Medicines Australia Code of Conduct Quarterly Report October - December 2019

The quarterly report of determinations of the Medicines Australia Code of Conduct and Appeals Committees

The Medicines Australia Code of Conduct was introduced in 1960 and is currently operating under Edition 18 (effective 16 May 2015).

This report covers all complaints finalised between October to December 2019. Complaints finalised during this period were in relation to materials or activities conducted under Edition 18 of the Code.

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.

Quarterly Reports preceding this Report are available from the Medicines Australia website: http://medicinesaustralia.com.au/code-of-conduct/code-of-conduct-reports/

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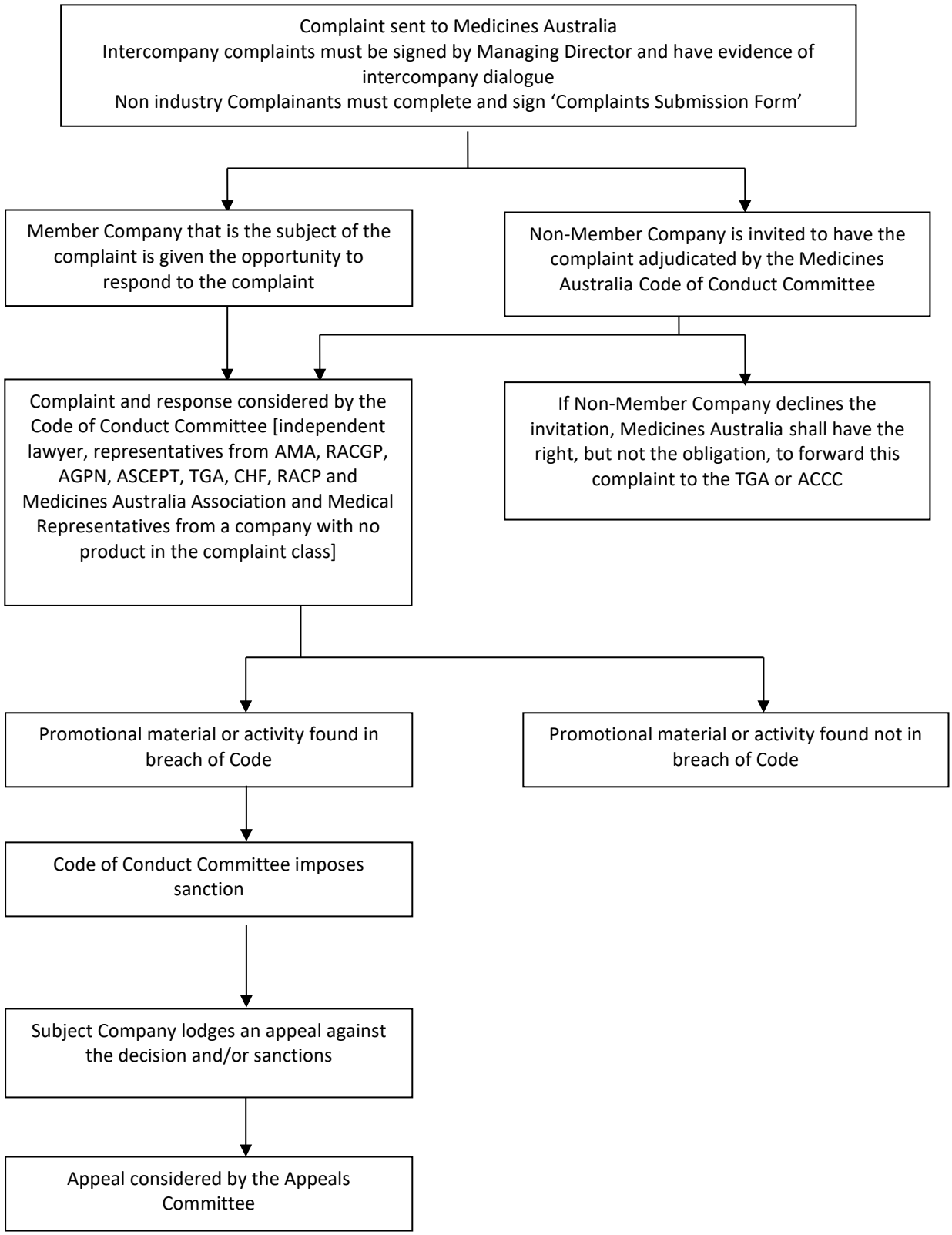
How do I obtain a copy of the Code?

Copies of Edition 18 of the Code (effective from 16 May 2015) and the Guidelines that accompany the Code are available from the website (http://medicinesaustralia.com.au/code-of-conduct/code-of-conduct-current-edition/)

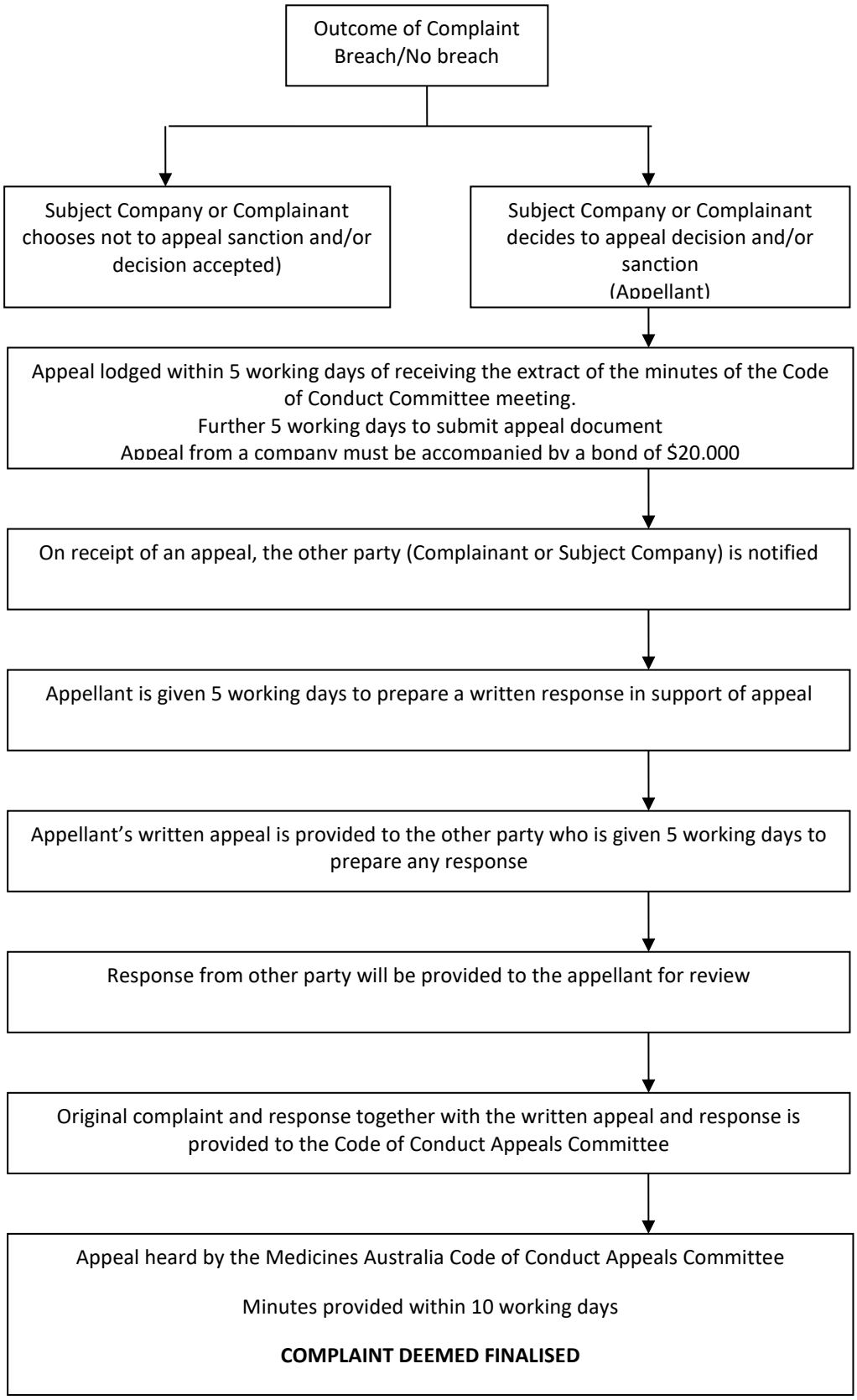
Contents

Medicines Australia Code of Conduct Complaints Handling Process



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

Medicines Australia Code of Conduct Appeals Committee Procedures



Committees and Secretariat

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.

Committee Member Biographies

Brief biographies for all Code, Appeals and Monitoring Committee members are available on the Medicines Australia website https://medicinesaustralia.com.au/code-of-conduct/committee-membership/

Code of Conduct Committee

Full Members (Voting rights)

- Independent Lawyer (Chairman) selected from a panel of up to 4 trade practices lawyers

Representatives nominated by:

- Australian General Practice Network (AGPN)
- Australian Medical Association (AMA)
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)
- Consumers Health Forum of Australia (CHF)
- Royal Australasian College of Physicians (RACP)
- Royal Australian College of General Practitioners (RACGP)
- Medicines Australia Association Representatives (maximum 3)
- Medicines Australia Medical/Scientific Directors (maximum 2)

Observers (No voting rights)

- Therapeutic Goods Administration (TGA)
- Medicines Australia member companies' employees (maximum 2)
- Observer nominated by Medicines Australia (maximum 1)

Advisors (No voting rights)

- Secretary, Code of Conduct Committee
- Medicines Australia Chief Executive Officer or delegate
- Medicines Australia officer responsible for Scientific and Technical Affairs

Appeals Committee

Full Members (Voting rights)

- Independent Lawyer (Chairman) selected from a panel of up to 4 trade practices lawyers

Representatives nominated by:

- The College and/or Society associated with the therapeutic class of the product subject to appeal
- The target audience to which the activity was directed eg: AMA, RACGP
- Consumers Health Forum of Australia (CHF)
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT)
- Medicines Australia Association Representatives (maximum 2)
- Medicines Australia Medical/Scientific Director (maximum 1)

Advisors (No voting rights)

- Secretary, Code of Conduct Committee
- Medicines Australia Chief Executive Officer or delegate

Sanctions that can be imposed by the Code of Conduct Committee

Sanctions

If the Code of Conduct Committee finds a breach of the Code it may impose a sanction on the company found in breach. In order to determine an appropriate sanction the Committee will refer to the "Guidelines for determining Code sanctions" which are available on the Medicines Australia website. The following sanctions may be imposed:

Withdrawal of material or activity

Where promotional material or activity is found in breach of the Code the Committee will always require the company to cease use of the item or cease undertaking the activity.

Corrective letter

The Code of Conduct Committee will determine the audience for the letter based on the original distribution of the material found in breach of the Code.

Corrective advertisement

A corrective advertisement must be placed in the same publication as that found in breach of the Code.

Fines (applicable under Edition 18 of the Code)

Breach	Fine
Technical breach Minor breach	Maximum of $100,000
Moderate	Maximum of $150,000
Severe breach	Maximum of $200,000
Severe breach where activities completed Repeat of previous breach	Maximum of $250,000
Cumulative fine for multiple breaches	Maximum of $300,000
Failure to complete corrective action in 30 calendar days Failure to pay a fine in 30 calendar days	Maximum of $50,000
Abuse of the Code (in accordance with Section 25)	Maximum of $200,000

Table of finalised complaints October - December 2019

No.	Subject Company	Material or Activity	Product	Complainant	Outcomes	Sanction
1154	Seqirus (Australia) Pty Limited	Promotional Material	Fluad® (Inactivated influenza vaccine)	Sanofi-Aventis Australia Pty Ltd (trading as Sanofi Pasteur)	Breach 1.1, 1.2.2, 1.3 and 1.8	Fine $80,000
1156	Pfizer Australia Pty Ltd	Promotional Material	Xeljanz® (tofacitinib citrate)	Takeda Pharmaceuticals Australia Pty Ltd (Takeda)	Breach 1.1, 1.2.2, 1.3	Fine $25,000
1157	Bayer Australia Limited	Promotional Material	Xarelto® (rivaroxaban)	Bristol-Myers Squibb Australia and Pfizer Australia Pty Ltd Alliance	Breach 1.1, 1.2, 1.3 and 1.8	Fine $150,000
1158	Eli Lilly Australia (ELA)	Professional Conduct	Taltz (Ixekizumab (RCH))	Healthcare Professional	Breach 9.2	Fine $15,000

Fluad® Promotional Materials

Complaint	Subject Company	Product	Complainant
1154	Seqirus (Australia) Pty Limited	Fluad® (Inactivated influenza vaccine)	Sanofi-aventis Australia Pty Ltd (trading as Sanofi Pasteur)

Complaint
Sanofi Pasteur alleged that four promotional pieces for Fluad vaccine published by Seqirus are in breach of the Code of Conduct because they are inconsistent with the Product Information (PI) and contain claims that are unsubstantiated, false and misleading.

Sanofi Pasteur alleged that the overall message of the promotional materials is that Fluad is a 'universal vaccine' that can prevent influenza caused by virus strains that are not contained in the vaccine, and provides a longer duration of protection than standard vaccines. Sanofi Pasteur argued that, by linking immunogenicity with clinical benefit, Seqirus had breached the Code of Conduct (Sections 1.1, 1.2.2, 1.3 and 1.8).

In its complaint, Sanofi Pasteur identified four specific claims as being of particular concern:

- *"The MF-59 adjuvant improves the magnitude, breadth and persistence of the immune response even in patients with co-morbidities, compared with standard dose non-adjuvanted influenza vaccines" (PIECES 1 and 4);*
- *''Adding MF59 adjuvant to the vaccine improves the magnitude, breadth and persistence of the immune response, compared with standard dose non-adjuvanted vaccines" (PIECES 2, 3 and 4);*
- *"MISMATCH: significant antibody rises after immunization with FLUAD has been shown against heterologous strains antigenically different from those included in the vaccine" (PIECES 3 and 4);*
- *"PERSISTENCE: FLUAD demonstrated significantly higher antibody responses against homologous H3N2 strain vs standard dose non-adjuvanted TIV up to 12 months after vaccination" (PIECES 1, 3 and 4)*

In addition, Sanofi Pasteur noted that the claims made in pieces 3 and 4 were directly under the heading of "Benefits" of Fluad, which is not defined. Sanofi Pasteur referred to the visual depiction of a jigsaw puzzle, which, combined with the headings of "Magnitude", "Persistence" and "Mismatch", it alleged suggested that Fluad provides a longer duration of protection and broader range of protection against strains not in the vaccine, and that it does this better than any other influenza vaccine.

Sections of the Code
The promotional materials were alleged to be in breach of the following Sections of Edition 18 of the Code:

- Section 1.1 Responsibility
- Section 1.2.2Level of Substantiating Data
- Section 1.3 False or Misleading claims
- Section 1.8 Comparative Statements

Response
Seqirus denied that the Fluad promotional materials were in breach of the Code of Conduct. Seqirus stated that the claims of breadth and persistence of immune response in the materials in question are factual, substantiated and consistent with the Fluad® Approved Product Information (PI).

Seqirus acknowledged that some claims about breadth and persistence of immune response in the materials could be clarified by the inclusion of relevant qualifiers.

Piece 1 was a healthcare professional media release; Piece 2 was an advertisement and Piece 3 was a once off journal insert. These materials could not be withdrawn. Seqirus did withdraw a leave behind Piece 4, which contained similar claims to the other materials, on 29 May 2019.

During correspondence with Sanofi Pasteur and intercompany dialogue, Seqirus stated that it had provided references and explanations as to why the claims of breadth and persistence of immune response in the materials in question are factual, substantiated and consistent with the Fluad® Approved Product Information (PI). During intercompany dialogue, Seqirus agreed to add a qualifying statement with respect to immune correlates of protection and clinical efficacy to avoid any perception that claims relating to immunogenicity are misinterpreted as claims of efficacy.

Seqirus alleged that Sanofi Pasteur has included various new elements in the complaint that Seqirus did not have the opportunity to address through correspondence or at intercompany dialogue.

Code of Conduct Committee decisions
The Code of Conduct Committee made the following decisions in relation to the promotional materials:

- Promotional Item 1: The Committee found by unanimous decision that the promotional material was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code;
- Promotional Item 2: The Committee found by unanimous decision that the promotional material was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code;
- Promotional Item 3: The Committee found by unanimous decision that the promotional material was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code;
- Promotional Item 4: The Committee found by unanimous decision that the promotional material was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code;

Sanctions
The Committee found by majority decision that the breaches were minor, as defined in the Code of Conduct (the materials had no safety implications for patients' well-being and will have no major effect on how the medical profession will prescribe the product).
- The Committee determined by majority decision to impose a fine of $40,000.
- The Committee determined by majority decision that no corrective letter should be required.

Consideration of the complaint

The Secretariat tabled a letter from Seqirus dated 15 August, which updated the company's response to the complaint. The letter informed the Committee that Seqirus would be producing a new promotional brochure for Fluad for use at an international conference to be held overseas. The Committee noted the letter and agreed that it was not relevant to the Committee's consideration of the materials subject to complaint.

The Chair summarised the complaint, noting that the central issues were the scope of the claims about the benefits and effects of Fluad and whether there is evidence to support such a claim. The Chair noted that there was evidently some public health rationale for regarding antibody response as a proxy for clinical effect and for the use of a vaccine with adjuvant.

The Committee noted that claims must be able to be substantiated; if there is no clinical evidence, the relevant supporting evidence for efficacy of the vaccine needs to be clear to a reader through appropriate qualification of the claims.

The Committee further noted that two of the claims refer to "the immune response" and two refer to "antibody response", which are not equivalent or interchangeable terms. Either term could be interpreted as meaning a clinical response, for which there did not appear to be any evidence. The Committee considered that the promotional materials implied that there was a direct correlation between immune response and clinical protection. An increase in "antibody response", which is a more specific term than "immune response", doesn't necessarily mean there is an increase in clinical protection. The line of correlation between antibody response and clinical effect is not necessarily direct or linear. The clinical effect might taper off after the antibody response reaches a certain level.

It was noted that influenza vaccines are produced annually, with the included virus strains determined each year. In the promotional materials subject to complaint, the claims are for the clinical benefits of the adjuvanted Fluad vaccine compared with the standard trivalent vaccine available to a wider demographic, whereas the only relevant comparison would be with the high-dose influenza vaccine for people aged 65 years and over.

The Committee discussed the claims under the heading "Mismatch". These claims are for broader efficacy against heterologous virus strains that are not included in Fluad. However, there was no evidence that Fluad has a clinical effect on viral strains other than those included in the vaccine. In addition, the comparison between the adjuvanted trivalent vaccine for people 65 years and over, Fluad, and the standard quadrivalent vaccine leads to a less clear comparison. This is compounded by the fact that the meaning of "immune response" is much broader than just "antibody response".

The Committee noted that Sanofi Pasteur had also drawn attention in its complaint to the reference in claim 4 to the persistence of the antibody response for "up to 12 months after vaccination". Sanofi Pasteur alleges that the claim was misleading and could impact on prescribing because healthcare professionals could think that annual vaccination was not necessary. Although prescribers of influenza vaccine, who are mainly GPs, generally do not have a choice between vaccine brands if they are prescribing under the National Immunisation Program (NIP), any claims must be correct and able to be substantiated.

The Committee referred to the Fluad Product Information, where it is stated that it has not been established that there is an absolute correlation between the antibody response against influenza antigens from strains causing disease and reduction in clinical symptoms. This is not adequately reflected in the promotional materials.

The Committee reviewed the four items of promotional material subject to complaint.

Item 1 – Healthcare professional media release dated 15 April 2019 (SEQ/FTIV/0419/0037)
The Committee discussed the third, fourth and fifth dot points on page one of the release which contain claim 1 and a similar claim to claim 4 subject to complaint. The Committee considered that these claims went further than the approved PI and evidence.

The claims refer to the persistence of the immune response due to the adjuvant included in the vaccine, but the claims are not qualified by stating that the persistence relates only to one virus strain included in the vaccine, A/H3N2. In addition, the second and third dot points refer to "immune response", which, as already noted, has a broader meaning than "antibody response", and is a clinical claim that has not been adequately substantiated.

The Committee noted that the fifth dot point on page one of the media release refers to Fluad inducing increased antibodies to heterologous vaccine strains, which is consistent with the mechanism of action described on page 7 of the Product Information (PI).

The Committee concluded that the claims in dot points three and four of the media release were in breach of the Code because they claimed that Fluad amplified or improved the magnitude, breath and persistence of the immune response, without any qualification confining their scopeto a higher antibody response. In addition, the claims in these dot points were not qualified to indicate that they only relate to people aged 65 years and older and therefore could be misinterpreted as relating to a broader population of people aged less than 65 years. In unanimous decisions, the Committee found that the claims were false and misleading, unable to be substantiated and were not consistent with the approved product information and in breach of Sections 1.1, 1.2.2 and 1.3 of the Code.

The Committee discussed whether the claims were in breach of Section 1.8, comparative claims. The claims compared Fluad with standard non-adjuvanted trivalent vaccines, claiming improved magnitude, breadth and persistence of the immune response, which was misleading because it referred to "immune response" rather than "antibody response". The Committee unanimously found that the claims were in breach of Section 1.8 of the Code.

Item 2 – Advertisement published in Australian Doctor (SEQ/FTIV/0318/0006(1)a) March 2019
Item 2 contained claim 2 subject to complaint, which claimed that Fluad improves the magnitude, breadth and persistence of the immune response. For the same reasons as determined in relation to the equivalent claim in Item 1, the Committee unanimously determined that the advertisement was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code of Conduct.

The Committee raised a concern in relation to the claim in the advertisement that Fluad is "tailored" to help protect against influenza, but did not make any decision in relation to this claim because it was not part of the complaint by Sanofi Pasteur and Seqirus had not had the opportunity to respond on this aspect of the promotional material.

Item 3 – Fluad 4 page leave behind (SEQ/FLUD/0419/0061), April 2019

The Committee reviewed the promotional item, and particularly the promotional claims on the page headed "Benefits of adjuvanted influenza vaccine (Fluad). Claims 2, 3 and 4 were included in this promotional piece in two dot points under the heading and in the tiles under the dot points.

The Committee noted that in the "Mismatch" tile, the claim (claim 2 in the complaint) refers to "significant antibody rises" after immunisation with Fluad, which is almost exactly the same wording as included in the PI (page 7). The "Persistence" tile includes claim 4, which also refers to antibody responses rather than immune response. However, the two dot points under the heading and the claim in the "Co-morbidities" tile each refer to the "immune response" to the Fluad vaccine, which the Committee considered to be in breach of the Code. The Committee considered that the claims conflated a clinical effect with "immune response" which cannot be substantiated, and which is false and misleading. The Committee noted that the Fluad PI (page 8) states that antibody titres measured against influenza antigens are a surrogate marker of efficacy, but an absolute correlation between magnitude of antibody titre and reduction in clinical symptoms has not been established. It follows that the broader claim of immune response cannot be directly related to clinical efficacy.

In addition, the Committee considered that each of the claims should have been qualified that they only relate to people who are 65 years and older, or the claims could be misinterpreted as claims in people under 65 years of age. There is no data in the PI or in the reference by Frey et al that suggests that the adjuvanted trivalent vaccine is more effective than the standard trivalent influenza vaccine in people under 65 years of age.

For the same reasons as determined in relation to the claims in Item 1, the Committee unanimously determined that the Fluad leave behind was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code of Conduct.

Item 4 – 6-page Fluad leave behind (SEQ/FLUD/0418/0007(1), March 2019

The Committee reviewed the promotional item. Claims 1, 2, 3 and 4 were included in substantially the same form in this promotional piece on pages 2, 3 and 5 of the item. Similarly to item 3, on the page headed "Benefits of Adjuvanted Influenza vaccine (Fluad)", the claims were not qualified as being only related to people aged 65 years and over.

For the same reasons as determined in relation to item 1 (the media release) and item 3 (4-page leave behind), the Committee unanimously determined that the Fluad leave behind was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code of Conduct.

Sanctions

The Committee discussed the severity of the breaches, having found each of the promotional materials in breach of Sections 1.1, 1.2.2, 1.3 and 1.4 of the Code. The Committee noted that the core issue in this complaint was the use of the term "immune response" rather than "antibody response" and the lack of qualification of the claims to indicate that they only related to people aged 65 years and over.

The Committee discussed whether a corrective letter was warranted. The Committee considered that there would not be any major impact on prescribing behaviour and no risk of patient harm. However, the Committee considered that materials directed at healthcare professionals must be

precise, correct and consistent with the PI and other supporting evidence. Companies have a duty to ensure that healthcare professionals are not going to be misled by promotional claims.

The Committee found by majority decision that the breaches were minor, as defined in the Code of Conduct (the materials had no safety implications for patients' well-being and will have no major effect on how the medical profession will prescribe the product).

- The Committee determined by majority decision to impose a fine of $40,000.
- The Committee determined by majority decision that no corrective letter should be required.

Appeal lodged by Seqirus

Seqirus disagreed with the Code of Conduct Committee's reasons, which defined the core issues in the complaint to be the use of the term "immune response'' rather than "antibody response" and the lack of qualification of the claims to indicate that they only related to people aged 65 years and over.

Seqirus proposed that the Appeals Committee should determine that the Code Committee had erred in its decision making in finding the term "immune response" incorrect. Seqirus acknowledged that the term "antibody response" is a more specific term than "immune response". However, Seqirus argued that it is not technically incorrect to use the term "immune response" in the context of the promotional pieces.

Seqirus also contended that the Code Committee had erred in its decision that by not qualifying each claim that it related to an over 65 year old population made the claims misleading. Seqirus identified a number of statements within the piece that, it argued, supported the overall qualification of the claims to be for the over 65 year old population.

Sanofi Pasteur's response to Seqirus' Appeal

In its response to Seqirus' appeal, Sanofi Pasteur rejected the argument that the use of "immune response" is not incorrect, noting that its main objection was to this term when used in conjunction with terms such as 'magnitude', 'breadth', 'persistence' and 'benefits', where this implies clinical efficacy.

However, Sanofi Pasteur also disagreed with Code Committee's assertion that the pieces were inadequately qualified to relate to the over 65 year old population. Sanofi Pasteur noted there may have been instances where it could have been clearer for the reader by additional qualification, but overall the items appeared to relate to the correct patient population.

Sanofi Pasteur agreed with the Code Committee's decisions relating to comparing the antibody response of Fluad with that of a non-adjuvanted standard dose trivalent influenza vaccine. Sanofi Pasteur argued that the Fluad PI states that increased efficacy compared with non-adjuvanted influenza vaccines has not been demonstrated.

Sanofi Pasteur acknowledged Seqirus' request for clarification about whether a comparison with non-adjuvanted trivalent influenza vaccine can be used at all. Sanofi Pasteur noted that it was not the use of the comparative data that was in question, but the way in which it was used in the promotional materials subject to complaint. Sanofi Pasteur accepted that the data from the PI should be able to be used as long as it is presented in an appropriate manner.

Appeal lodged by Sanofi Pasteur

Sanofi Pasteur stated in its appeal submission that it agreed with the findings of the Code Committee, but disagreed with the decision to find the breaches 'minor' because they would have no effect on how the medical profession will prescribe the product. In addition, Sanofi Pasteur argued that the complaint comprised of four items of promotional material, which it claimed demonstrated the widespread dissemination of the claims. Sanofi Pasteur requested that the Appeals Committee determine that the promotional materials would impact how the medical profession prescribe the product, therefore elevating the breaches beyond the threshold of 'minor'.

Sanofi Pasteur rejected the Code Committee's implication that, because Fluad is the only influenza vaccine available on the National Immunisation Program (NIP) for patients over 65 years, GPs do not have a choice as to which vaccine to prescribe. Sanofi Pasteur stated that over 10,000 patients had received the privately prescribed vaccine in the 2019 flu season.

Sanofi Pasteur also disagreed with the Code Committee's assertion that the core issue in the complaint was the use of the term "immune response" rather than "antibody response". Sanofi Pasteur asserted that the issue is the use of immunologic data to imply vaccine efficacy, which cannot be substantiated. Sanofi Pasteur argued that the misleading impression that Fluad has a clinical response that is better than the standard non-adjuvanted influenza vaccine should be corrected through a corrective letter.

Seqirus' response to Sanofi Pasteur's Appeal

Seqirus denied that the Code Committee had erred in its decision making in finding that the breaches were minor in nature. Seqirus did not agree that the materials would have had an effect on how the medical profession would prescribe Fluad. Seqirus argued that availability of the vaccine via the NIP is a major factor in deciding which vaccine to prescribe and it was unlikely that the promotional materials had inappropriately led to increased use of Fluad. Therefore, any breaches found do not meet the threshold for elevating the complaint beyond minor.

Seqirus argued that Sanofi Pasteur had not provided any evidence to support its claims that the Code Committee had erred in its decision making. Moreover, Seqirus had withdrawn the materials promptly and had proposed modifications to claims and qualifiers when these issues were raised during intercompany dialogue. Seqirus noted that Sanofi Pasteur did not accept or acknowledge these actions during intercompany dialogue, but had persisted with the complaint in which Sanofi Pasteur had introduced additional matters to which Seqirus had not had sufficient opportunity to address.

Code of Conduct Appeals Committee decisions

- Promotional Item 1: The Appeals Committee unanimously upheld the decision that the promotional material was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code
- Promotional Item 2: The Appeals Committee unanimously upheld the decision that the promotional material was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code
- Promotional Item 3: The Appeals Committee unanimously upheld the decision that the promotional material was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code
- Promotional Item 4: The Appeals Committee unanimously upheld the decision that the promotional material was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code

Sanctions

- The Appeals Committee upheld the appeal by Sanofi Pasteur and agreed by majority that the breaches were moderate, as defined in the Code of Conduct (the materials had no safety implications for patients' well-being and may have an effect on how the medical profession will prescribe the product).
- The Appeals Committee unanimously determined to increase the fine to $80,000.
- The Appeals Committee unanimously determined that Seqirus should be required to distribute a corrective letter to all healthcare professionals who had received the promotional materials or media release, with a template draft letter to be provided by Medicines Australia.

The Appeals Committee also determined unanimously that the $10,000 bond paid by Seqirus will be retained by Medicines Australia, and the $10,000 bond paid by Sanofi Pasteur will be returned in full.

Consideration of the Appeals

The Chair welcomed the Appeals Committee to the meeting and noted that this was an unusual matter where both companies had appealed the decisions. The Chair noted that each company will be given sufficient time to put forward both their appeal as well as their response to the other company's appeal. The Chair noted there was some overlap between the appeals, in addition to points of clarification in relation to the Code Committee's reasons for decision.

The Appeals Committee initially sought to understand the commercial impact of promotional activities on the National Immunisation Program (NIP) allocation of influenza vaccine in the market, and specifically whether there may be an impact on prescribing of Fluad or Sanofi Pasteur's product Fluzone. The Appeals Committee noted that, in the past, the method of allocating different vaccines to GP practices may have contributed to confusion about which product to administer to adults and children. Therefore, now the vaccines distributed under the NIP are randomly allocated to clinics so that one practice always receives the same vaccine, leaving little choice for healthcare professionals when administering these vaccines under the NIP.

The Appeals Committee also noted that the influenza virus strains for each year are only identified and released to manufacturers early in the year, which, due to the time required to manufacture the vaccines, does not allow companies to complete clinical trials on which to base efficacy claims.

The Chair then invited the company representatives to join the meeting.

The Chair advised the companies that they each have the opportunity to present both their appeal and their response to the other company's written appeal, as well as to provide a response to any matters raised in the hearing.

The Chair explained the process for consideration of an appeal. 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.

Before asking the companies to present their appeals, the Appeals Committee sought to clarify the commercial impact of the NIP on vaccine suppliers. Specifically, would a company supplying a vaccine on the NIP be penalised if fewer doses were administered, or incentivised if more doses were administered. The Companies both noted that if fewer doses were administered, there is no loss of company revenue as the government orders and receives a specific number of doses of the

product. The Companies did confirm, however, that if additional doses are required, companies would receive additional income from supplying more than the initial ordered NIP quantity.

The Seqirus representatives were then asked to present to the Appeals Committee, and the following summarises their presentation:

- Seqirus noted that the Code Committee minutes stated that the core issues in the complaint were the use of the term 'immune response' rather than 'antibody response' and the lack of qualification that the claims related to the population aged 65 years and over. Seqirus argued that the Code Committee had erred in their rationale for finding the four promotional items in breach of the Code on the basis of these issues.
- Seqirus stated that the term 'immune response' and the way it is used in the pieces is consistent with the use of the term by TGA and the Commonwealth Chief Medical Officer to describe adjuvanted influenza vaccines.
- Seqirus are concerned that if the reasons for the Code Committee's decision were to stand, the company will not be able to use the information contained in the Fluad Product Information.
- Seqirus noted that the only way patients could receive Fluad is through the NIP; it is not sold on the private market. It is not available other than for patients over 65 years of age and through the NIP.
- Seqirus addressed the qualification of the claims to the over 65 years of age population, and demonstrated to the Committee the ways that all of the pieces had been clarified as relating to the over 65 population. For example, the first point in the media release states that the vaccine is available for the over 65 years age group and the population is referred to four other times in the media release. Each of the promotional pieces refers to "older patients" and includes a statement referring to the 65 years and over age group. Seqirus argued that taking one dot point among a series of appropriately qualified statements is not appropriate and does not take into account the full context of each the pieces.
- Seqirus then discussed the matter of the terms 'immune response' and 'antibody response'.
- Seqirus argued that the use of the term 'immune response' may be less specific than 'antibody response' but it is technically correct. Further, the term 'immune response' cannot be misleading, as the same terminology is used in the description of adjuvanted influenza vaccines by key immunisation authorities including:
    - TGA Alert, Seasonal Influenza: "To continue to provide the best possible protection for those 65 years and over, an enhanced trivalent vaccine, Fluad (Seqirus), is being supplied through the NIP for this age group in 2019…It works by generating a stronger immune response through the use of an adjuvant which stimulates the immune system.."
    - CMO, Early advice on Seasonal influenza Vaccines: "This vaccine [Fluad®] should be given in preference to the QIVs for those aged 65 years and older as it is specifically designed to provide increased protection for those aged 65 years and older by creating a greater immune response than a QIV."
    - Australian Immunisation Handbook: "Standard-dose TIVs have lower effectiveness in people aged ≥65 years than in younger people. Because of this, 'enhanced' formulations were developed to increase the immune system's response to the vaccine."
- Seqirus also referred to a presentation given by a Sanofi Pasteur employee to an Immunisation Nurses Special Interest Group which also uses the term "immune response" to describe Sanofi Pasteur's product Fluzone.
- In summary, Seqirus argued that it had made adequate clarification in the materials that Fluad is for older adults aged 65 years and over and specific qualification of each claim would be

redundant. Seqirus argued that using the term 'immune response' was technically correct and was not misleading because it is generally used by the immunisation community to describe adjuvanted vaccines.

Sanofi Pasteur were invited to provide a short response to this presentation, and the following summarises that response:

- Sanofi Pasteur agreed that the promotional pieces were adequately referenced to the over 65 years population and did not object to the Appeals Committee with overturning the decision of the Code Committee on that issue.
- In relation to use of the term 'immune response', Sanofi Pasteur considered that 'immune response' is a broader term and is sometimes used interchangeably with 'antibody response', but argued that companies should be more specific in their language and educate the population in those matters. Just because a term is used generally by TGA or the CMO doesn't make it correct when used in promotional materials.

Sanofi Pasteur then presented its appeal, and the following summarises that presentation:

- Sanofi Pasteur noted that the Code Committee was unanimous in its decisions that the claims in question were in breach of the Medicines Australia Code. However, Sanofi Pasteur disagrees with the determination that the claims under the headings 'Mismatch', 'Magnitude' and 'Persistence' would have little impact on prescribing behaviour in the future.
- Sanofi Pasteur argued that the pieces included very broad claims that it considers would cause healthcare professionals to believe that Fluad would work for every influenza virus and has greater persistence. Sanofi Pasteur argued that these claims are unbalanced in the context of the Australian Product Information, which states that "*increased efficacy in the prevention of influenza in comparison with non-adjuvanted vaccines has not been demonstrated*".
- Sanofi Pasteur noted that healthcare professionals can choose to prescribe an influenza vaccine outside the NIP, on the private market. This is evidenced by the fact that 10,000 doses of Sanofi Pasteur's product, Fluzone, were prescribed during the time that the Fluad marketing campaign was in effect.
- Sanofi Pasteur argued that the inflating claims for Fluad will have an impact on Sanofi Pasteur's positioning in the private market and negatively impact its intention for Fluzone to be on the NIP in the future.
- Sanofi Pasteur noted that the Code Committee had stated that the core issue was the use of 'immune response' rather than 'antibody response' in the Fluad promotional claims. While these terms are often used interchangeably and arguably shouldn't be, the core issue is that Seqirus was claiming clinical efficacy that lacks supporting evidence, is inconsistent with the PI and seeks to influence prescribing behaviour.
- Sanofi Pasteur argued that each of the Fluad claims in question was made in the context of a clinical discussion either in a promotional piece targeted at GPs or in trade media going to the same audience. Placing these claims for the adjuvanted influenza vaccine under a banner titled "Benefits of Fluad" make it clear that Seqirus was seeking to mislead the prescriber into interpreting these claims in a clinical context.
- Sanofi Pasteur considered that because the claims are for clinical efficacy and claim superiority of Fluad over currently available standard influenza vaccines (trivalent or quadrivalent vaccines), the impact on future prescribing behaviour is like to be significant and must be corrected.
- Sanofi Pasteur noted that the Code Committee took the fact that Fluad was on the NIP as a mitigating factor in its decision regarding the severity of the breach. Sanofi Pasteur argued that while the NIP provides certain vaccines at no cost, it does not mean that prescribers have no

choice. Sanofi Pasteur argued that if were true that prescribers had no choice, they would not be able to prescribe vaccines that are not on the NIP. Therefore, Sanofi Pasteur argued that this cannot be a consideration when looking at claims that certainly will influence future prescribing behaviour.

- Sanofi Pasteur also noted that the Code Committee stated that there was "evidently some public health rationale for regarding antibody response as a proxy for clinical effect and for the use of a vaccine with an adjuvant". Sanofi Pasteur argued that this is not in line with the Medicines Australia Code or the Fluad PI which states:
    - *Increased efficacy in the prevention of influenza in comparison with non-adjuvanted influenza vaccines has not been demonstrated.*
    - *Although it is generally recognised that vaccine-induced haemagglutination inhibition antibody titres measured against influenza antigens from strains causing disease in the community are a surrogate marker of efficacy, a precise threshold for protection or an absolute correlation between magnitude of antibody titre and reduction in clinical symptoms has not been established*.
- Sanofi Pasteur argued that the claims for Fluad will be recalled by healthcare professionals when both Seqirus' and Sanofi Pasteur's products are in the market in future, either through the NIP on via private prescription.
- Sanofi Pasteur called on the Appeals Committee to uphold the Code Committee's determination and to find that the breaches were more than minor, to increase the fine and to require corrective action.

Seqirus were invited to respond to Sanofi Pasteur's presentation, and the following summarises that response:

- Seqirus argued that an increase in fine or penalty is not warranted. If a breach is found, it should remain as minor, noting that the definition of a minor breach is that there is no safety implications for patients and no major effect on prescribing.
- Seqirus responded to the question of impact of the NIP on prescribing, noting there are three factors that contribute to product selection:
    - Cost: If there is a free vaccine available it is more widely prescribed to patients. This is the major factor in the decision on which vaccine to prescribe.
    - Availability: the Government buys the vaccine at the start of the season; it buys from whichever supplier it has agreed the price with, after which, products are randomly distributed to clinics and there is no choice from a healthcare professional's perspective which vaccines to prescribe under the NIP.
    - Communication at the start of the season: The Government issued a public health campaign asking older patients to get vaccinated through the NIP, encouraging them to help protect against flu.

  Seqirus argued that these three factors are much more influential in the prescribing of vaccines than any promotional materials.
- Seqirus argued that as Fluad is not available on the private market, and is only available through the NIP, this would not have an impact on the current prescribing of Fluzone. However, Seqirus questioned why a healthcare professional would prescribe a non-NIP product – such as Fluzone – at a cost of approximately $50 to the patient. Seqirus speculated that the patients who were prescribed Fluzone were likely to be ineligible for the NIP.
- In responding to the issue of the terms 'immune response' and 'antibody response', Seqirus referred to communications with a healthcare professional audience which stated:
    - ATAGI: "In 2019, only Fluad® (TIV containing an adjuvant) is NIP-funded. The high-dose (Fluzone High-Dose) and adjuvanted (Fluad) TIVs are recommended in preference to

quadrivalent influenza vaccines for adults aged ≥65 years. However, neither of these 2 TIVs is preferred over the other."

- CMO: "To provide the best possible protection for those aged 65 years and over, independent medical experts have recommended enhanced trivalent vaccines be made available for people aged 65 years and over through the NIP. In 2019, the Australian Government will make Fluad® (Seqirus), an adjuvanted vaccine specifically designed for this age group."

Seqirus argued that both Fluad and Fluzone were approved based on immunogenicity data alone. The regulator clearly believed that use of the same methodology across all vaccines is sufficient for prescribing.

- Seqirus disagreed that the promotional materials would have an impact on prescribing behaviour, nor were patient safety issues raised. Seqirus strongly argued that the Code Committee did not err in taking the NIP into consideration with respect to influenza vaccine prescribing behaviour. The NIP is the major driver for which vaccine is received in Australia. Other points raised by Sanofi Pasteur in its appeal did not suggest, or provide evidence of, any impact from Seqirus' materials on prescribing behaviour.
- Further, Seqirus contended that there were no grounds to consider that the Code Committee should have imposed a higher level of breach or required corrective action.

Sanofi Pasteur was then given the final right of response to these matters, and the following summarises that response:

- Sanofi Pasteur disagreed with the logic presented by Seqirus as to why a doctor would prescribe the Sanofi Pasteur product when there is free vaccine available, on the basis that it postulates that there are people ineligible to receive it under the NIP. Seqirus had not provided any evidence to support this assertion.
- Sanofi Pasteur noted that the NIP agreements with the Government account for 'leakage', whether that is patients being prescribed outside the NIP eligibility criteria or otherwise.
- Sanofi Pasteur contended that this is the crux of the impact of prescribing behaviour, noting that there are healthcare professionals who will be convinced by the data and will make a clinical decision notwithstanding the availability of a free vaccine on the NIP. The number of Fluzone doses sold by Sanofi Pasteur prompts it to ask how many more vaccines could have been sold on the private market if the Fluad promotional claims had not influenced the perspective of healthcare professionals.
- Sanofi Pasteur argued that the easier availability of the Seqirus product (on the NIP) does not make the claims in the marketing materials correct or inconsequential to influencing prescribing habits.
- Sanofi Pasteur also noted that prescribing Fluzone needs the healthcare professional to believe that the product is better for their patient due to a variety of reasons. In addressing the 10,000 dispensed doses, Sanofi Pasteur noted that pharmacies don't have access to supply under the NIP and many of the Fluzone doses were dispensed through pharmacies.
- In addressing the use of immunological response as a proxy for efficacy, Sanofi Pasteur agreed that this is appropriate for the purpose of registration; however claims above and beyond that the vaccine is effective would be inappropriate. Sanofi Pasteur also noted that most influenza vaccines are registered on the basis of antibody response, however the TGA qualified in the PI any statements that would require clinical evidence.

The Chair thanked both companies for their presentations, and invited the Appeals Committee to ask any clarifying questions.

An Appeals Committee Member asked Sanofi Pasteur whether the claims in the Seqirus pieces relating to 'mismatch' and 'persistence' could also be claimed for Fluzone. Sanofi Pasteur responded that its antibody data showed a response in magnitude, whereas in relation to persistence there is no evidence of carry over. As to mismatch, the response to humoral (antibody) would be increased antibodies. Sanofi Pasteur noted that it did not have the data, but Seqirus does. Sanofi Pasteur argued, however, that its appeal relates to the impact of the claims on prescribing behaviour and not on antibody response. Specifically, that the antibody response rates are used by Seqirus to claim clinical effects, but these data are not sufficient to support the claims.

Seqirus responded that the Code Committee minutes implied that Seqirus was promoting Fluad for a wider population (i.e. under 65 years old patients) and argued that the Code Committee had erred in its decision. Seqirus was not promoting the product for anyone other than the 65 years and older age group. Seqirus was concerned that the Code Committee had suggested that by comparing the adjuvanted vaccine with a standard trivalent vaccine this was misleading. However, this was the basis for the registration of Fluad and Seqirus should be able to promote it on that basis.

Sanofi Pasteur agreed that the Code Committee had erred in its decision on this point, and conceded that the minutes should be clarified to note that the standard of care at the time of registration of both products was trivalent influenza vaccine. Sanofi Pasteur agreed that there was no evidence that Seqirus had tried to promote Fluad for the under 65 years age group.

An Appeals Committee Member asked both companies to explain how they interpret the comparative claims in the pieces. Seqirus stated the promotional claims were not comparing Fluad with Fluzone HD. It is not possible to be prescribed a trivalent (non-adjuvanted) vaccine, therefore there is no comparative claim with those products, and the comparison was not being made against Fluzone HD. Sanofi Pasteur responded that ATAGI and TGA have stated that there is no difference in efficacy between the influenza vaccines for the over 65 years age group. However, by making clinical efficacy claims for Fluad a healthcare professional is unable to compare like with like. Fluzone HD is not adjuvanted, whereas Fluad is. Sanofi Pasteur reiterated that it considers that the promotional claims will have an impact on prescribing. Seqirus responded that it had made no comparison with Fluzone HD.

An Appeals Committee Member asked Seqirus what was the purpose of the promotional pieces. Seqirus responded that they were educative pieces that explained what the adjuvanted vaccines do to enhance the immune response in older patients. Specifically, Seqirus stated that its campaign was designed to educate healthcare professionals to understand the new class of adjuvanted vaccines; it was to avoid healthcare professionals not giving the new vaccine, even though it was on the NIP, simply because they don't know about them. Sanofi Pasteur responded that it is not Seqirus' responsibility to be conducting that type of education in a way that is obviously promotional, and that the responsibility for such education rests with the authorities, such as ATAGI and the TGA.
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 addressed the core issues as outlined in the Code Committee's reasons for decision, being that the claims were not sufficiently qualified to the 65 years and over population and the use of 'immune response' versus 'antibody response'.

The Appeals Committee agreed that the promotional materials contained sufficient qualification and visual cues that this campaign was directed at the older population. Sanofi Pasteur had also agreed that there had been adequate qualification and that the claims were not seeking to promote Fluad to people under 65 years of age.

In relation to the use of 'immune response' in the promotional claims, the Appeals committee noted that the claims implied clinical efficacy whereas there is no clinical evidence to support these claims. The claims should have been qualified with language consistent with the Fluad Product Information, which clearly states that clinical efficacy had not been demonstrated. The Appeals Committee were of the opinion that the campaign was clearly making clinical efficacy claims which were not consistent with the Product Information, which were misleading and would have impact on prescribing, and particularly with regard to persistence of the protection. The Appeals Committee noted that impact on prescribing isn't solely related to which product a healthcare professional would choose, but it is also about the administration of a product and education of the patient. The Appeals Committee were of the opinion that elevating the claims of efficacy beyond the evidence potentially misleads prescribers, and compromises the education they provide to patients at the time of administration.

The Appeals Committee accepted that materials were to some extent educational about the adjuvanted vaccine, however the inclusion of unsubstantiated efficacy claims leads to the conclusion that the materials were in breach of the Code of Conduct.

The Appeals Committee discussed the matter of using 'immune response' rather than 'antibody response', noting that while they are relevant sources of information, relying on statements by a regulatory body such as the TGA or the CMO does not make those statements compliant with the Code of Conduct when used in promotional materials. The Appeals Committee agreed that context and appropriate use of terms is important, and that any statements or claims adapted from such sources should always be consistent with the Australian Product Information.

The Appeals Committee agreed unanimously that the decisions of the Code Committee in relation to the four claims found in breach stand in relation to each section of the Code of Conduct as previously determined.

The Appeals Committee considered whether this should be classified as a minor or moderate breach, taking into consideration potential impact on prescribing. The Appeals Committee noted that the NIP must be seen as having a major influence on prescribing, as it accounts for the majority of flu vaccination. The figures put before the Appeals Committee show that the current effect on prescribing is low based on 2019 data. However, the Appeals Committee questioned whether there is also potential influence on future prescribing. The Appeals Committee noted the discussion relating to commercial benefits, where influencing healthcare professionals to prescribe more of the NIP listed vaccine over and above the agreed number of doses could boost company profits.
The Appeals Committee considered the original decision to find the breaches minor was mischaracterised by the Code Committee. The Appeals Committee agreed by majority decision that, based on the evidence put before it in the papers and the presentations made at the hearing, the breaches should be elevated to moderate. It was the Appeals Committee's opinion that Fluad promotional materials and media release would have an effect on the prescribing of influenza vaccines by healthcare professionals. The Appeals Committee also determined unanimously that

the fine should be increased, and that the misleading understanding resulting from the promotional claims should be corrected by Seqirus distributing a corrective letter.

In relation to the request for clarification by Seqirus in relation to the statement in the Code of Conduct Committee's reasons for decision about the comparison between the adjuvanted vaccine and the standard trivalent vaccine, the Appeals Committee noted that both Seqirus and Sanofi Pasteur had agreed that the data from the PI should be able to be used as long as it is presented in an appropriate manner and context.

Sanctions

The Appeals Committee upheld the appeal by Sanofi Pasteur and agreed by majority decision that the breaches were moderate, as defined in the Code of Conduct (the materials had no safety implications for patients' well-being and may have an effect on how the medical profession will prescribe the product).

- The Appeals Committee unanimously determined to increase the fine to $80,000.
- The Appeals Committee unanimously determined that Seqirus should distribute a corrective letter to all healthcare professionals who had received the promotional materials or media release, with a template draft letter to be provided by Medicines Australia.

Bonds

The Appeals Committee also determined unanimously that the $10,000 bond paid by Seqirus will be retained by Medicines Australia, and the $10,000 bond paid by Sanofi Pasteur will be returned in full.

Xeljanz® Promotional Material

Complaint	Subject Company	Product	Complainant
1156	Pfizer Australia Pty Ltd	Xeljanz® (tofacitinib citrate)	Takeda Pharmaceuticals Australia Pty Ltd

Complaint
Takeda alleged that a promotional trade display for Xeljanz contained prominent promotional claims of clinical efficacy using emotive language. Takeda further alleged that the claims included multiple qualifying statements which lack detail and context from the supporting evidence. Takeda asserted that these prominent clinical claims did not have balancing risk information, which are particularly relevant for a product with significant precautions for use and which has been subject to a safety communication to relevant prescribers in Australia.

Takeda argued that:

- the claim *"Rapid … efficacy"* is not supported by evidence of sufficient quality to justify a prominent clinical promotional claim;
- the claim "*powerful efficacy"* uses emotive language and qualifying data which diminishes rather than clarifies the meaning of "powerful"; and
- the piece contains prominent efficacy claims with no risk information.

The promotional banner was used and observed at the following events:

1) Sydney International Endoscopy (SIES) meeting – 13 March 2019
2) St Vincent's IBD meeting, Melbourne – 30 March 2019

Sections of the Code
The promotional material is alleged to be in breach of the following Sections of Edition 18 of the Code:

- Section 1.1 Responsibility
- Section 1.2.2 Level of Substantiating Data
- Section 1.3 False or Misleading claims

Response
In its response, Pfizer asserted that the claim *"Rapid and powerful efficacy"* is robustly supported by a pivotal registration study published in the *New England Journal of Medicine*, as well as an accompanying *post hoc* analysis of the same study. Pfizer also noted in its response that these two pieces of data are included in the Xeljanz Approved Product Information as evaluated by the TGA. Pfizer rejected that the evidence provided to support the claim was unbalanced or misleading in any way.

Pfizer rejected the complaint about the absence of balancing safety information, noting that the promotional piece was a banner advertisement used at a trade display and included a statement alerting prescribers to review the full Product Information, which was available from the stand. Pfizer asserted that this is satisfactory to provide the balancing information for a single claim of efficacy.

Code of Conduct Committee decisions

The Code of Conduct Committee made the following decisions:

- Unanimous decision that the claim *"Rapid … efficacy"* was in breach of Sections 1.1, 1.2.2 and 1.3 of the Code
- Majority decision that the *"powerful efficacy"* claim was not in breach of Sections 1.1 or 1.3 of the Code; and
- Unanimous decision that the piece was not in breach of Section 1.1 of the Code in relation to not including safety data on the promotional banner.

Sanctions

The Committee determined by unanimous decision that the breaches were minor, as defined in the Code of Conduct (the claim had no safety implications for patients' well-being and would have no major effect on how the medical profession will prescribe the product). The Committee unanimously determined to impose the following sanctions:

- That the materials using the "rapid … efficacy" claim must be withdrawn from use, and the claim must not be used again in the same or similar form; and
- A fine of $25,000.

The Committee determined unanimously that no corrective letter or other corrective action should be required.

Consideration of the complaint

The Committee noted that the complaint related to a banner which used the words "rapid" and "powerful" in a claim for Pfizer's product Xeljanz. This banner was displayed at two educational meetings in March 2019.

The Committee noted that the word "powerful" was referenced to *Tofacitinib as induction and maintenance therapy for ulcerative colitis,* Sandborn, W J et al, *New England Journal of Medicine* 2017 (OCTAVE). The claim "rapid … efficacy" was referenced to *Tofacitinib induction therapy reduces symptoms within 3 days for patients with ulcerative colitis*, Hanauer, S et al, *Clinical Gastroenterology and Hepatology*, 2019 (Hanauer et al).

<u>Complaint 1: The "rapid … efficacy" claim</u>

The Committee discussed the use of the word "rapid", qualified with the statement "Subscore reductions from baseline at day 3 with XELJANZ 10mg BID: stool frequency -0.27; and rectal bleeding -0.30 (post-hoc analysis)" which was referenced to the Hanauer et al study. The Committee noted that the qualifying statement appropriately identified the Hanauer et al study as a post-hoc analysis, and the Committee accepted that the 3-day data showed elements of reduction in risk of bleeding and was consistent with the overall 8-day end-point. However, the Committee raised concerns about the quality of the post-hoc analysis, which utilised patients' self-reported diary evidence. The Committee was of the opinion that it is difficult to evaluate the quality of the retrospective analysis of diary evidence, especially when it was not clear in the study design if the study had controlled for patients who did not make any diary entries. In addition, the qualifying statement did not state that the outcomes were compared with placebo.

The Committee agreed that, although the claim was qualified and identified that the referenced study was a post hoc analysis, it remained concerned about the quality of the post-hoc analysis used to support the claim. The Committee considered that self-reported diary evidence is a low level of evidence and should not be used to support this claim, especially when there is no other evidence to support efficacy from day 3 of treatment. The Committee noted that there is

evidence of decreased rectal bleeding and stool frequency subscores by week 2 in the Xeljanz Product Information.

The Committee agreed unanimously that the use of the word 'rapid' in this claim was in breach of Sections 1.1, 1.2.2 and 1.3 of the Code.

Complaint 2 – Use of the word 'powerful' in the claim "powerful efficacy"

The Committee considered the use of the word 'powerful' and noted that the claim was qualified by the statement: "Efficacy at week 52 with Xeljanz 5mg BID: remission rate 34.3%, mucosal healing rate 37.4% and clinical response rate 51.5%". The Committee agreed that the level of efficacy that was shown in the OCTAVE study, in terms of clinical outcomes, was statistically significant and consistent with other efficacious products for ulcerative colitis. That said, the Committee considered the use of the word 'powerful' and whether it was the most appropriate term to express the OCTAVE study outcomes.

The Committee agreed that "powerful efficacy" did not convey that the product was 'the most powerful', but simply that it was 'powerful'. The data used to substantiate the claim was considered to be correct and adequate, although the definition of 'powerful' was lacking.

The Committee noted Pfizer's reference to previous Code complaints where findings had been made on use of the term 'powerful' in promotional claims. While precedence is important to be taken into consideration, it does not necessarily influence another complaint in a different context. The Committee agreed that all complaints are decided on their merit, and that the context of the use of 'powerful' is important.

The Committee was uncomfortable with the use of the claim 'powerful efficacy' as it was emotive and was trying to influence prescribers. However, the Committee determined by majority decision that the claim was not in breach of Sections 1.1 or 1.3 of the Code. In this majority decision, the Committee indicated that while the evidence supported the use of the claim 'powerful' in this instance, there may be other claims where it will not be appropriate and care should be taken with ensuring the appropriate context and meaning conveyed by such terms in the future.

Complaint 3 – Claims of efficacy made without any safety information

The Committee discussed the presentation of the promotional banner at two medical educational meetings with a highly qualified specialist audience in attendance. The Committee noted that the banner included the mandatory information required for a trade display banner, including the reference to obtain the product information from the stand and a link to a website.

The Committee agreed unanimously that the banner did not breach Section 1.1 of the Code.

Sanctions

The Committee discussed the severity of the breaches, having found a breach of Sections 1.1, 1.2.2, and 1.3 of the Code in relation to the claim "rapid … efficacy". The Committee noted that the core issue in this complaint was the use of the post-hoc analysis of self-reported patient diaries.

The Committee considered that the presentation of the banner conveys a potent message to the viewer. While the evidence to support part of the claim was sufficient, in relation to the 'powerful' claim, the Committee considered that the language was emotive. The Committee agreed that the intended audience was well informed in the relevant therapeutic area and would

have sufficient context to understand and interpret the claims for Xeljanz. However, the Committee cautioned against using these claims in a different setting without further qualification or amendment.

The Committee discussed whether a corrective letter was warranted. The Committee considered that there would not be any major impact on prescribing behaviour and no risk of patient harm. However, the Committee considered that materials directed at healthcare professionals must be precise, correct and consistent with the PI and other supporting evidence. Companies have a duty to ensure that healthcare professionals are not going to be misled by promotional claims.

The Committee found by unanimous decision that the breaches were minor, as defined in the Code of Conduct, and determined unanimously:

- that no corrective action should be required;
- that the materials using the claim "rapid… efficacy" must be withdrawn from use, and not used again in the same or similar form; and
- to impose a fine of $25,000.

Appeal

Pfizer appealed the Code Committee's decision that the claim *"rapid…efficacy"* was in breach of Sections 1.1, 1.2.2 and 1.3 of the Code, and the Code Committee's rationale for its decision determining that *"self-reported evidence is a low level of evidence and should not be used to support this claim"*. Pfizer noted that patient-reported outcomes for the assessment of efficacy in ulcerative colitis registration trials are recognised by major regulatory authorities including the EMA and FDA. Pfizer contended that the Code Committee's decision directly contradicted the recommendation of major regulatory authorities and the established use of patient-reported data for efficacy assessment.

Appeal Response

Takeda agreed with the Code Committee's decision and restated what it believed to be the limitations of the Hanauer et al (2019) post hoc analysis. It was Takeda's opinion that the Code Committee did not err in its decision making and that the Hanauer study is unacceptable to support a significant clinical claim. Takeda argued that it believed much of Pfizer's appeal was irrelevant and asked the Appeals Committee to focus on the limitations of the Hanauer et al study.

Code of Conduct Appeals Committee decisions

The Appeals Committee unanimously upheld the decisions of the Code of Conduct Committee that the claim *"Rapid … efficacy"* was in breach of Sections 1.1, 1.2.2 and 1.3 of the Code.

Sanctions

The Appeals Committee unanimously confirmed the sanctions imposed by the Code of Conduct Committee:

- That the materials using the "rapid … efficacy" claim must be withdrawn from use, and the claim must not be used again in the same or similar form; and A fine of $25,000.

The Appeals Committee agreed that as the appeal was not upheld, the bond paid by Pfizer would be retained by Medicines Australia.

Consideration 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.

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

- Pfizer outlined that the claim of *"rapid… efficacy"* was derived from Hanauer et al 2018 study, which is a peer-reviewed, post hoc analysis of the tofacitnib OCTAVE registration trials published in the journal *Clinical Gastroenterology and Hepatology*.
- The post hoc analysis was of the stool frequency and rectal bleeding scores collected on a daily basis, in accordance with the OCTAVE Induction study protocol, and investigated daily changes in these measures in the first 15 days of the study, before the first scheduled visit in week 2.
- Pfizer questioned the Code Committee's decision that *"self-reported evidence is a low level of evidence and should not be used to support this claim"*; and noted that self-reported evidence/patient-reported outcomes have an established place in the assessment of efficacy in ulcerative colitis (UC) trials. Pfizer further noted that major regulatory authorities recommend and/or accept these outcomes for efficacy assessment in UC trials.
- Pfizer reasserted that the claim *"rapid… efficacy"* is fully supported by the post hoc analysis, was clearly identified in the promotional material as a post hoc analysis, and was clinically significant and highly relevant to physicians and patients.
- Pfizer addressed Takeda's response to Pfizer's written appeal, where Takeda recommended that the Appeals Committee should disregard the Code Committee's reasons for decision and focus on the limitations of the post hoc analysis. Pfizer argued that this is a spurious argument and urged the Committee to focus on the error made by the Code Committee in reaching its decision.
- Pfizer provided the Appeals Committee with an overview of Tofacitinb's mode of action in inhibiting cytokine production, and the time to clinical response of all agents used to treat inflammatory bowel disease (IBD). This overview showed the time to clinical response ranged from 3 days with IV corticosteroids to 9 weeks for methotrexate.

- Pfizer then described the Hanauer et al post hoc analysis methodology, the Mayo score which is used as an efficacy assessment in UC trials, and discussed the OCTAVE Induction 1 and 2 Studies that were the basis for the Hanauer et al study:
    - the Mayo score is the most commonly used instrument for measuring disease activity and measuring efficacy in UC trails, and has been used unchanged since 1987
    - o the Mayo score ranges from 0 to 12 points and comprises 4 subscores, each graded from 0 to 3, with higher scores indicating more severe disease. These subscores assess Stool Frequency, Rectal bleeding, Endoscopic features, and Physician Global Assessment (PGA).
    - o OCTAVE Induction 1 and 2 studies used a phone-based interactive voice response system (IVRS) where subjects recorded their daily stool and rectal bleeding data. The IVRS data were used for the efficacy endpoint assessment in the OCTAVE trails, with the first two weeks of daily diary data analysed in the Hanauer et al study.

    - o The primary and most secondary efficacy endpoints of the OCTAVE registration trial were derived from the IVRS patient self-reported data. Hence Pfizer maintained that its use of these data as supporting evidence is appropriate.
- Pfizer noted that major regulatory authorities, included the European Medicines Agency and US FDA recommend the use of patient self-reported data for evaluating symptomatic change in stool frequency and rectal bleeding as the co-primary efficacy endpoint.
- Pfizer noted that the reporting of rapid changes in symptoms in UC is important to patients and physicians. The purpose of the Hanauer analysis was to explore if the onset of induction efficacy was earlier than week 2 (the first scheduled trial visit). It is the only realistic means of assessing onset of efficacy in UC.
- Pfizer restated to the Appeals Committee that the use of post hoc analyses is permitted in the Code of Conduct, and that the claim *"rapid…efficacy"* was clearly identified as post hoc and met all the requirements of the Code. Pfizer defended the use of the word "Rapid" in the claim, noting it had been used to inform gastroenterologists of an important attribute of tofacitinb for the treatment of UC.
- Pfizer then discussed the evidence of clinical significance of the claim, outlining for the Appeals Committee that the claim *"rapid…efficacy"* was qualified to report that the least square mean (LSM) change from baseline in subscores at day three. This LSM change was a pre-specified methodology for the OCTAVE trials used to report change from the baseline in the Mayo score. The OCTAVE trials showed significant reduction in stool frequency and rectal bleeding subscores of at least one point at all days from 3 to 15.
- Pfizer responded to the question of missing data, which was originally raised by the Code Committee in its reasons for decision and further explored by Takeda in its response to the appeal. Pfizer outlined that in any analysis of clinical data, missing data is managed using an appropriate statistical methodology. The Hanauer et al study used a linear mixed-effects model, which is a statistically valid method. Whilst management of missing data is not explicit in the manuscript, it is implied because the statistical methodology is clearly described. Data analysed from the OCTAVE study was the full dataset, with dropout rates of 2.4% for tofacitanib group and 3.4% of the placebo group during the first 15 days. There is nothing to suggest that there would be any study bias due to missing data.
- Pfizer disagreed with Takeda's assertion that the non-integer reductions from baseline in Mayo subscores at day 3 have no demonstrated clinical significance, as the claim is qualified using the LSM change, which is demonstrated by the proportion of patients with a reduction in baseline of 1 point, and the positive predictive value for clinical response at week 8.
- Pfizer maintained that the Hanauer study is appropriate to support the claim of *"rapid…efficacy"* and was therefore not in breach of the Code of Conduct.

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

- Takeda firstly addressed the issue of the use of patient self-reported data, noting it is unusual to have an issue raised by the Code Committee which weren't raised in the initial complaint. Takeda agreed with Pfizer that the use of these data is important in UC, and is standard data required for product registration.
- While Takeda agrees that Pfizer has the right to use self-reported patient data, Takeda agrees with the final decision made by the Code Committee, which found the claim "rapid…efficacy" to be in breach of the Code of Conduct.
- Takeda asserted that Pfizer cannot use the claim *"rapid…efficacy"* based solely on the post hoc data because it is a novel claim of clinical efficacy at day 3 of treatment, which is not

consistent with the Product Information. This claim is supported only by the post hoc data analysis, and is designed to influence the prescribing decision of the gastroenterologist audience, something that Takeda asserts is contrary to the Code of Conduct requirements.

- Takeda contended that Pfizer could utilise many sources of data to support a claim for efficacy at day 14, which is also included in the Product Information. The Hanauer post hoc analysis is the only data that supports the day 3 rapid efficacy claim, and Takeda asserted that the post hoc analysis is not sufficient to be the sole supporting evidence for this novel claim.
- Takeda argued that in using the day 3 data from the Hanauer study, Pfizer has cherry picked the most supportive data, which ignored pre-specified study end points and did not align with the day 14 data in the approved Product Information
- Takeda agreed that the Code of Conduct allows for the use of post hoc analyses, with the proviso that such data must be transparent to the reader and contextualised by the primary end points of a study.
- Takeda asserted that Pfizer's use of LSM score is erroneous, as scores are rounded upwards meaning that a reduction of 0.27 out of 1 is counted as a score of 1. The result of this is that small or minimal changes are amplified. There is no demonstrated clinical significance of a reduction in Mayo score of 0.27 at day 3.
- Takeda also noted that the Hanauer study is a very large statistical analysis, and by virtue of the large number of patients, any change can be shown to be statistically significant. Takeda contended that it is a picture of a number of patients, which doesn't necessarily make the results clinically significant.
- Takeda outlined to the Appeals Committee that there are key limitations of the Hanauer study, which render it unsuitable to support the claim of *"rapid…efficacy"*. Specifically, with the large number of data points that were analysed, Takeda believe that Pfizer's use of $p > 0.05$ without adequate adjustment for end point or time point evaluations would identify numerous any magnitude of outcomes. Further, the standard method is to average the scores over three days, not to just take the score on one day; day 3 in this case.
- Takeda further noted that the post hoc analysis used observed case data that were not evaluated. The standard method for using the Mayo score for registration is to average the scores over three days, not to just take the score on a single day because for a single subject their score could change day to day even with no intervention. Takeda asserted that Pfizer had ignored the standard regulatory method to assess these data, and used a methodology that would give a statistically relevant result.
- Takeda argued that the claim *"rapid…efficacy"*, supported by the Hanauer study, cherry picks data that portrayed Xeljanz in the best possible light. Takeda is not asserting that the use of post hoc analyses is not appropriate. However the Code of Conduct requirements are so that the use of post hoc analyses are not misleading. Takeda considered that the Pfizer claim misleads by omission without being transparent about the limitations of the Hanauer Study. The statistical significance of the data in the Hanauer study between days 1 and 14 varies; Pfizer chose to use the most novel data at day 3.
- Takeda noted the data did not demonstrate clinically significance if all the data points were taken into account and therefore the Hanauer study is not appropriate to support a claim of rapid efficacy.

Pfizer then provided its response to the arguments put forward by Takeda:

- Pfizer rejected Takeda's assertion that the data presented in the Hanauer Study does not show clinical significance at day 3. The Hanauer study analysed specific measures that are clinically significant to patients, such as rectal bleeding and stool frequency, which were

directly reported by patients. The results were both statistically significant and clinically significant.

- Pfizer contended that the Hanauer Study showed that the results at day 3 were predictive of clinical efficacy at day 14. Pfizer noted that the data are include on the banner for a specialist to interpret.
- Pfizer addressed concerns of the placebo effect in response to a question raised by an Appeals Committee Member. Pfizer noted that in the trajectory of the separation of patients treated with tofacitinib from placebo, there is a change that the patients are showing at day 3. This data is reported in stool frequency at day 3. The clinically significant markers in this area do not have a minimum clinically important difference identified, but the patients know there are fewer trips to the toilet and less rectal bleeding at day three. The Hanauer study looked at rapid onset of treatment and identifying reportable changes which are obvious to the patient and reported using the standard methodology.

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

The Appeals Committee discussed the use of the Hanauer Study, and noted that the central argument made by the Code Committee was accepted by both parties in that the use of self-reported data in this area is appropriate and acceptable. The Appeals Committee accepted the standard of the post hoc analysis and the use of patient self-reported data. However, the limitations of the Hanauer study were clearly articulated by Takeda in its arguments and the Appeals Committee discussed that reasoning further.

The Appeals Committee noted that the Hanauer study used a methodology to interpret the data that was not standard in this therapy area, UC – that is, analysing responses on single days rather than averaging three days of data. This is not sufficiently clear to the reader, and it is likely that it would be judged as having used the standard methodology, which would have the impact of influencing the viewer to be more favourable in their interpretation of that claim, which was therefore misleading.

The Appeals Committee agreed unanimously that the appeal by Pfzer was not upheld. The Appeals Committee did agree that the statements made by the Code Committee regarding the use of self-reported diary evidence being low level evidence was correctly disputed in this context. However, that did not alter the main reasoning of the Code Committee that the way in which the evidence was used didn't support the strength of the claim, which was clearly promotional and designed to influence prescribing. The Appeals Committee agreed that the claim was misleading, unable to be adequately substantiated and was not consistent with the approved Product Information and was therefore in breach of Sections 1.1, 1.2.2 and 1.3 of the Code.

<u>Sanctions</u>

The Appeals Committee upheld the decision of the Code Committee unanimously that the breaches were minor, as defined in the Code of Conduct (the material had no safety implications for patients' well-being and would have no major effect on how the medical profession will prescribe the product). The Appeals Committee unanimously confirmed the sanctions imposed by the Code of Conduct Committee:

- That the materials using the "rapid … efficacy" claim must be withdrawn from use, and the claim must not be used again in the same or similar form; and
- A fine of $25,000.

Bond

The Appeals Committee agreed that as the appeal was not upheld, the bond paid by Pfizer would be retained by Medicines Australia.

Xarelto® Promotional Material

Complaint	Subject Company	Product	Complainant
1157	Bayer Australia Limited	Xarelto® (rivaroxaban)	Bristol-Myers Squibb Australia and Pfizer Australia Pty Ltd Alliance

Complaint
The BMS-Pfizer Alliance alleged that a promotional Clinical Paper Carrier includes claims that are referenced to a single study of low quality, Martinez BK et al (2018); that the claims are not consistent with key clinical trial data or the body of evidence; and that the distribution of the piece has the potential to confuse and mislead clinicians.

The Martinez et al study used to support the claims in the piece is a retrospective claims database analysis, which the BMS-Pfizer Alliance contended is subject to multiple limitations rendering such studies low quality evidence.

The BMS-Pfizer Alliance further alleged that the following claims:

1) *At 2 years, Xarelto was associated with a significant:*
    - *32% reduction in stroke/SE*
    - *31% reduction in ischaemic stroke alone*
2) *At 2 years, neither apixaban nor dabigatran were associated with difference in the hazard of stroke/SE or ischaemic stroke alone versus warfarin*
3) *At 2 years, neither Xarelto, apixaban nor dabigatran were associated with differences in the hazard of major bleeding versus warfarin*
4) *Our study found rivaroxaban but not apixaban or dabigatran to be associated with reduced SSE [stroke/systemic embolism] versus warfarin in frail nonvalvular atrial fibrillation patients. No direct-acting oral anticoagulants demonstrated a significant difference in major bleeding versus warfarin.*

included in the Clinical Paper Carrier are inconsistent with the body of evidence, the Approved Product Information for Xarelto and cite the results of the Martinez et al publication in a favorable manner that misleadingly suggest that the results are typical.

Sections of the Code
The promotional material was alleged to be in breach of the following Sections of Edition 18 of the Code:

- Section 1.1 Responsibility
- Section 1.2 Substantiating Data
- Section 1.3 False or Misleading claims
- Section 1.8 Comparative Claims

Response
Bayer responded that the Clinical Paper Carrier in question is a compliant non-promotional supportive element that forms an integral part of the dissemination of peer-reviewed material. Bayer asserted that the piece contains statements directly substantiated and referenced from the Martinez et al publication without additional content or subjective interpretation. Bayer argued that the allegations that it does not comply with the Code are without basis.

Further, Bayer contended that the Clinical Paper Carrier and its contents are not inconsistent with the body of clinical evidence as alleged by the BMS-Pfizer Alliance, because the distinct, frail nonvalvular atrial fibrillation (NVAF) population cannot be compared with data from studies that had included generic study populations other than frail NVAF patients.

Bayer rejected that the Clinical Paper Carrier is likely to mislead clinicians that rivaroxaban has a superior clinical profile to other available NOACs because no overall impression of superiority is conveyed in the piece, and physicians are well aware that there are currently no head-to-head RCTs comparing the non-Vitamin K oral anticoagulants (NOACs).

Sanction
The Committee determined unanimously that the Clinical Paper Carrier was promotional material and was in breach of Sections 1.1, 1.2, 1.3 and 1.8 of the Code of Conduct.

The Committee found by unanimous decision that the breaches were moderate, as defined in the Code of Conduct (the materials had no safety implications for patients' well-being but may have effect on how the medical profession will prescribe the product). The Committee unanimously determined to impose the following sanctions:

- The Clinical Paper Carrier must be withdrawn from circulation and not be used again in the same or similar format.
- Issue a corrective letter to all healthcare professionals who received the piece, with the distribution list detailing the scope of who would receive the corrective letter (but not the individual healthcare professionals' names) to be approved by the Committee. A draft corrective letter will be provided by the Committee with the reasons for decisions.
- Pay a $150,000 fine.

Consideration of the complaint
The Committee noted that this complaint related to a Clinical Paper Carrier (CPC) which contained the study *Effectiveness and safety of Apixiban, Dabigatran, and Rivaroxaban versus Warfarin in Frail Patients with Nonvalvular Atrial Fibrillation (Martinez, et al)* (Martinez Study) published in the *Journal of the American Heart Association* (JAHA) in conjunction with the American Heart Association and the American Stroke Association in April 2018. This CPC was distributed to a broad healthcare audience over a period of 14 months from May 2018. The Committee noted that the Martinez Study was sponsored by Bayer, and is a retrospective US claims database analysis, which had used a propensity analysis to identify matching patients taking warfarin.

The Committee reviewed the complaint lodged by the BMS-Pfizer Alliance and noted the four individual claims that BMS-Pfizer Alliance alleged were in breach of the Code. However, in its discussion, the Committee reviewed the claims in the context of the other information presented in the CPC.
The Committee agreed unanimously that the CPC should be considered promotional material, rejecting Bayer's assertion that the material was only educational material provided in conjunction with a reprint of medical literature. The Committee determined that the statements identified by BMS-Pfizer were clearly promotional, with the item including comparative claims, product branding, tables presenting data adapted from the Martinez study with coloured highlighting for Xarelto, and promotional claims for Xarelto. This determination was supported by the item's circulation by the Bayer sales force channel.

The claims used in the CPC were statements taken directly from the Martinez Study; however Bayer had selected and included statements that claimed superiority of rivaroxaban over apixaban and dabigatran. It was the Committee's opinion that there is no evidence to support those claims. There are no head to head studies in atrial fibrillation demonstrating superiority of one NOAC over another. The Committee particularly noted that the Martinez study was a post-hoc database analysis that was funded by Bayer and that the number of patients in each of the apixaban and dabigatran groups were approximately half the number in the rivaroxaban group, which meant that the study was not likely to have been sufficiently powered for the apixaban and dabigatran groups to reach statistical significance versus warfarin. .

The Committee agreed that the four claims subject to complaint were selected based on their positive outcomes for rivaroxaban, and had been used to make comparative claims against the other NOACs. The comparative claims are not reflective of the body of evidence, nor are they consistent with the Approved Product Information for Xarelto.

The Committee discussed the Martinez Study, to determine its suitability to support comparative clinical claims. The Committee noted that paper outlined the retrospective study design comparing effectiveness of NOACs versus warfarin in frail NVAF patients, but it lacked information about the methodology, analytic methods or on sample sizing and power calculations. Specifically, the sample sizes differed significantly between the three treatment arms of the study, without any explanation of why the rivaroxaban group was almost twice the size of the other groups. This led the Committee to the conclusion that the study was not designed to make comparisons between the three arms of the study. The study limitations also state that it is possible that some analyses were underpowered to detect differences between treatment cohorts, however the claims are comparative between rivaroxaban and the other NOACs. The Committee remained concerned as to the validity of the Martinez Study, and the continued analysis of the dataset, to support the claims for Xarelto and comparative claims against apixaban and dabigatran. The circulation of the Martinez Study as the basis for making promotional claims in the CPC has the potential to persuade doctors to prescribe Xarelto.

The Committee determined unanimously that the CPC was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code.

Sanction

The Committee discussed the severity of the breaches, having found it was in breach of Sections 1.1, 1.2.2, 1.3 and 1.8 of the Code. The Committee noted that the core issue of this complaint turned on whether the CPC was considered promotional, and whether the Martinez Study was appropriate to support the claims being made.

The Committee agreed unanimously that the promotional presentation style of the CPC, coupled with the selective use of data had the potential to impact prescribing behaviours. The Committee discussed whether corrective action was warranted, and agreed that, having been circulated to a wide audience over a lengthy timeframe, it was necessary to correct any possible misunderstanding that may be held about the NOACs from the promotional use of this study. The Committee therefore determined that a corrective letter should circulated to all healthcare professionals who had received the CPC. The Committee noted from the intercompany dialogue that Bayer refused to provide any clarity to BMS-Pfizer Alliance as to the breadth of its distribution. Therefore the Committee agreed that the distribution list for the corrective letter should be approved by the Committee, to ensure that it was sufficiently broad. The Committee

noted that it should not see individual HCP names on the distribution lists, however it needed assurance from Bayer that any HCP who was exposed to the material receives the corrected information. The Committee agreed that it would initially draft the corrective letter.

The Committee considered the seriousness of the conduct that led to its decisions finding breaches of the Code. As the CPC could influence prescribing behaviors but there were no safety implications for patients, the Committee found by unanimous decision that the breaches were moderate, as defined in the Code of Conduct, and determined unanimously:

- that the material should be withdrawn and not used again in the same or similar form;
- that a corrective letter should be distributed to all healthcare professionals exposed to the material; and
- pay a fine of $150,000

Appeal

Bayer argued that the Clinical Paper Carrier did not breach Sections 1.1, 1.2, 1.3 and 1.8 of the Code. However, without conceding the issue, Bayer did not challenge the Code Committee's finding that item was promotional. Bayer asserted that the Martinez study and therefore the claims made in the Clinical Paper Carrier are consistent with Xarelto approved Product Information and the body of evidence and do not make head to head comparisons between NOACs.

Appeal Response

The BMS-Pfizer Alliance maintained its strong view that the Clinical Paper Carrier is in breach of the Code and argued that the findings and sanctions as determined by the Code Committee should be upheld. The BMS-Pfizer Alliance highlighted that the Martinez study has multiple limitations, which render the data low quality evidence. Further, the BMS-Pfizer Alliance highlighted that the comparative claims are based exclusively on the Martinez study, which is inconsistent with key clinical trial data. Finally, the BMS-Pfizer Alliance confirmed its opinion that the Clinical Paper Carrier has the potential to confuse clinicians to believe that rivaroxaban has superior clinical profile to the other available NOACs.

Code of Conduct Appeals Committee decisions

The Committee unanimously upheld the decisions of the Code Committee that the Clinical Paper Carrier was promotional material and was in breach of Sections 1.1, 1.2, 1.3 and 1.8 of the Code of Conduct.

Sanctions

The Appeals Committee unanimously confirmed the sanctions imposed by the Code of Conduct Committee:

- The Clinical Paper Carrier must be withdrawn from circulation and not be used again in the same or similar form.
- Bayer must issue a corrective letter to all healthcare professionals who received the piece, with the distribution list detailing the scope of who would receive the corrective letter (but not the individual healthcare professionals' names) to be approved by the Committee. A draft corrective letter will be provided by the Committee with the reasons for decisions.
- Pay a $150,000 fine.

The Appeals Committee agreed that as the appeal was not upheld, the bond paid by Bayer would be retained by Medicines Australia.

Consideration 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.

The Bayer representatives, which included a specialist consultant cardiologist, were then asked to present the appeal to the Appeals Committee, and the following summarises their presentation:

- Bayer accepted that the Clinical Paper Carrier (CPC) was promotional in nature, but believed that it complies with Section 1 of the Code of Conduct.
- Bayer rejected the assertion that Martinez study was of low quality. While the study, a retrospective claims database analysis, is lower on the hierarchy of evidence than a clinical trial, real world evidence is regularly sought. The Martinez study is the highest level of evidence available for frail NVAF patients.
- Bayer queried the proportionality and application of the corrective letter in this case, noting that the fine imposed was the maximum allowable under the Code for a moderate breach. Bayer did not agree that its conduct was commensurate with the most severe breaches within the moderate category, nor does it believe the fine and the requirement for a corrective letter was proportionate to previous sanctions imposed.
- Bayer asserted that the CPC only summarised the effect of all NOACs compared with warfarin. It rejected that the CPC made comparative claims between different NOACs and argued that the design of the CPC as a whole demonstrated that.
- The specialist consultant discussed the utility of real world evidence (RWE), and the analysis of big data sets that are used to analyse patients' treatment outcomes and product safety after the conclusion of studies and post-registration. These data are often useful in clinical settings where physicians are treating patients outside the original trial cohorts, who are taking various medications, and have to make clinical judgements. RWE is used as a reassurance that trial results are generalisable to a broader population when no randomised controlled trial is available.
- The consultant outlined the hierarchy of evidence, noting that a randomised control trial and meta-analyses of them are the highest level of evidence. RWE sits slightly lower in the hierarchy (second tier). It has utility in clinical settings and its use is increasing with the availability of more data sources. RWE looks at safety and efficacy in routine clinical practice, in the real world setting.
- The consultant explained that the Martinez study analysed a sub-set of patients seen in a clinical setting who were categorised as "frail". It used a systematic approach to defining frailty determined using the Johns Hopkins model, which assesses not only age, body weight and immobility, but also includes interactions between various comorbidities. This methodology is a validated tool for assessing frailty. The study used a very narrow calibre to propensity match with similar patients in the database.
- The Martinez study was clear that the comparisons were between NOACs and warfarin and not head-to-head comparisons of the NOAC treatments. It concluded that there was no excess bleeding in frail elderly NVAF patients on NOACs compared with warfarin. With regard to safety data, the study showed there was consistent safety between warfarin and the NOACs – the NOACs presented no greater risk than standard warfarin therapy.
- Bayer agrees that the Martinez study was not designed to make comparative claims between NOACs. Healthcare professionals are well versed in understanding that while RWE is useful, it not appropriate for comparisons between NOACs. Bayer asserted that the Martinez study was not used to make general claims for safety and efficacy of rivaroxaban (Xarelto).

- Bayer contended that the Martinez Study is consistent with the approved Product Information and the body of evidence. The Martinez study analysed the frail NVAF population. The registration study ROCKET-AF, which is included in the Xarelto Product Information, was not powered to analyse ischaemic stroke. The ARISTOTLE study, the pivotal registration study for apixaban, did not include a specific sub-group analysis of the frail NVAF sub-group.
- Bayer contended that if the Code Committee's decision is upheld, the outcome may inhibit the exchange of scientific and medical information, be inconsistent with the way clinical practice works and science progresses. Bayer sought confirmation that companies can continue to use current and future RWE as a basis for claims, to help support QUM and informed prescribing, especially in populations where RCT data is lacking.

A member of the Committee asked Bayer to further explain its contention that the claims were not comparative between the NOACs, noting that the Martinez study conclusions stated that there was a difference between rivaroxaban and apixaban or dabigatran with regard to stroke and systemic embolism. Bayer responded that the statement goes on to refer to a difference between NOACs and warfarin. A Committee member also noted that claims 1 and 2 claim referring to results for Xarelto which were not observed with apixaban or dabigatran. Bayer responded that it was not inferred that this was a statistically significant difference.

The BMS-Pfizer Alliance was invited to provide a response to Bayer's presentation, and the following summarises that response:

- The BMS-Pfizer Alliance highlighted its concerns with its interaction with Bayer in the intercompany dialogue for this complaint. The BMS-Pfizer Alliance alleged Bayer had been unwilling to cooperate, and would not concede that the CPC was promotional material until presenting at the hearing. Bayer had also refused to provide information on the distribution of the CPC.
- The BMS-Pfizer Alliance strongly agreed with the Code Committee's determination that this piece is promotional. The layout of the CPC juxtaposed data that implies indirect comparisons between the NOACs, and the limitations of the Martinez study cannot be viewed at the same time as the results.
- The BMS-Pfizer Alliance argued that the use of the Martinez study, a retrospective, claims cohort study, as standalone evidence in support of comparative claims is in appropriate, and not consistent with key clinical trial data, the Xarelto Product Information, or the body of evidence for NOACs.
- The BMS-Pfizer Alliance further noted that the authors of the Martinez study noted that RWE has the potential to supplement randomised controlled trial data, however there are limitations and cannot be used as standalone evidence to validate the efficacy and/or safety of a treatment.
- The BMS-Pfizer Alliance asserted that the Martinez study is associated with multiple limitations, many of which are not listed in the 'Study limitations' section of the CPC. Specifically, the study numbers were not balanced across the study arms, reducing the likelihood that comparisons between NOACs and Warfarin would reach statistical significance.
- The BMS-Pfizer Alliance raised concern with the frailty indicator used to select the patients, noting it is an exploratory measure and not an established clinical research tool. The BMS-Pfizer Alliance highlighted that as at 2017 there have been 35 frailty scores identified in published literature.
- The BMS-Pfizer Alliance reaffirmed the concerns it had raised to the Code Committee, outlining that the four claims used in the CPC were inappropriate and should not be used.

- The BMS-Pfizer Alliance summarised its position that the CPC had been in use since May 2018, featuring claims that were based exclusively on low quality evidence in a patient subset for which there is no standardised definition. Further, the claims in the CPC are inconsistent with key trial data and the body of evidence, which leave the reader with the understanding that Xarelto is more effective when compared with other NOACs, rendering the CPC misleading by implication and having the potential to have a major impact on prescribing.

Bayer then provided its response to the arguments put forward by the BMS-Pfizer Alliance:

- Bayer denied that its decision not to disclose the distribution of the CPC is to be construed as lack of cooperation in intercompany dialogue. The dialogue commenced on 22 February 2019 and included numerous telephone calls and exchanges. Bayer noted that the BMS-Pfizer Alliance had not been prepared to look at the frail population as a defined subgroup within the licensed indication in Australia. Bayer contended that it had offered a number of different alternatives and amendments in order to move forward. Bayer had elected not to disclose the audience and distribution for the CPC to BMS-Pfizer as it was believed to be commercially in confidence. [POST MEETING NOTE: Bayer has subsequently confirmed 5,000 copies of the CPC were produced, of which 4,000 were distributed]
- Bayer noted that the use of RWE has been increasing in the last 10 years, and all NOACs used in the Martinez study represented clinical practice and were used within their indication.
- Bayer rejected the BMS-Pfizer Alliance assertion that there is no clinical definition of frailty, noting that there is a specific category for frailty in cardiology. Bayer identified that the BMS-Pfizer Alliance has undertaken a study that uses the same Johns Hopkins frailty score, which has not yet been published.

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

The Appeals Committee agreed unanimously with the Code Committee in finding that the CPC was promotional in nature. The Appeals Committee also noted that Bayer had conceded this in its appeal.

In reviewing the CPC, the Appeals Committee discussed the use of the retrospective claims database study in promotional activities and determined that while it was appropriate to conduct such studies, with a defined methodology to interpret the data for a specific sub-population, it is not suitable evidence to make comparative efficacy claims. In the Martinez study, there were different numbers of patients included in the Xarelto group and the apixaban and dabigatran groups, which meant that it is not possible to appropriately compare between the groups or to attain significance.

The Appeals Committee discussed the study limitations as set out in the CPC, and the additional limitations identified by BMS-Pfizer Alliance. The Appeals Committee agreed that RWE studies have limitations, and the inclusion of any limitations is appropriate, but an exhaustive list does need to be included when they are used in this way. That said, the Appeals Committee cautioned the use of RWE as the basis for making comparative claims.

The Appeals Committee agreed unanimously that the grounds of appeal were not made out, and that no errors were demonstrated in the reasoning of the Code Committee. However, the Appeals Committee is not suggesting that RWE cannot be used to support claims; in this particular

complaint, the study was not adequate to support the claims made and therefore the claims were in breach of the Code.

The Appeals Committee unanimously upheld the decision of the Code Committee in determining that the Clinical Paper Carrier was promotional material and was in breach of Sections 1.1, 1.2, 1.3 and 1.8 of the Code of Conduct.

The Appeals Committee discussed the level of the fine, and agreed that it was not inappropriate having regard to the apparently wide distribution of the piece, and the potential to affect prescribing.

Sanctions

The Appeals Committee unanimously confirmed the sanctions imposed by the Code of Conduct Committee:

- The Clinical Paper Carrier must be withdrawn from circulation and not be used again in the same or similar form.
- Issue a corrective letter to all healthcare professionals who received the piece, with the distribution list detailing the scope of who would receive the corrective letter (but not the individual healthcare professionals' names) to be approved by the Committee. A draft corrective letter will be provided by the Committee with the reasons for decisions.
- Pay a $150,000 fine.

Bond

The Appeals Committee agreed that as the appeal was not upheld, the bond paid by Bayer would be retained by Medicines Australia.

Eli Lilly Professional Conduct

Complaint	Subject Company	Product	Complainant
1158	Eli Lilly Australia (ELA)	Taltz (Ixekizumab (RCH))	Healthcare Professional

Complaint
The Healthcare Professional alleged that Eli Lilly Australia used his name, image, words and brand without obtaining his final consent in a video presentation. This video was used by Eli Lilly in communications with the Healthcare Professional's peers without his knowledge or approval.

Sections of the Code
The activity is alleged to be in breach of the following Section of Edition 18 of the Code:
- Section 9.2 Medical Ethics

Response
In its response, Eli Lilly outlined that while the company had significant engagement with the Healthcare Professional in the planning and production of the video, it acknowledged that it had failed to obtain documented approval in respect of the final production of the video. Eli Lilly noted that it had apologised to the Healthcare Professional in writing and had identified process improvements to prevent such oversights occurring again.

Code of Conduct Committee decisions
The Committee agreed by unanimous decision that the conduct was in breach of Section 9.2 of the Code of Conduct.

Sanctions
The Committee further agreed that the breach was minor, as defined in the Code of Conduct (the activity had no safety implications for patients' well-being and would have no major effect on how the medical profession will prescribe the product) and imposed the following sanction on the subject company:
- Pay a $15,000 fine

Consideration of the complaint
The Committee noted that the complaint centred on the release of four videos produced and used by Eli Lilly without the final consent of the featured Healthcare Professional. The videos provided educational and promotional messages for Taltz (Ixekizumab (RCH)) Solution for Injection as follows:
- Managing Injection Site Reactions with Taltz – Tips and Guidance
- Injection Site Reactions with Taltz – what to expect
- Genital Psoriasis – Diagnosis and Treatment
- Genital Psoriasis – Prevalence and Impact of Disease

The videos featured a healthcare professional with whom Eli Lilly had a long-standing relationship which included their involvement in advisory boards and other consultancy arrangements. The videos were filmed in February 2018, after the healthcare professional had provided input into

content and transcript. The Healthcare Professional answered three questions at the time of filming, although only two of the answers were included in the videos.

The Committee noted that the Healthcare Professional entered into a Master Services Agreement (MSA) in January 2018 which covered payment of an honoraria for this activity. The MSA set out the terms and conditions for a number of activities between the healthcare professional and Eli Lilly. Eli Lilly had stated that it is the company's policy to ensure separate consent and release forms are executed in association with individual activities. Eli Lilly conceded in its response that this separate consent and release form was not executed for this particular activity. Eli Lilly advised that the consent and release form had been provided to the healthcare professional several times via email, however it had not been returned. Eli Lilly identified during its investigation of this complaint that there had been a change in staff responsible for the activity between the filming in 2018 and the release of the videos in 2019, which explained the failure to ensure this consent and release form was properly executed.

The Committee discussed the concept of implied consent and formal consent as it would relate to this matter. The Committee judged that while the healthcare professional had been involved in the development of the script for the videos, participated in the filming of the videos, had been provided with copies of the videos for review, and had been paid an honoraria for the activity, this did not constitute formal consent. The Committee agreed unanimously that without the executed consent and release form, Eli Lilly should not have used the videos.

The Committee understood from the information provided by the healthcare professional and Eli Lilly that the healthcare professional did not object to the content of the videos; the complaint related to the timing of their release and the healthcare professional not knowing they were in use with other healthcare professionals. The Committee therefore agreed unanimously that the failure to secure written consent for the release of the videos breached Section 9.2 of the Code.

Sanction

In discussing the severity of the breach, the Committee determined by unanimous decision that the breach was minor. It was unable to be categorised as a technical breach, as it did not meet the criteria for such a breach, although the Committee agreed it could loosely be described as such. The Committee noted that Eli Lilly had, in effect, admitted to the breach in its response to the complaint. Eli Lilly advised it had formally apologised to the Healthcare Professional and had removed the videos from circulation immediately upon being notified of the error.

The Committee found by unanimous decision that the breach was minor, as defined in the Code of Conduct, and determined by majority to impose a fine of $15,000.