Medicines Australia
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COMPLAINT OUTCOME

1162 - RINVOQ Promotional Material

DETERMINATIONS OF THE MEDICINES AUSTRALIA CODE OF CONDUCT AND APPEALS COMMITTEES

The administration of the Code is supervised by the Code of Conduct Committee. The Code of Conduct Committee has the power to make a determination as to a breach of the Code and impose sanctions. The right of appeal is available to both the Complainant and Subject Company. An appeal is heard by the Appeals Committee which has the power to confirm or overturn the decision and to amend or remove any sanctions.

The decisions of the Code of Conduct and Appeals Committees are relevant to the date of publication of the materials subject to complaint and approved Product Information (PI) at that time. A complaint is not deemed finalised until the Subject Company has advised Medicines Australia that they will not appeal the outcome of the Code of Conduct Committee decision (following circulation of the Code minutes) or, in the case of an appeal, the minutes of the Appeals Committee meeting have been provided to both parties.

This report is an extract of the minutes of the complaint heard on 18 January 2021, and subsequent appeal heard on 9 April 2021

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COMPLAINT 1162 - RINVOQ PROMOTIONAL MATERIAL

SUBJECT COMPANY	PRODUCT	COMPLAINANT
AbbVie Pty Ltd (AbbVie)	RINVOQ (Upadacitinib)	Pfizer Australia (Pfizer)

COMPLAINT

Pfizer alleged that multiple promotional materials for RINVOQ, indicated for the treatment of moderate to severe rheumatoid arthritis were in breach of the Code. Specifically, Pfizer alleged that the materials contain claims of efficacy and safety of RINVOQ that are false and misleading, as well as portraying an advantageous clinical profile of RINVOQ that is not supported by key clinical data.

Of note, Pfizer assert that the leading promotional tagline "Defy Expectations" is clearly intended to imply beneficial treatment outcomes with RINVOQ that would otherwise not be expected. Pfizer contended that this comparative statement was unsubstantiated. Further, Pfizer alleged that other elements of these materials exaggerated the clinical superiority of RINVOQ.

SECTIONS OF THE CODE

This complaint was heard under both Edition 18 and Edition 19

EDITION 18

- 1.2.2 Level of substantiating data
- 1.3 False or misleading claims
- 1.6 Unqualified superlatives
- 1.8 Comparative statements

EDITION 19

- Principle 3: companies are responsible providing current, accurate, balanced, and scientifically valid information products to support their use.
- Principle 7: information relevant to prescribing, in particular product and safety information, are clearly communicated in all promotional materials.
- Section 1: Requirements for promotional claims directed at healthcare professionals
- Section 1.1: Substantiating data

RESPONSE TO THE COMPLAINT

AbbVie disagreed with Pfizer's assertions that materials for RINVOQ are in breach of the Code of Conduct and maintained that the materials and the claims and substantiating data are neither false nor misleading.

AbbVie raised in its response an allegation of abuse of the Code under Section 16.4 of Edition 19; detailing several concerns of failure to follow process and an allegation that Pfizer did not act in the spirit of the Code. AbbVie sought that the Code Committee dismiss the complaint or limit determination to those matters which remain outstanding.

CODE OF CONDUCT COMMITTEE DECISIONS

Complaint	Edition 18	Edition 19
AbbVie's allegation of abuse of the Code	N/A	Section 16.4: No Breach
Imagery and claim "Defy Expectations"	Section 1.3: Breach	• Principle 3: Does not comply • Section 1: Breach
Defy Expectations Claim – RINVOQ + MTX, the first therapy with proven superiority vs adalimumab + MTX for ACR6, Pain and Physical Function at week 12	• Section 1.2.2: Breach • Section 1.3: Breach • Section 1.6: Breach • Section 1.8: Breach	• Principle 3: Does not comply • Principle 7: Does not comply • Section 1: Breach • Section 1.1: Breach
Comparative superiority claims for time points other than 12 weeks	• Section 1.2.2: No breach • Section 1.3: No breach • Section 1.8: No breach	• Principle 3: Compliant • Principle 7: Compliant • Section 1: No breach • Section 1.1: No breach
RISK CLAIM Proven superiority	• Section 1.2.2: No breach • Section 1.3: Breach • Section 1.8: Breach	• Principle 3: Does not comply • Principle 7: compliant • Section 1: Breach • Section 1.1: No breach
RISK CLAIMS consistent efficacy;	• Section 1.2.2: No breach • Section 1.3: No breach • Section 1.8: No breach	• Principle 3: Compliant • Principle 7: Compliant • Section 1: No breach • Section 1.1: No breach
RISK CLAIMS well-characterised Benefit:	• Section 1.2.2: Breach • Section 1.3: Breach • Section 1.8: No breach	• Principle 3: Breach • Principle 7: Breach • Section 1: Breach • Section 1.1: No breach
Dear Doctor Letter	• Section 1: Breach • Section 1.2.2: Breach • Section 1.3: Breach	N/A
SANCTION	The Committee unanimously agreed that the breaches were classified as moderate, having regard to the probable impact this would have on the way a HCP may prescribe the product. The Committee also agreed unanimously to impose the following sanctions: • Materials using the claims found in breach should be ceased and withdrawn immediately; • Claims found in breach should not be used in the same context in future material; and • Pay a fine of $125,000.	

APPEAL	Pfizer appeals the Code Committee's determination that found that pre-defined ranked secondary endpoints that were the substantiating basis for superiority claims central to the complaint, were appropriate for making the promotional claim in this instance. Pfizer contended that the Committee did not fully consider whether the HAQ-DI and Pain VAS secondary endpoints used to substantiate the promotional claim met the Code requirement that care should be taken to distinguish between mathematically determined statistical significance on one hand and clinical significance on the other. AbbVie did not provide any qualification to the reader that clinical significance for HAQ-DI and Pain VAS measure has not been met in the SELECT-COMPARE study. Therefore, the use of these endpoints in the materials without the clarification that clinical significance was not achieved is in breach of the Code
APPEAL RESPONSE	AbbVie disagreed with Pfizer's assertions and submitted that the Code Committee did not err in its findings. AbbVie contends that in the construction of the claim of superiority for the mean change in measures of Pain and HAQ-DI, AbbVie included immediately below the claim a suitable qualifier which details the rates achieved for the various measures, the p-values, as well as the nature of the endpoints in the clinical study. AbbVie assert that the information clearly provides the reader with sufficient detail to understand both the statistical and clinical relevance of the claim. Further, AbbVie submitted that change from baseline in HAQ-DI and Pain are common outcome measures used in clinical trials and are well understood by rheumatologists Abbvie noted that the changes for HAQ-DI and Pain between RINVOQ and adalimumab represented clinically meaningful differences to patients. AbbVie further argued that the MCID for group means were not defined in th SELECT-COMPARE protocol (or any SELECT-RA trial). AbbVie also outlined that MCID in its truest form is derived on an individual patient level, which may not be directly applicable to a group level.
CODE OF CONDUCT APPEALS COMMITTEE DECISIONS	The Appeals Committee upheld the appeal made by Pfizer, in that it agreed the claim needed additional qualification to ensure the reader could understand the clinical significance.
SANCTIONS AND BOND	The Appeals Committee determined unanimously that the fine imposed by the Code Committee was sufficient and did not require alteration. Further, they agreed with the Code Committee's findings that the claim found in breach should not be used in the same context in future material without appropriate qualification as to the clinical significance. As the appeal was successful, the Appeals Committee determined unanimously to return the bond paid by Pfizer.

Please note: due to the complexity of this complaint and the reference to two editions of the Code, readers should refer to the table above for the Committees specified findings against each edition of the Code. The following consideration of individual complaint/s will only note findings of breach or no breach. Unless specified otherwise, all decisions were made unanimously.

CONSDIERATION OF THE COMPLAINT

The Committee noted that this complaint centred on several items of promotional material that was in circulation between January and July 2020, resulting in both Edition 18 and Edition 19 of the Code applying to this complaint. These materials are categorised as follows:

- Defy Expectations Leave Behind (AU-RNQR-200008) January 2020
- SELECT-COMPARE Leave behind (AU-RNQR-200024) February 2020
- RINVOQ Website (AU-RNQR-200043/4/5) May and July 2020
- RINVOQ Dear Doctor Letter (AU-RNQ-190034) January 2020

The Committee resolved to make determinations against both Codes as appropriate.

Allegation of Abuse of the Code

The Committee first turned to the allegation raised by AbbVie that Pfizer over-simplified resolutions reached between the parties in its complaint cover letter and disagreed with the assertion that it had not implemented modifications to materials discussed during intercompany dialogue. Specifically, AbbVie argued that agreements had been reached for future materials. Further, AbbVie noted that the timeline for intercompany dialogue was inconsistent with recommended guidelines and were implemented to commercially disadvantage AbbVie.

The Committee reviewed the evidence supplied by AbbVie to support this argument. It was agreed that this was a complicated complaint, given the application of both Codes and the complex nature of the materials in question. The Committee recognised its role in only adjudicating on matters that were not resolved during the intercompany dialogue process. It was the Committee's view that there was sufficient evidence that intercompany dialogue was undertaken with purpose and commitment. The Committee agreed that the actions taken during intercompany dialogue satisfied the requirements and were sufficient for the Committee to proceed in hearing the matter.

That said, the Committee recognised that the complaint submitted by Pfizer was difficult to interpret and included a number of elements with conflated arguments. The evidence submitted by both parties by way of intercompany dialogue minutes affirmed the comprehensive engagement between the parties. However, the Committee recognises that the purpose of intercompany dialogue is intentional action on resolving issues, not merely complying by a guideline before proceeding to lodge a complaint. Further, the insistence on corrective action acted as a barrier in reaching resolution in this matter.

The Committee also formed the view that given the environment during 2020, where many organisations were working remotely and efforts focussed on responding to the global pandemic, it was reasonable to expect some degree of mutual flexibility in relation to intercompany dialogue; though only if in doing so neither party were disadvantaged. The Committee agreed that the delays and challenging engagement evident in this matter did not give rise to an abuse of the Code.

Code Precedent

The Committee discussed the evidence submitted by Pfizer to support its arguments for comparative superiority claims, including the determination of a previous, unrelated complaint. This precedent refers to a determination made by the Code Appeals Committee in 2015 relating to the use of mathematically determined statistically significance and clinical significance in promotional materials. The Committee recognised similarities between the cases however note that in the precedent material the referenced study was included in the clinical trials section of the PI, whereas in this current matter refers to a registrational study. It is the Committee's view that AbbVie could properly use the studies to support appropriate promotional claims.

The Committee agreed that companies should be able to rely on the approved PI as the dictum for information relating to the product. That said, the Committee agreed that the Therapeutic Goods Administration is not reviewing product information to approve promotional statements. The Committee further noted that the mere appearance of a statement in an approved PI does not automatically cause the statement to be an appropriate promotional claim. Companies are still responsible for ensuring the appropriate use of any promotional claims.

Claim "Defy Expectations"

The Committee recognised that this complaint centred on the use of the claim "Defy Expectations" and the associated artistically rendered image of a young-appearing woman on a zip line. The claim and imagery were used in the Defy Expectations Leave Behind and the RINVOQ Website.

In discussing this complaint, the Committee noted that during intercompany dialogue it was conceded that the evidence shows marginal statistical and clinical superiority for RINVOQ in select measures. The Committee agreed that the debate concentrates on whether the difference in the performance between the products in itself meets the minimum clinical effect standard. It was acknowledged that Minimal Clinically Important Difference (MCID) has been widely debated with no universally accepted criteria. The Committee further acknowledged that the SELECT-COMPARE trial protocol had already included a predefined MCID protocol, with outcomes that showed a clinically meaningful difference in a number of measures. That said, the Committee were of the opinion that the clinical and statistical differences shown in the SELECT-COMPARE study were marginal.

The Committee turned to the matter of Early Rescue where clinical trial subjects who are not responding adequately to the assigned study agent are switched to another agent in order to increase the chance of achieving adequate response. The Committee note that Early Rescue is a standard ethical protocol and data are reflected accordingly. The Committee agreed that the statistical method used in the SELECT-COMPARE study is valid and reflected current ethics principles, and did not form the view that the Early Rescue element of the trial invalidated the results or their interpretation as reported in the study.

Claim "Defy Expectations" (continued)

In addition, the fact that a superiority analysis had been determined in the study protocol implies the investigators had an expectation that the treatment group may demonstrate superiority. Therefore, to use the term 'defy expectations' does not marry up with a study protocol that demonstrates that superiority had been contemplated prior to study commencement.

The Committee discussed the imagery used consistently throughout the campaign and noted that it reflected what could be possibly identified as an early-stage patient. This imagery is not reflective of the patient cohort in the SELECT-COMPARE, nor is it reflective of the target audience. The Committee recognised that the claims are related to specific aspects of the SELECT-COMPARE study, which the context of the imagery does not match.

The Committee agreed that while statistical and clinical superiority has been shown for RINVOQ in the SELECT-COMPARE study, the claim "Defy Expectations" overstates the superiority observed in this trial. The Committee further noted that other JAK Inhibiters have suggested similar effects, which strengthened its decision. The Committee also agreed that the imagery used did not represent the patient population and therefore misleads the reader. The Committee agreed unanimously that the claim "Defy Expectations" and the imagery of a woman on a zipline were in breach of the Code, both as individual elements and as a combined campaign.

Claim: "RINVOQ + MTX, the first therapy with proven superiority vs adalimumab + MTX for ACR50, Pain and Physical Function at week 12"

As discussed under the previous claim, the Committee accepted the proven clinical and statistical superiority shown in SELECT-COMPARE as the basis for this claim. The Committee noted the primary endpoints in the SELECT-COMPARE study were met, with pre-defined ranked secondary endpoints also met. These endpoints then were the basis for the superiority claims central to this complaint. The Committee agreed that making clinical claims on the basis of secondary endpoints was in this instance appropriate.

The Committee noted the use of the word first in the claim and discussed whether it could be substantiated appropriately. It was recognised that there were other studies that showed other therapies with proven superiority to adalimumab. Therefore, the Committee agreed that the body of evidence did not support the use of the word first in this claim.

The Committee agreed unanimously that the claims of superiority to the week 12 measures is technically correct, consistent with the approved PI and the SELECT-COMPARE study. However, the inclusion of the words 'first therapy' renders the claim misleading and therefore in breach of the Code.

Comparative superiority claims for time points other than 12 weeks

The Committee again referenced the discussions relating to the accepted proven clinical and statistical superiority for RINVOQ, as well as the appropriateness of companies making clinical claims based on prespecified secondary endpoints that align with the body of evidence, and the use of Early Rescue being standard practice.

The Committee noted that the use of p-values represented in multiple charts throughout the SELECT-COMPARE leave behind. Pfizer argued that the data could not be relied upon to make comparative statements due to the impact of Early Rescue, and that the p-values would mislead a reader on the basis of fluctuating treatment numbers. The Committee recognised that materials clearly articulated the study design, which adequately detailed how Early Rescue subjects had been handled during the study.

The Committee agreed that it would have been misleading if the p-values had been omitted, that the materials clearly specify the primary endpoint of 12 weeks and provide sufficient detail on the study design to enable a reader to adequately understand the graphs. The Committee agreed that there was no breach of the Code.

Risk Claim: “Proven Superiority”

The Committee referred to its decision under the previous complaint relating to the claim “RINVOQ + MTX, the first therapy with proven superiority vs adalimumab + MTX for ACR50, Pain and Physical Function at week 12”. The Committee agreed that while this representation did not include “the first therapy” in the claim, it was presented in similar context associated with imagery and claims that had been found in breach. By extension, therefore, it was considered to be an inappropriate comparative claim and was false and misleading. The Committee found a breach of those sections of the Code.

Consistent with previous determinations, the Committee found that this claim was appropriately substantiated and did not find a breach of Section 1.2.2 of Edition 18 of the Code and subsequently no breach of Section 1.1 of Edition 19 of the Code.

Risk Claim: “Consistent Efficacy”

This claim was utilised in the Defy Expectations leave behind, the RINVOQ website, and linked to graphical representations of data in both pieces. The pieces utilised design elements to highlight the effectiveness of RINVOQ compared with placebo.

The Committee noted that the representation provided evidence of three different patient populations to demonstrate effect. The difference in patient populations is noted, as well as a clear statement that results cannot be compared across studies is present. That said, the Committee noted that a reader is naturally inclined to compare the data when represented side-by-side. This is compounded by consistent design elements drawing a reader’s eye to potentially link the data and make comparisons to other products rather than placebo.

Risk Claim: "Consistent Efficacy" (continued)

The Committee agreed that the graph and the claim are adequately substantiated and are not false or misleading. Therefore, the Committee agreed that there was no breach of the Code. That said, the Committee expresses concern that the consistent design elements create a possibility of misleading the reader, and side-by-side comparisons such as this should be carefully considered. In this instance, there was sufficient qualification to displace the concern.

Risk Claim: "Well characterised benefit: risk"

The use of Well characterised benefit appears in multiple locations across the campaign, with qualification on the number of patients and patient years exposed to RINVOQ to establish safety and efficacy.

The Committee recognise that there are data to support the efficacy and safety of RINVOQ to 48 weeks. However, the Committee was of the opinion that the claim implies long-term safety data that are not established. The inclusion of patient years exposure is a subjective marker, and a reader would not be aware of minimum data that would make the claim meaningful. The Committee also noted that representations of the data under the claim pooled studies with different exclusion criteria.

It was on this basis that the Committee agreed that the claim of well characterised benefit was in breach of the Code. Again, with other findings in this complaint, the Committee determined that the data showed efficacy and safety but the claim overstated the outcomes of that data.

Dear Doctor Letter

This complaint refers to a letter circulated to rheumatologists on the registration of RINVOQ and includes references to venous thrombotic events (VTE), claiming consistency with rates in the RA population. The claims were supported again by the SELECT-COMPARE study where the cohort of subjects have cardiovascular co-morbidities. The Committee agreed that as the SELECT-COMPARE study utilised the Early Release protocol, a number of patients from the pool were excluded. This exclusion introduces uncertainty that was not sufficiently qualified in the letter. The Committee acknowledged that it is appropriate for companies to report background incident rates, however the lack of qualification of this claim led the Committee to find to a breach of the Code.

CONSDIERATION OF THE COMPLAINT (continued)

Sanction

The Committee first turned to classification of the breaches found. It should be noted that classifications and sanctions available to the Committee remain consistent across both editions of the Code under which this complaint is being heard. The Committee agreed unanimously that the breaches found represented a moderate breach of the Code, as there was no safety implication on patient wellbeing, but the materials presented would have an impact on the way the medical profession would prescribe the product.

The Committee then unanimously determined to impose the following sanctions:

- Materials using the claims found in breach should be ceased and withdrawn immediately,
- Claims found in breach should not be used in the same context in future material, and
- Pay a fine of $125,000.

The Committee discussed corrective action and agreed unanimously that corrective action was not warranted in this matter.

CONSDIERATION OF THE APPEAL

The Chair explained the process for consideration of an appeal. In order for an appeal to be successful, the Appeals Committee must be persuaded that the findings of the Code of Conduct Committee (Code Committee) involved an error on the basis of which the decisions of the Code Committee should be set aside or varied.

Pfizer representatives were then asked to present their appeal to the Appeals Committee, and the following summarises their presentation and their written submission:

- The appeal pertained to claims of statistical superiority of RINVOQ to HUMIRA for pain and physical function outcomes in promotional material without identifying that the differences are not clinically significant.
- Pfizer accepts all other decisions made by the Code Committee, however contended that the Committee erred when it determined that evidence shows marginal statistical and clinical superiority for RINVOQ in select measures. Pfizer maintained that the HAQ-DI and Pain VAS results are not clinically significant.
- Pfizer further asserted that the Code Committee did not give sufficient weight to Code precedent in making its determination.
- Pfizer outlined that the minimal clinically important difference (MCID) can be defined as the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects or excessive cost, a change in the patient's management.
- Pfizer provided an outline of the HAQ-DI and Pain instruments used by AbbVie in the SELECT-COMPARE trial, which demonstrated how patient reported outcomes are used to assess changes in physical function and pain in patients with Rheumatoid Arthritis (RA). Where comparisons are made regarding patient reported outcomes, differences can be found that are statistically significant that are not clinically meaningful.

- The HAQ-DI has been used for measuring physical function in RA trials for 30 years, with the MCID of 0.22 (for group means) broadly accepted. Pfizer argued that this measure is the threshold for reporting clinically significant differences, regardless of any smaller values being reported in the data.
- Pfizer noted to the Appeals Committee that regulatory bodies globally use clinical importance/relevance in assessment of products. Specifically, Pfizer highlighted submissions made to NICE, FDA, CADTH which noted that RINVOQ showed statistically significant but not clinically significant differences.
- Pfizer outlined to the Appeals Committee that MCIDs have been used by AbbVie in reporting the results from the SELECT-COMPARE study, specifically referencing the MCID values of >10-point decrease in Pain VAS, and >0.22-point decrease in HAQ-DI.
- Pfizer asserted that the SELECT-COMPARE protocol included HAQ-DI MCIDs >0.22 and >0.3, and that the protocol further noted these are established MCIDs in RA studies. Pfizer also noted that the SELECT-COMPARE protocol did not include MCID for pain specifically.
- Pfizer asserted its opinion that these MCIDs for HAQ-DI and Pain VAS are broadly accepted, and that these measures have been used by AbbVie in its analyses of these endpoints in the SELECT-COMPARE trial.
- Pfizer addressed information provided by AbbVie in its written response, specifically AbbVie's rebuttal that other more stringent measures derived from HAQ-DI and pain-VAS show clinical significance of RINVOQ + MTX vs HUMIRA + MTX. Pfizer contended that the other measures presented by AbbVie are highly selective and demonstrate statistical difference applying to small percentages of overall study population at week 12.
- Pfizer then turned to Code precedent when demonstrating Minimally Important Differences (MID) and reiterated that it believed the Code Committee did not place sufficient emphasis on the determination made in the Votrient complaint (complaint 1115 – December 2016). In this case, the Code Committee determined that in omitting the established MID, the material was misleading. Pfizer argued that the same should be determined in this matter.
- In summary, Pfizer sought that the Appeals Committee determine that superiority claims are qualified with a statement such as: "Differences in RINVOQ + MTX and HUMIRA + MTS for HAQ-DI measures were below the MCID of >0.22 and for pain were below the MCID of >10mm.

AbbVie was invited to provide its response to the Pfizer appeal, and the following summarises that response:

- AbbVie noted that, during its presentation, Pfizer had elaborated on the history of the MCID in RA, including the limitations acknowledged by both parties. AbbVie acknowledged that an MCID of >0.22 is well used in RA but asserted that definitions have evolved over time.

- AbbVie outlined the requirements relevant during the development and publication of the materials in question; namely Editions 18 and 19 of the Code. Specifically, AbbVie contended that the claim was sufficiently qualified and included the study design, and therefore complied with both editions of the Code. Further, AbbVie asserted that the claim is supported by robust clinical data, clearly qualified with endpoints, rates, and p-values, and study design shown. AbbVie noted that the changes for HAQ-DI and Pain between RINVOQ and adalimumab represented clinically meaningful differences for patients.
- AbbVie demonstrated to the Appeals Committee evidence that showed Group Mean Change from baseline, explaining how HAQ-DI is used in RA. Using data from the SELECT-COMPARE study, showing RINVOQ is superior to HUMIRA at week 12, with the level of improvement maintained to 72 weeks. This SELECT-COMPARE study was the basis for registration and assessed by the TGA. This data was then included in the approved Product Information for RINVOQ, which confirms superiority over adalimumab in ACR50, HAQ-DI and pain measures.
- AbbVie further demonstrated that there is a clinically meaningful difference for RINVOQ over HUMIRA at week 12. The treatment goal in RA is to achieve remission whereby the patient feels as close to being disease free as possible. This is assessed by achieving close to normal physical function. A normative value for HAQ-DI is reflective of the general population. The achievement of a HAQ-DI score of <0.25 by an individual patient is considered to match the physical function capability expected of a member of the general population.
- AbbVie presented data that represented the body of evidence in support of clinical significance. These data showed that more patients on RINVOQ achieved greater improvements in pain compared to HUMIRA across all thresholds.
- AbbVie contested that the Code Committee did not err in its determination that statistical and clinical superiority has been shown for RINVOQ in the SELECT-COMPARE study. Further, AbbVie agreed with the Code Committee's statement that MCID had been widely debated with no universally accepted criteria.
- AbbVie noted that under Edition 19, the minimum clinically important difference, when available and defined for the trial, is the accepted level of clinical significance. AbbVie argued that the MCID for group means were not defined in the SELECT-COMPARE protocol (or any other SELECT-RA trial). The claims in question relate to the comparison of group mean changes from baseline of RINVOQ versus HUMIRA. AbbVie contend that there was sufficient detail included to enable the expert reader to understand the significance of the data.
- AbbVie expanded on the argument regarding MCID in the SELECT-COMPARE trial, noting it had not been defined for Pain at the individual level. The HAQ-DI was defined at the individual level as an exploratory outcome, it was not statistically different between RINVOQ and HUMIRA. AbbVie reiterated that claims were made at a group level, not at an individual patient MCID level.

- AbbVie provided the opinion of an independent expert who noted that "*there is no universal MID…the MID is not an immutable characteristic, but may vary by population and context. At both the group and patient level, the MID may depend on the clinical context and decision at hand, the baseline from which the patient starts, and whether they are improving of deteriorating.*" It was the expert's further opinion that specific estimates of MIDs should not be overinterpreted. Further, MCID in its truest form is derived on an individual patient level, which may not be directly applicable to a group level comparison.
- AbbVie highlighted that MCID is the lowest bar for improvement, and that more stringent measures may be required to discrivinate between active therapies
- AbbVie turned to the precedent raised again in the appeal by Pfizer. AbbVie noted that the in the Votrient case, the MCIDs for group level were defined in the study. Further, the case demonstrated the use of MCIDs for mean versus individual measures. Two measures were defined in the Votrient trial – a higher level for individual response; and a lower level for group assessment. AbbVie maintained its argument that the Votrient case has no bearing on the materials presented.
- AbbVie summarised its response noting that the claims are supported by robust clinical data, clearly qualified with study design shown – all of which provide the intended audience of knowledgeable rheumatologists with sufficient detail to understand both the statistical and clinical significance of the data. AbbVie contended that it would be misleading to qualify that the endpoints of HAQ-DI and Pain as having not met clinical significance. Further, AbbVie noted it would be inconsistent with the regulator's assessment of superiority in the RINVOQ label for these endpoints.

The Appeals Committee sought clarification from AbbVie in relation to the statements made in FDA, CADTH, and NICE documents which determined no clinical significance is shown for RINVOQ. AbbVie acknowledged these statements and noted that each agency assesses the data for different purposes, whether that is as a regulator determining efficacy or determining suitability for funding. The assessments made by FDA and NICE are through the lens of a payor, determining cost-effectiveness. It is also unclear from the papers how the MCID is being applied, noting that it is assumed it is being applied at a group level though no studies have validated it at a group level.

The Appeals Committee queried the post-hoc analysis provided to affirm the body of evidence that supports the claim, seeking to understand the timeline of development for those data. AbbVie confirmed that they were available at the same time the materials were in circulation. AbbVie believed it was important to share this data with the Appeals Committee to demonstrate the change from baseline, which represents a clinically meaningful difference. AbbVie confirmed that the data presented to the Appeals Committee is published or Data on File, however as it is exploratory data it is insufficient to support a claim.

The Appeals Committee questioned the study protocol, and the lack of definition of MCID for group means and whether this was a limitation of the SELECT-COMPARE study. AbbVie recognised that MCID for group means has not been defined in this or in any other SELECT-RA trial for modern active treatments. AbbVie reiterated that the normative values for HAQ-DI are a substitute for MCID, and that as these are stringent data cuts, they should be more influential than the MCID.

Pfizer was then given the right of reply to AbbVie's presentation. The following summarises that response:

- Pfizer acknowledged that this complaint and associated appeal included complicated and nuanced materials.
- Pfizer reasserted its opinion that the MCID of >0.22 is broadly accepted and should be used to qualify claims of clinical significance.
- Pfizer noted that the additional studies looking at normative values presented by AbbVie were not specified in SELECT-COMPARE, were post hoc analyses and entirely exploratory.
- Pfizer contended that there was an element of cherry-picking data by AbbVie in its presentation to the Appeals Committee. These endpoints demonstrated favourable outcomes only.
- Pfizer disputed claims that MCIDs were not defined in the protocol. Also, Pfizer noted RINVOQ is a unique modern therapy, that reference to MCIDs is a generally acceptable norm across trials and that it is a general practice across RA trials and literature.
- Pfizer disagreed with AbbVie's claims that it would be difficult to consider adding information about the clinical significance to future statements. Pfizer asserted that stating that the measure was below an MCID is not difficult.

The Chair thanked the company representatives and asked them to retire from the meeting to allow the Appeals Committee to deliberate.

The Appeals Committee first turned to the matter of the claim of superiority reflected in the Approved Product Information. The Appeals Committee accepted that comparisons across regulatory agencies are challenging, given their differing points of view (payor, regulator, or both). Further, the Appeals Committee confirmed the Code Committee's determination that companies should be able to rely on the approved PI, but that companies are responsible for ensuring the appropriate use of any promotional claims. That said, the Appeals Committee determined that where claims for clinical superiority are made for a general population of patients it is important that readers can distinguish what these claims for clinical superiority are based on, so that they can make their own evaluation.

The Appeals Committee discussed the interpretation of MCID, and the relevance of this measure in relation to the claims made. The Appeals Committee acknowledged that there are established MCIDs in RA as expressed by both Pfizer and AbbVie in their presentations, however with differing points of view as to the applicability in this situation.

However, the Appeals Committee further noted the post hoc analyses of HAQ-DI and Pain VAS results used by AbbVie to justify the clinical superiority claim to the Code Committee and Appeals Committee. The Appeals Committee noted, however, that readers would not have been aware that these were the criteria that AbbVie were using to support the clinical superiority claim in respect of HAQ-DI and pain-VAS.

The Appeals Committee determined that the claim was in breach, as there was insufficient reference to support the clinical superiority claim. The Appeals Committee reaffirmed that the claims of superiority for RINVOQ + MTX vs adalimumab + MTX are included in the approved PI. However, although this may infer clinical superiority, on the basis of the HAQ-DI and Pain-VAS data presented in SELECT-COMPARE, this remains an inference unsupported in the advertising material.

In turning to the discussion of the inclusion of a qualifier to identify that RINVOQ failed to meet the generally accepted MCIDs for HAQ-DI and Pain VAS, the Appeals Committee acknowledged that there was conjecture on what an appropriate measure would be (e.g. between active comparator, between group, etc). It is for this reason that the Appeals Committee determined that it may not be appropriate to include the generally accepted MCIDs based on an active comparator versus placebo. The Appeals Committee determined, however, that additional qualification on the basis for determining clinical superiority is needed to enable the reader to interpret the data.

Sanctions and Bond

The Appeals Committee determined unanimously that the fine imposed by the Code Committee was sufficient and did not require alteration. In addition to the sanctions imposed by the Code Committee, the Appeals Committee agreed that where any inference of clinical superiority is made in future material, appropriate qualification must be included so that the reader can adequately interpret the basis for clinical superiority.

As the appeal was successful, the Appeals Committee determined unanimously to return the bond paid by Pfizer.