Section 5.1 the pharmacodynamic properties of the therapeutic monoclonal antibody, bimekizumab, in relation to (i) its mechanism of action and (ii) clinical efficacy and safety in the following terms:

i) Bimekizumab was a humanised IgG1/k monoclonal antibody that selectively binds with high affinity to IL-17A, IL-17F and IL-17AF cytokines, blocking their interaction with the IL-17RA/IL-17RC receptor complex. Elevated concentrations of IL-17A and IL-17F had been implicated in the pathogenesis of several immune-mediated inflammatory diseases including plaque psoriasis. Bimekizumab inhibits these proinflammatory cytokines, resulting in normalization of skin inflammation and as a consequence improvement in clinical symptoms associated with psoriasis. From in vitro models, bimekizumab was shown to inhibit psoriasis-related gene expression and cytokine production to a greater extent than inhibition of IL- 17A alone (emphasis added)

ii) Bimekizumab had been shown to be clinically superior over a number of therapeutic monoclonal antibodies which had been approved for treatment of psoriasis, e.g., adalimumab, secukinumab.

UCB submitted that the clinically meaningful and highly statistically significant ($p<0.001$) differential treatment effects between bimekizumab and secukinumab were described in Section 5.1 of the SPC. Secukinumab was a therapeutic monoclonal antibody which targeted IL-17A alone.

The SPC stated, amongst other things, 'bimekizumab-treated patients achieved significantly higher response rates compared to secukinumab for the primary endpoint of PASI100 (complete skin clearance) at Week 16. Significantly higher response rates were also achieved with bimekizumab for the secondary endpoint of PASI 100 at Week 48 (for both Q4W/Q4W and Q4W/Q8W regimens). Comparative PASI response rates were presented in Table 6 [in the SPC]. Differences in response rates between bimekizumab and secukinumab-treated patients were noted as early as week 1 for PASI-75 (7.2% and 1.4% respectively) and as early as Week 2 for PASI 90 (7.5% and 2.4% respectively). Consistency in the differential treatment effects demonstrating clinical superiority of bimekizumab over secukinumab was also noted in other clinical studies.

UCB submitted that the standard for incorporating pre-clinical and clinical data into Section 5.1 was guided by the European Commission's adopted Guideline on Summary of Product Characteristics (Copy provided) which stated at page 20/29:

'It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified

> end points or clinical outcomes in the major trials, and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant, and balanced, and should summarise evidence from relevant studies supporting the indication. The magnitude of effects should be described using absolute figures. (Relative risks or odd ratio should not be presented without absolute figures).
>
> In the exceptional cases when clinically relevant information from subgroup or post- hoc analyses is presented, it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations.'

UCB submitted that nothing in the Medicines Regulations or the Code prohibited a pharmaceutical company making a comparative claim based on factual grounds and methodologically valid direct or indirect evidence. Indeed, the established case-law of the European Court of Justice – which remained applicable following the UK's exit from the EU – indicated that a pharmaceutical company was permitted to provide additional information to healthcare professionals to confirm or clarify the particulars already provided in the approved SPC, provided that such information did not distort and was compatible with the terms of the SPC. The European Court recognised that healthcare professionals had a higher professional knowledge to make an informed assessment on the data provided that the data were compatible with the approved SPC.

UCB submitted that the information presented in the leavepiece followed essentially the same order as set out in Article 11 of the Directive and, accordingly, the approved SPC. Page 2 focused exclusively on 'Mechanism of Action' without reference to clinical outcomes, consistent with the particulars set out in the SPC. The mechanism of action sought to explain the biological rationale or plausibility of the observed clinical efficacy and/or safety of the approved medicinal product. Page 3 *et seq.* described an overview of the clinical profile and characteristics relevant to the prescriber – all substantiated with references to Bimzelx full clinical development programme and the approved SPC. Moreover, specific reference was made in page 3 in **bold** type requesting healthcare professionals to do the following: 'Please consult the BIMZELX Summary of Product Characteristics (SPC) for more information before prescribing'.

UCB submitted that the front cover of the leavepiece appeared to be the focus of the PMCPA's assessment and the complaint made by Eli Lilly. It referred to the recommendations made by the National Institute for the Clinical Health and Excellence ('NICE') (copy provided).

The positive recommendations adopted by NICE were statutorily binding for a new medical technology to be adopted for clinical use in the National Health Service in England (See the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) 2013 (SI 2013 No. 259).

On the basis of both direct and indirect evidence submitted by UCB, NICE considered the following in its final appraisal decision. NICE's decision on the cost-effectiveness assessment of bimekizumab stated, amongst other things, the following:

> 'Bimekizumab is an alternative to other biological treatments already recommended by NICE for treating severe plaque psoriasis in adults. Evidence from clinical trials shows that bimekizumab is more effective than adalimumab, secukinumab [targeted only IL-

> 17A] and ustekinumab. Indirect comparisons suggest that bimekizumab is similarly or more effective than other biological treatments.
>
> For the cost comparison, it is appropriate to compare bimekizumab with brodalumab, risankizumab and ixekizumab [targeting IL-17A] because they work in a similar way and would likely be used as an alternative to those treatments.'

UCB submitted that the indirect comparisons referenced in NICE's health technology appraisal were based on UCB's Network Meta Analysis, which was an accepted technique for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies. This Network Meta Analysis followed NICE's methodology as stated in the manuscript: 'This study explored clinical heterogeneity and the performance of NMA models using unadjusted and adjusted models per the NICE Decision Support Unit recommendations'. Furthermore, it concluded that 'Bimekizumab demonstrated statistical superiority over all biologics in achieving PASI 90 and PASI 100 threshold'. In this regard, all therapeutic monoclonal antibodies such as those targeting IL- 17A are by definition biologics.

The validity of the Network Meta Analysis performed by NICE was noted, particularly at paragraph 3.5, page 16, that there was not selection-bias in the indirect comparisons against other biologics. Of note, in the health technology appraisal document with respect to UCB's Network Meta Analysis it specifically stated, amongst other things, the following:

> 'The company did a series of network meta-analyses on PASI response rates (50, 75, 90 and 100) and safety outcomes. These compared bimekizumab with all other NICE-recommended biological agents and systemic non-biological treatments. The ERG noted that studies included in network meta-analyses varied considerably in the proportion of patients who had had previous biological therapies. It noted that disease response to subsequent biological treatments might be lower than the level of response achieved by the initial biological therapy. However, it explained that because the proportion of people who had previous biological therapy in bimekizumab trials was at the higher end of the range for the network as a whole, this is unlikely to bias the results in favour of bimekizumab. The ERG also noted that the company had not included DLQI as an outcome in the network meta-analysis.
>
> However, it was satisfied that the company's approach was appropriate. The committee accepted the ERG's view, concluding that the network meta analyses provided by the company was suitable for decision making.' (emphasis added).

UCB submitted that, in addition to the clinical superiority of bimekizumab over secukinumab based on direct evidence, better clinical effectiveness of bimekizumab compared with ixekizumab (another IL-17A therapeutic monoclonal antibody) – and this appeared to be the central pillar of Eli Lilly's complaint to the PMCPA – was also confirmed by NICE in its appraisal report at paragraph 3.6 of page 16 based on UCB's indirect evidence using the Network Meta Analysis against a clinically important variable for assessing clinical effectiveness:

> 'The committee acknowledged that in previous psoriasis appraisals, PASI 75 is the key outcome when deciding whether to continue treatment. It noted that the results of the network meta-analysis suggested that bimekizumab was similarly effective compared

with brodalumab, risankizumab and ixekizumab in terms of PASI 75 response. The committee appreciated that PASI 90 and 100 were increasingly becoming important outcomes to patients and were collected in newer clinical trials. It noted that bimekizumab was more effective compared with brodalumab, risankizumab and ixekizumab in terms of PASI 90 and 100 response.' (emphasis added).

Conclusion

UCB submitted that in its entirety, consistent with standards set out in the Medicines Regulations and the Code, the leavepiece was not misleading. Claims were substantiated and complete and followed a structure well acquainted to dermatologist prescribers. In any event, the leavepiece drew particular attention at page 3 that the healthcare professionals should consult the approved SPC, which ought to be the reference information to guide good prescribing behavior.

It was factually correct, and consistent with the approved SPC, to describe that bimekizumab was a different type of therapeutic monoclonal antibody with dual pharmacological actions targeting both IL-17A and IL-17F cytokines which were recognised to be involved in the pathogenesis of proinflammatory diseases such as psoriasis. It was appropriate to present such scientific findings from pre-clinical studies while not making clinical claims. Description of these scientific findings in the leavepiece was entirely consistent with Section 5.1 of the approved SPC. The information presented in the leavepiece did not breach the Code (nor the Medicines Regulations) by informing the prescribers of unique pharmacological properties exhibited by bimekizumab.

Whilst UCB submitted that it did not intend to imply clinical superiority through the *in vitro* mechanism of action, the data from various sources, as well as their analysis, supported the clinical relevance of the claim. Such direct and indirect evidence included:

- The head-to-head comparison between bimekizumab and secukinumab which was expressly referenced in the SPC approved by the MHRA.

- The methodologically valid indirect comparisons based on Network Meta Analysis that formed the basis of the NICE recommendations as referenced in the cover of the leavepiece.

UCB acknowledged that the Panel was entitled to take a divergent position from that adopted by the MHRA and NICE in relation to an assessment of better clinical efficacy or effectiveness of bimekizumab (targeting both IL-17A and IL-17F) over secukinumab and ixekizumab (targeting IL-17A only). However, the statutorily binding effect of an approved SPC and a NICE final appraisal decision to guide, respectively, (i) safe and effective conditions of use of an approved product and (ii) clinical adoption of a new medical technology in the National Health Service could not be summarily ignored as supportive evidence of demonstrating clinical superiority of a bi-specific monoclonal antibody, bimekizumab, over the approved mono-specific monoclonal antibodies, secukinumab and ixekizumab. These differential treatment effects were biologically plausible by reference to the underlying mechanism of action expressly stated in Section 5.1 of the approved SPC.

For the above reasons, UCB submitted that the Panel's rulings of a breach of Clause 6.1 and

a consequential breach of Clause 6.2, and Clause 5.1 for not maintaining high standards in publishing the leavepiece was manifestly wrong according to the requirements of the Code. Specifically, the Code required Panel rulings to be made on the basis that a complainant had the burden of proving their complaint on the balance of probabilities. This evidentiary standard had not been adequately discharged for a finding of breach of Clause 6.1 and the consequential breaches of Clauses 6.2 and 5.1.

UCB submitted that within the context of advancing medical knowledge in optimising patient care, UCB would continue its efforts to clarify the unique pharmacodynamic properties of bimekizumab consistent with, among other things, Section 5.1 of the approved SPC, confirming the role of IL- 17A and IL-17F in the pathogenesis and the benefit of dual inhibition of both cytokines in the treatment of psoriasis. UCB also reserved its right to make reference to valid, accurate and up-to-date clinical data and analyses that demonstrably establish clinically meaningful differential treatment effects between bimekizumab and other therapeutic monoclonal antibodies which target IL-17A only. Per the approved SPC, the differential pharmacological properties had already been translated into clinically relevant and statistically significant differences in the treatment effects between bimekizumab and secukinumab according to the approved SPC. Secukinumab was specifically designed to target IL-17A only. Accordingly, UCB would update the leavepiece to provide greater clarity on the references to describe the unique pharmacological properties of bimekizumab.

RESPONSE FROM ELI LILLY

Eli Lilly noted that the Panel had ruled UCB in breach of Clauses 5.1, 6.1 and 6.2 of the Code and was supportive of its findings. Eli Lilly was surprised that UCB had decided to appeal the rulings and Lilly continued to dispute its rationale.

Eli Lilly noted UCB's assertion at appeal that its claims formed part of the bimekizumab SPC approved by the MHRA referencing in particular Section 5.1; the pharmacodynamic properties of the medicine as noted below:

> 'Bimekizumab SPC Section 5.1 Mechanism of Action:
>
> Mechanism of action Bimekizumab was a humanised IgG1/κ monoclonal antibody that selectively binds with high affinity to IL-17A, IL-17F and IL-17AF cytokines, blocking their interaction with the IL-17RA/IL-17RC receptor complex. Elevated concentrations of IL117A and IL-17F had been implicated in the pathogenesis of several immune-mediated inflammatory diseases including plaque psoriasis. Bimekizumab inhibits these proinflammatory cytokines, resulting in the normalization of skin inflammation and as a consequence improvement in clinical symptoms associated with psoriasis. From in vitro models, bimekizumab was shown to inhibit psoriasis-related gene expression and cytokine production to a greater extent than inhibition of IL-17A alone.'

Eli Lilly alleged that the wording in the SPC in relation to *in vitro* data made no comparative clinically valid claims between bimekizumab and all IL-17A inhibitors. Additionally, Eli Lilly had not found the specific claim 'IL-17F levels were approximately 30-fold higher than IL-17A in psoriatic skin' to be stated within the bimekizumab SPC, as noted by UCB in its appeal.

Eli Lilly had already explained in detail the limitations of the publications underlying such pre-clinical claims in its response to the Panel. Overall, it remained very doubtful that any regulator

would accept that the current *in vitro* information from Section 5.1 of the bimekizumab SPC could be extrapolated into broad clinical claims about the medicine in a promotional leavepiece.

Whilst UCB explained in depth the factual basis of its claims on appeal, it appeared to not recognise that it was the combination of claims and associated artwork in the leavepiece (font size of the title vs disclaimer and claim positioning) that was of concern as it depicted a misleading impression that bimekizumab was superior to all medicines that inhibit IL-17A (ie secukinumab, ixekizumab).

Eli Lilly acknowledged the UCB-sponsored trial between bimekizumab and secukinumab (BE RADIANT). However, as UCB itself had appreciated during inter-company dialogue previously, there was no head-to-head data for bimekizumab vs ixekizumab to support the assertion made that this clinical data applied across the IL-17A class of medicines.

Eli Lilly stated that, as outlined below, there were many differences between secukinumab and ixekizumab despite them both being IL-17A inhibitors which prevented a simple extrapolation between medicines:

- Differences in dosing, frequency and pharmacology (Paul, C. (2018), Ixekizumab or secukinumab in psoriasis: what difference does it make? Br J Dermatol, 178:1003-1005)
    - Secukinumab had a longer half-life, and its administered dose was about three to four times higher than ixekizumab, resulting in significantly higher systemic exposure.
    - The in vitro binding affinity for IL-17 was about 50–100 times higher for ixekizumab than for secukinumab.

- Eli Lilly stated that no direct head-to-head comparative data between ixekizumab and secukinumab existed today. At appeal, UCB had utilised its own NICE network meta-analysis to justify its position, but it was also a well-understood scientific point that such indirect comparisons had many limitations. Eli Lilly summarised below a wealth of high-quality evidence and UK-expert consensus that ixekizumab was ranked higher on efficacy than secukinumab and, furthermore, that there might be limited differences between bimekizumab and other biologics in psoriasis which the leavepiece in question suggested.
    - British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020 clearly stated: ‘For IL17 agents, for clear/nearly clear (PASI90), ixekizumab ranked higher than secukinumab and brodalumab’ (C.H. Smith and others, British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update, British Journal of Dermatology, Volume 183, Issue 4, 1 October 2020, Pages 628–637).
    - A network meta-analysis of 60 Phase 2, 3 or 4 randomised clinical trials published in JAMA Dermatology (Impact Factor 11.8) demonstrated higher efficacy response at PASI 100 (100% skin clearance) with ixekizumab vs secukinumab in the short and long term (Armstrong AW, Puig L, Joshi A, Skup M, Williams D, Li J, Betts KA, Augustin M. Comparison of Biologics and Oral Treatments for Plaque Psoriasis: A

Meta-analysis. JAMA Dermatol. 2020 Mar 1;156(3):258-269).

- In a British Journal of Dermatology (Impact Factor 11.1) publication, Ixekizumab had higher PASI 90 and PASI 100 responses at week 12 compared with secukinumab using adjusted indirect comparisons too. Lilly noted that the lead UK author Professor Richard Warren for this study was also the co-author for the Bimekizumab versus Secukinumab in Plaque Psoriasis Phase 3 (BE RADIANT) study quoted by UCB (Warren *et al*. Matching adjusted indirect comparison of efficacy in patients with moderate-to-severe plaque psoriasis treated with ixekizumab vs. secukinumab Br J Dermatol 2018; 178:1064–1071).

- The highly respected Cochrane network meta-analysis published in 2022 also concluded: 'Compared with placebo, four biologic medicines worked best to treat psoriasis, with little difference between them: infliximab (targets TNF-alpha); ixekizumab and bimekizumab (targets interleukin-17); and risankizumab (targets interleukin-23)' (Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, Hughes C, Naldi L, Afach S, Le Cleach L. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database of Systematic Reviews 2022, Issue 5. (Accessed 14 June 2023.)).

Eli Lilly stated that it was reassuring that on review of this case, the Panel had noted that 'Clause 6.1 and its supplementary information required that material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine and that "data derived from *in vitro* studies, studies in healthy volunteers and in animals" stated that such data must not be used in such a way that misleads as to its significance'.

Eli Lilly alleged that the inappropriate and misleading use of claims based on *in vitro* data which had been extrapolated to suggest clinical superiority to all IL-17A inhibitors did not meet the required standards set by the Code and continued to support the Panel's ruling.

APPEAL BOARD RULING

The Appeal Board observed that the claim at issue in the original leavepiece (Sept 2021 IE-P-BK-PSO-2100004) read 'Blocking IL-17A and IL-17F results in superior inhibition of inflammatory responses vs blocking IL-17A and IL-17F alone' and in the updated leavepiece (Nov 2021 IE-P-BK-PSO-2100004) read '*In vitro blockage of* IL-17A and IL-17F results in superior inhibition of inflammatory response*s* vs blocking IL-17A alone'. The Appeal Board noted that the Panel ruled upon the claim at issue in the original leavepiece and commented on the updated version in its ruling.

The Appeal Board considered that context was important and, in this regard, noted that the front page of the leavepiece featured the strong claims 'Put psoriasis on high alert' and 'The next innovation in skin has arrived'. The reader would then see the claim at issue and *in vitro* data on page 2. This was immediately followed on the facing page, page 3, by clinical claims including the prominent heading 'An opportunity to challenge expectations:' which sat above efficacy claims including 'Superior efficacy in pivotal and head-to-head studies with Bimzelx'.

The Appeal Board observed that the claim in question in the original leavepiece was prominently placed at the top of the inside cover on page 2 in bold light blue font with 'superior inhibition' in darker blue font, thus designed to catch the reader's eye. A very small footnote in black font at the bottom of the page stated 'Mechanism based on in vitro and human studies'. The footnote referenced Glatt *et al* 2018 and Cole *et al* 2020. The limitations of in vitro studies were not highlighted.

The Appeal Board considered that the location of the *in vitro* data on page 2 implied that there was evidence to show that it was of direct relevance and significance to the clinical data presented on Page 3 and within the leavepiece. The Appeal Board considered that the very small footnote at the bottom of the page was insufficient to negate the primary impression of clinical significance given by the claim in question.

The Appeal Board considered UCB's submission that a Phase 3B head-to-head study against the IL-17A inhibitor secukinumab in patients with moderate to severe plaque psoriasis (BE RADIANT study), showed that dual inhibition of IL-17A and IL-17F with bimekizumab was clinically superior to inhibition of IL-17 A with secukinumab at both Weeks 16 and 48 and data from this study was included in the Bimzelx GB SPC and also shown within the same leavepiece but not referenced on the page on which the claims in question appeared.

The Appeal Board concluded that the claim in question was a comparative superiority claim, differentiating Bimzelx from anti-IL-17A targeting molecules approved for the treatment of moderate-severe psoriasis. There was some data in relation to secukinumab and the BE RADIANT study which was reflected in the Bimzelx SPC but no comparative data had been submitted in relation to ixekizumab.

The Appeal Board considered that the position of the *in vitro* data alongside clinical claims for superiority extrapolated *in vitro* data to imply clinical significance which was misleading as alleged. The Appeal Board considered that the implication of clinical superiority of IL-17A and IL-17F blockade over IL-17A alone had not been substantiated. The Appeal Board **upheld the Panel's ruling of a breach of Clauses 6.1 and 6.2**. The appeal on this point was unsuccessful.

The Appeal Board noted that the claim 'BIMZELX provides more complete inhibition of the IL-17A and IL-17F pathway compared with blocking IL-17A alone' appeared as the third of four bullet points that appeared beneath the headline claim considered above. Eli-Lilly alleged that this claim misled as to its clinical significance as the reference used was Cole *et al* 2020 which stated 'Using an *in vitro* skin cell activation assay, we demonstrate that dual neutralization of both IL-17A and IL-17F resulted in greater suppression of inflammatory proteins than inhibition of IL-17A alone'.

The Appeal Board considered that claims must be able to standalone without the need for additional qualification from footnotes and the like. The Appeal Board noted that Cole *et al* 2020 stated that its investigations 'demonstrate *in vitro* dual inhibition of IL-17A and IL-17F is required to fully suppress IL-17 driven inflammation by activated MAIT [Mucosal associated invariant T] cells. Whether MAIT cells are drivers of pathogenesis during inflammation still requires investigation'. The Appeal Board considered that the extrapolation of such *in vitro* data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance, noting the study authors' comments in Cole *et al* 2020. The Appeal Board concluded that the implied clinical relevance and significance was misleading as alleged

and the Appeal Board **upheld the Panel's ruling of a breach of Clause 6.1**. The appeal on this point was unsuccessful.

UCB submitted that the claim 'IL-17F levels are approximately 30-fold higher than IL-17A in psoriatic skin' in question accurately reflected the ratio of IL-17F vs IL-17A in psoriasis skin lesions in Kolbinger *et al* 2017 and that the paper also showed that neither IL-17A or IL-17F could be detected in the skin of healthy subjects. The Appeal Board noted that the same paper stated that 'Although IL-17F protein levels in patients with psoriasis were much higher than IL-17A levels, they … did not correlate with psoriasis disease activity as measured by using PASI scores'. Therefore, the Appeal Board concluded that this claim misled as to the clinical significance of the relative concentrations of IL-17 protein levels as evidenced in the *in-vitro* data and the Appeal Board **upheld the Panel's ruling of a breach of Clause 6.1**. The appeal on this point was unsuccessful.

When considering Clause 5.1 the Appeal Board was concerned that the claims at issue appeared prominently on the inside front cover, page 2, of the leavepiece. The front cover, page 1 of the leavepiece, described Bimzelx as the 'next innovation' and the page facing that in question contained clinical claims. In the Appeal Board's view, there was an implication that the *in vitro* data supported the comparative nature of the clinical claims in relation to all relevant products. The Appeal Board was concerned about the use of a footnote in very small font size at the bottom of the page in question as referred to in relation to the first and second claim above. Any qualification required to ensure that a claim complied with the Code should form part of the claim or be within the immediate visual field of the claim. The Appeal Board agreed with Eli Lilly's assertion that the incomplete information, associated artwork and combined use of claims within the leavepiece created a misleading impression to a prescriber that bimekizumab was superior to all IL-17A inhibitor biologics in plaque psoriasis.

The Appeal Board considered that UCB had failed to maintain high standards and it **upheld the Panel's ruling of a breach of Clause 5.1**. The appeal on this point was unsuccessful.

During its consideration of this case, the Appeal Board was concerned about the nature of UCB's defence and the level of its understanding of self-regulation. In particular, the Appeal Board was concerned that UCB appeared to believe that using parts of wording from the SPC in promotional material could not be a breach of the Code. The Appeal Board rejected UCB's submission that if the Panel's rulings were upheld, it could potentially undermine the decisions of the MHRA, EMA and NICE following their approval processes. The Appeal Board rejected UCB's submission that if the breaches were upheld the self-regulatory system would, in effect, be supressing UCB's ability to communicate information to guide prescribing based on those decisions. The Appeal Board noted that how a pharmaceutical company promoted its medicines was governed by the Code as set out in the Memorandum of Understanding with the ABPI, PMCPA and MHRA. The Appeal Board further noted the difference between information within the SPC about a medicine's pharmacodynamic properties and using such data within promotional material with an inference of clinical significance.

Complaint received **27 May 2022**

Case completed **22 August 2023**