NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal of efalizumab and etanercept for the treatment of psoriasis

Decision of the Panel

1. Introduction

1.1 An Appeal Panel was convened on 27th January 2006 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS, on the use of efalizumab and etanercept in the treatment of psoriasis.

1.2 The Appeal Panel consisted of Professor Sir Michael Rawlins (chair of panel and chair of the Institute), Mark Taylor and Mary McClarey (non-executive directors of the Institute), Dr David Webster (industry representative) and Ms Gill Donovan (patient representative).

1.3 The Panel considered appeals submitted by:

- British Association of Dermatologists ("the Association")
- Serono Ltd ("Serono")
- Wyeth Pharmaceuticals

1.3.1 The Association were represented by Dr A.D. Ormerod and Prof Jonathan Barker.

1.3.2 Serono were represented by Don Cowling, Dr Andrea Rappagliosi, Dr Ian Parsons, Dr Eduardo Sabate, Michel de Preter and Mr Arundel McDougall.

1.3.3 Wyeth were represented by Dr David Gillen, Garth Baxter, Pete Conway.

1.4 In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor David Barnett (chair of the Appraisal Committee), Nina Pinwell (Associate Director, Centre for Health Technology Evaluation), Dr Sarah Garner (Technical Lead), Professor Mark Sculpher and Neil Hawkins (both from the Centre for Reviews and Dissemination, York).

1.5 The Institute's legal advisor (Mr Stephen Hocking, Beachcroft Wansbroughs) was also present.

1.6 Under the Institute's appeal procedures members of the public are admitted to appeal hearings and a number of members of the public were present at this appeal.

1.7 There are three grounds on which a panel can hear an appeal:

1. The Institute has failed to act fairly and in accordance with its procedures;
2. The Institute has prepared guidance which is perverse in light of the evidence submitted;
3. The Institute has exceeded its legal powers.

1.8 The chair of the appeals committee (Roy Luff, acting vice-chair of the Institute), had confirmed that the appellants had potentially valid grounds of appeal as follows

- BAD: ground 2
- Serono: grounds 1, 2 and 3
- Wyeth: ground 1

2. Appeal Ground One: The Institute has failed to act fairly and in accordance with the Appraisal Procedure set out in the Guidance to the Technology Appraisal Process

2.1 Serono alleged that the FAD failed to provide reasons, in the guidance (sections 1.3, 1.4, 1.5), for recommending restrictions in the use of efalizumab to patients who had either failed to respond to, were shown to be intolerant to, or had contra-indications to, etanercept. The appellant claimed that this restriction appeared to ignore the provisions of the marketing authorisation for efalizumab, the results of the CLEAR study and the lack of evidence supporting the use of etanercept in the specific patient population under appraisal.

Professor Barnett accepted that the FAD could have possibly provided a clearer account of the reasons for recommending the restricted use of efalizumab which was based on cost effectiveness comparisons. He stated, however, that the results of the CLEAR study had been fully considered by the Appraisal Committee: and that they committee had concluded it did confirm the clinical effectiveness of efalizumab in the specific patient population. However, additional evidence for the clinical effectiveness of etanercept in the same patient population, submitted by the manufacturer as "commercial-in-confidence", had also been considered by the Appraisal Committee. The Committee's recommendations were based on the balance of all of the evidence before it.

The Committee cannot be criticised for considering commercial in confidence data in relation to etanercept nor, (although argument could not be heard on this point), for the conclusions it drew from that data. However Serono were unaware not only of the content of the confidential data, (as would inevitably have been the case) but also

of its very existence. The Appeal Panel determined that as a result Serono were genuinely unsure why the Committee's recommendations were (as Serono saw it) at variance with the CLEAR data and the perceived lack of evidence supporting the use of etanercept in the specific patient population under appraisal.

. This may have compromised Serono's ability to engage with the consultation process and could therefore be unfair.

The Appeal Panel agreed that the FAD failed to adequately explain the reasons for restricting the use of efalizumab in the guidance; and that a fuller explanation should be provided in the FAD (especially section 4.3), whilst still respecting commercial confidentiality. The Appeal Panel did not consider that the Institute's procedures had been breached in relation to the Appraisal Committee's consideration of the evidence submitted to support the use of either efalizumab or etanercept. The panel, however, accepted that the existence of "commercial-in-confidence" data supporting the use of etanercept , in the specific patient population, should also have been incorporated into, or referenced in, the FAD and that the failure to do so was unfair, even if it was not a breach of published procedures.

The appeal panel upheld the appeal on this point. The panel requests the Appraisal Committee to clarify, in the FAD, its reasons for concluding that the use of efalizumab should be restricted on grounds of cost effectiveness; and, as a minimum, to indicate the existence and relevance, in the FAD, of the "commercial-in-confidence" data supporting their conclusions. The Appraisal Committee should also reconfirm whether this data is still "Commercial in Confidence".

2.2 Serono alleged that in its determination on the use of efalizumab in the treatment of psoriasis, the Appraisal Committee had failed to take account of mandatory relevant considerations. In particular, it had given insufficient weight to the results of the CLEAR study; it had ignored information in the EMEA's EPAR (etanercept scientific discussion paper) on re-treatment response rates to eternacept; it had ignored the economic consequences of the decay in re-treatment rates and lost QALYS due to relapse; it appeared to have relied on the testimony of clinical experts about the therapeutic equivalence of efalizumab and etanercept in the specific patient population; it had ignored the fact that that there was no primary evidence supporting the use of etanercept either in patients with severe psoriasis refractory to, or intolerant of, standard systemic treatment; and it did not have adequate information to support the efficacy of re-treatment, with etanercept , in patients who had relapsed following previously successful treatment with this product.

Professor Barnett confirmed (see paragraph 2.1 above) that the Appraisal Committee had given full consideration to the results of the CLEAR study. He stated, however, that there was "commercial in confidence" evidence supporting the use of etanercept in patients who had failed to respond to standard systemic therapies. Consequently, the committee had not relied solely on the testimony of clinical experts on this point. For those who had relapsed after successful treatment with etanercept , additional evidence had been submitted as "commercial-in-confidence". This evidence bore inter alia on the issues of retreatment response rates, the economic consequences

of decay in retreatment rates and QALYs lost due to relapse, and efficacy in relapsing patients. The Appeal Panel concluded that there had been no failure of the Institute to consider relevant material and dismissed the appeal on this point. It requested the Appraisal Committee, however, to indicate in the FAD the existence and relevance of the "commercial-in-confidence" data that supported its conclusions.

The Appeal Panel dismissed the appeal on this point.

2.3 Serono alleged that the Appraisal Committee had taken irrelevant considerations into account in the FAD. The appellant alleged that the committee had been influenced by clinical opinion regarding a non-authorised indication (FAD 4.3.2); and that it had considered a non-authorised use (FAD 4.2.4.2) – etanercept continuous – in its deliberations.

Both Serono and Wyeth, in response to a direct question from the Appeal Panel, agreed that the guidance (FAD 1.1 to 1.5) was consistent with the marketing authorisations of both products. The panel noted that neither FAD 4.3.2, nor FAD 4.2.4.2, recommended the non-authorised use of either product. Professor Barnett explained that the cost utility analysis of etanercept continuous had been included in the Technology Assessment Report (TAR) but that it had not contributed to the committee's conclusions.

The Appeal Panel did not consider that evidence from an unlicensed use was by definition irrelevant to an appraisal within licensed uses: the appellant would have to show that this was so on the facts of a given case. The panel concluded that there was no evidence irrelevant material had been considered and dismissed the appeal on this point. However it did accept that the inclusion in the FAD of the results of a cost utility analysis relating to a non-authorised use (ie etanercept continuous), was unnecessary and likely to be confusing.

2.4 Serono alleged that there had been procedural unfairness, and a breach of legitimate expectation, in this appraisal. First, the Institute had failed to provide the economic model. Without this the appellant was unable to understand the basis for the guidance nor make a fully informed submission to the Institute. Second, although Serono was informed that the reason for failing to provide the model was that it included "commercial-in-confidence" data, this was procedurally unfair. The appellant claimed that procedural fairness was not outweighed by obligations to uphold the confidentiality of information submitted as "commercial-in-confidence".

Professor Sculpher explained that the structure behind the economic model) was fully described in the TAR (page 357 to 358); and that the full model itself was also available in the TAR (334 to 344). Collectively, these provided a complete basis for anyone to create a working model of the approach used by the Technology Assessment Group (TAG). Dr Garner stated that approaches to Wyeth, for the release of the "commercial-in-confidence" data used to populate the model, had been rejected.

The Appeal Panel did not accept that the Institute had failed to disclose the economic

model used in the cost utility analysis. The Institute had clearly done so. As for the argument that material submitted as confidential ought to have been disclosed, the panel accepted Serono's argument that it is not an absolute legal rule that confidential material may not be disclosed. However the panel considered that it is of the utmost importance to the Institute's work that it can receive material in confidence from consultees, and that consultees can be confident that an undertaking of confidentiality from the Institute is reliable. Hence, the Institute's procedures allowed for non-disclosure of information submitted as "commercial-in-confidence"; and the Institute seemed to have acted fairly and properly in contacting the consultee to see if it would consent to disclosure. In the light of the consultee's refusal, and in the absence of a compelling reason requiring disclosure (or non-use), the panel concluded that the failure to disclose does not constitute a breach of the Institute's processes or unfairness.

The Appeal Panel therefore dismissed the appeal on this point.

2.5 Wyeth noted that the statement in the Appraisal Consultation Document (ACD) 4.1.2.4 *"The larger RCT also provided data on patients who were re-treated. Across all doses, the mean difference in PASI score after 12 weeks re-treatment [with etanercept t} compared with the initial 12 week treatment was -0.5 (95% CI, -1.09 to 0.09), indicating that there was no statistically significant difference"* had been omitted from the FAD without explanation. It appeared to the appellant that the decision to remove this statement in some way related to the detailed comments in Appendix A of Serono's submission on the ACD. Serono's submission on the ACD had been provided to Wyeth only in summary form and Appendix A had not been included. Since the comments in Appendix A related to Wyeth's published data they could not be "commercial-in-confidence"; and they should have been made available to the appellant for consideration and comment.

The Appeal Panel noted that according to the April 2004 edition of the *Guide to the technology appraisal process* (paragraph 4.5.4.3) consultee comments should be circulated with the FAD. In response to questions from the panel, Ms Pinwell stated that although this appraisal commenced and was conducted under the June 2001 appraisal process, which did not require disclosure of consultees' comments, the Institute had nevertheless tried to ensure that consultees' comments were disclosed. Due to an error, this had not occurred in this instance. The representatives of Serono, present at the appeal, confirmed that Appendix A of their submission on the FAD was not "commercial-in-confidence".

In response to questioning by the Appeal Panel, Prof Barnett stated that he could not recall why the particular sentence that appeared in the ACD 4.1.2.4 had been omitted from the FAD.

The Appeal Panel considered that the Institute had not, strictly, failed to apply its published procedures (because the June 2001 procedures did not require the disclosure of comments on an ACD). However as Ms Pinwill had very fairly admitted it did fail to apply its normal processes in not disclosing Serono's comments to the appellant. The Appeal Panel considered Wyeth had a legitimate expectation that those comments would have been provided. Furthermore, it was clear to the panel

that Appendix A of Serono's submission was, at least in part, a critique of the efficacy of etanercept during re-treatment. In the absence of any explanation as to why the sentence in ACD 4.1.2.4 had been omitted from the FAD the Appeal Panel considered that there were *a priore* grounds for considering that it may have been due to the arguments raised in Appendix A of Serono's ACD submission.

As Wyeth did not have material which may well have prompted the removal of the sentence in question, and would genuinely have been unclear as to what the reason for the deletion was, they were not able to consider whether or not that removal should have been appealed against on the grounds of perversity. The Appeal Panel additionally considered that this was unfair.

The Appeal Panel upheld the appeal on this point. The failure of the Institute to apply its normal processes frustrated a legitimate expectation and placed the appellant at a disadvantage in addressing an issue that was germane to the appraisal of their product.

3. Appeal Ground Two: The Institute has prepared guidance which is perverse in light of the evidence submitted.

3.1 The Association claimed that the choice between efalizumab and etanercept should depend on an overall assessment of the patient including consideration of the relative potencies of the products and their side effect profiles. In addition, because efalizumab is a slower acting agent, the results of its therapeutic efficacy at 12 weeks may underestimate its full clinical benefits in an individual patient.

Prof Barnett accepted that there might be good reasons, on clinical grounds, to use efalizumab before a trial of etanercept . The guidance (FAD 1.3) was intended to provide such flexibility. Nevertheless, etanercept was more cost effective than efalizumab and was therefore, generally, to be preferred. He also pointed out that the requirement to assess patients' on efalizumab at 12 weeks was necessitated by the terms of the product's marketing authorisation.

The Appeal Panel did not consider that the Appraisal Committee had prepared guidance that was perverse in the light of the evidence. FAD 1.3 provided reasonable flexibility for prescribers; and the Appraisal Committee had been correct in recommending use of efalizumab as advised in its marketing authorisation.

The Appeal Panel therefore rejected the appeal on this point.

3.2 The Association pointed out that there would be some NHS patients who were already undergoing treatment with efalizumab without undergoing a trial of etanercept . It would be reasonable for them to be allowed to continue.

The appeal panel considered, as a point of policy, that the Institute did not

recommend the withdrawal of treatments for individual patients that had been started before the publication of NICE Technology Appraisal Guidance.

The Appeal Panel felt that the failure to make the Institute's policy clear in this case was likely to have been an oversight rather than a deliberate action. It therefore considers that this is a case for a correction of an error in the FAD rather than a successful ground of appeal as such. However it requests the inclusion of an appropriate sentence that allows for continued treatment with efalizumab for those who are already undergoing treatment with it at the time the guidance is issued, unless and until the patients and their clinicians consider it is appropriate to stop.

3.3 The Association pointed out that the guidance restricted patient choice.

The Appeal Panel felt that, whilst patient choice was desirable, this should not be such as to promote the use of, for example, cost ineffective treatments. Legitimate restriction of patient choice in one technology on cost or clinical effectiveness grounds may well free resources to increase patient choice in other technologies. The panel did not, therefore, consider that the Appraisal Committee had acted perversely.

The panel dismissed the appeal on this point

3.4 The Association claimed that guidance will impede the ability of the proposed UK patient register to compare the safety profiles of the two treatments.

The Appeal Panel reminded the Association that the Institute was required to base its guidance primarily on considerations of clinical and cost effectiveness rather than the requirements of research convenience. The panel therefore did not consider that the Appraisal Committee had acted perversely.

The Appeal Panel dismissed the appeal on this point.

3.5 The Association alleged that the NHS tariff, for 20 days admission to hospital for severe dermatological conditions, was £5,214.51 rather than £2,681 as claimed in the FAD (2.12).

Dr Hawkins stated that the costs for hospital inpatients, used in the economic model, had been based on the NHS tariff for severe dermatological conditions and that the figure of £2,681, in the FAD (2.12) was erroneous but had not been used in calculations.

The Appeal Panel did not consider that the Appraisal Committee had acted perversely. But, in dismissing the appeal on this point, the panel requests that the figure in FAD 2.12 be corrected with the figure actually used in the calculations.

3.6 Serono claimed that the therapeutic sequence recommended in the FAD was self-evidently perverse because it subjects patients to a greater risk of relapse from intermittent therapy. Serono claimed that such sequencing could only be justified if there was clear advantages in terms of efficacy and cost effectiveness.

Professor Barnett pointed out that the intermittent use of etanercept, as described in the FAD, was strictly in accordance with the terms of its marketing authorisation. He pointed out that for efalizumab, its marketing authorisation permitted continued use, indefinitely, in patients who had achieved a satisfactory response by 12 weeks. By contrast, patients who had achieved a satisfactory response to etanercept , by 12 weeks, were only permitted (under the terms of its marketing authorisation) to continue for a further 12 weeks before a mandatory withdrawal of treatment. The marketing authorisation for etanercept allowed it to be re-instated in patients who relapsed following withdrawal at 24 weeks.

Professor Barnett went on to state that it was largely the withdrawal of etanercept, and the treatment-free period before relapse, that underpinned the difference in cost utilities between the two products. He accepted that the FAD did not, perhaps, explain this as well as it might; and that amendments might be helpful. In response to questioning, by the panel, he agreed that if etanercept were to be given continuously, like efalizumab, the two treatments would have similar cost utilities. .

The Appeal Panel considered that the Appraisal Committee's reasoning was logical and that it had not acted perversely. Nevertheless, the FAD failed to indicate, clearly, the basis for the committee's differentiation between the two products on grounds of cost effectiveness. This may be of some importance, for example, to inform the judgement of a clinician who treats a patient who relapses very rapidly indeed when etanercept is withdrawn.

Although the panel dismissed the appeal on this point, as the FAD will be remitted to the Committee on other grounds in any case, it advises the Institute to amend the FAD in such a way as to indicate, more clearly, the basis for the differential treatments of the two products, and specifically the significance of the treatment-free period when treating with etanercept.

3.7 Serono alleged that the Appraisal Committee had given insufficient weight to the CLEAR study. The creation, in the guidance, of a subset of patients who failed to respond to etanercept was not evidence-based.

The Appeal Panel noted its comments in paragraph 2.2 (above) and were satisfied that the Appraisal Committee had, indeed, given considerable attention to the CLEAR study. It did not consider that the Appraisal Committee had taken a perverse approach in its evaluation. Nor did it consider that the Appraisal Committee had been perverse in positioning the two treatments on the basis of their differential cost effectiveness ratios (see paragraph 3.6 above).

The Appeal Panel dismissed the appeal on this point.

3.8 Serono alleged that the Appraisal Committee had perversely made assumptions about the efficacy of etanercept in its licensed indications; and, given the paucity and poor quality of the published prospective data on etanercept , it had been biased in its approach.

Professor Barnett explained that much of the data supporting the clinical effectiveness of etanercept had been submitted as "commercial-in-confidence". The Appraisal Committee had considered this evidence most carefully and had been persuaded that the available data supported the use as described in the FAD.

The Appeal Panel accepted that the Appraisal Committee had given appropriate consideration to the quality of the evidence about etanercept ; and that it had not acted perversely.

The Appeal Panel dismissed the appeal on this point but requests that, at appropriate points in the FAD, the existence and relevance of the "commercial-in-confidence" data that supports the committee's conclusions be included.

3.9 Serono alleged that the Appraisal Committee appeared to have relied on clinical opinion, rather than the evidence base, in coming to its conclusions.

The Appeal Panel noted Professor Barnett's comments in paragraphs 2.2 and 3.8 (above) and did not consider that the Appraisal Committee had given inappropriate weight to clinical opinion. It found, therefore, that the committee had not been perverse in its appraisal of the totality of the relevant information.

The Appeal Panel dismissed the appeal on this point.

3.10 Serono alleged that the creation of a sequence for a rare condition was susceptible to bias in respect of patients' response rates. The appellant additionally claimed that there were uncertainties in the economic modelling and consequent uncertainties in the estimates of cost effectiveness.

Professors Barnett and Sculpher indicated that the model had included data that had been submitted as "commercial-in-confidence". The appellants were, therefore, unable to assess its quality and veracity. In response to a question from the panel, Professor Barnett stated that other health economists on the Appraisal Committee had examined the TAG's model in very great detail and considered that it had captured the totality of the available data in an appropriate manner.

The Appeal Panel were reassured that the Appraisal Committee had given appropriate scrutiny to the TAG's economic model, and did not consider that its approach had been perverse.

The Appeal Panel dismissed the appeal on this point.

3.11 Serono alleged that there had been a failure to take account of the re-treatment data relating to the efficacy of etanercept . In particular, it had ignored information in the EMEA's EPAR (etanercept scientific discussion paper) on re-treatment response rates to eternacept.

The Appeal Panel noted Prof Barnett's statements in paragraph 2.2 (above) and were satisfied that, on the totality of the available evidence, the Committee had not acted perversely.

The Appeal Panel dismissed the appeal on this point but requested (see paragraph 2.2 above) that the FAD draws attention to the existence and relevance of the "commercial-in-confidence" data that supported the Appraisal Committee's reasoning and conclusions.

3.12 Serono alleged that the failure to take account of the re-treatment data relating to the efficacy of etanercept had resulted in perverse conclusions about its cost effectiveness.

The Appeal Panel noted Prof Barnett's statements in paragraph 2.2 (above) and were satisfied that, on the totality of the available evidence, the Committee had not acted perversely.

The Appeal Panel dismissed the appeal on this point but requested (see paragraph 2.2 above) that the FAD draws attention to the existence and relevance of the "commercial-in-confidence" data that supported the Appraisal Committee's reasoning and conclusions.

3.13 Serono alleged that the Appraisal Committee had failed to take proper account of the QALYs lost due to relapse following the withdrawal of treatment with etanercept .

Professor Barnett stated the economic model took account of this using data submitted "commercial-in-confidence" by the manufacturer of etanercept .

The Appeal Panel accepted that the Appraisal Committee had based its conclusions about the cost effectiveness of etanercept on appropriate information; and that it had not acted perversely

The Appeal Panel dismissed the appeal on this point but requested (see paragraph 2.2 above) that the FAD draws attention to the existence and relevance of the "commercial-in-confidence" data that supported the Appraisal Committee's conclusions.

3.14 Serono alleged that there was insufficient justification to discriminate between the two products (efalizumab and etanercept) and to do so was therefore perverse.

The Appeal Panel, noting Professor Barnett's comments in paragraph 2.2 (above), considered that the Appraisal Committee had not been perverse in its conclusions.

The Appeal Panel dismissed the appeal on this point.

4. Appeal Ground Three: That the Institute has exceeded its legal powers

4.1 Serono alleged that the Appraisal Committee had exceeded the scope of the appraisal and that the sequencing advice was therefore ultra vires. The FAD created a subset of patients who failed "to respond to etanercept " and imposes a de facto restriction on the use of efalizumab which is not part of the product's authorised indications.

The Appeal Panel noted that the objective, in the final scope of the appraisal (issued February 2004), was *"to establish the clinical and cost effectiveness of efalizumab and etanercep t within their licensed indications for the treatment of psoriasis and to produce guidance to the NHS in England and Wales".* The Appeal Panel also noted that the Institute's Establishment Order (1999) (SI 1999, 220) as amended (SI 1999, 2219) requires that the Institute shall *"perform such functions as in connection with the promotion of clinical excellence and of the effective use of available resources in the health service as the Secretary of State may direct".* The panel also noted that the appellant accepted (see paragraph 2.3 above) that the guidance was consistent with the terms of the marketing authorisation for efalizumab.

The panel considered that, provided the clinical and cost effectiveness of each product was separately and objectively evaluated, (which it had been,) it was clearly within the scope of an instruction to "produce guidance" to go a step further. It was legitimate to take those evaluations and to carry out a comparative exercise that resulted in guidance that "favoured" one product over the other. This amounted to little more than making explicit what would be implicit in the two separate evaluations.

Nor did the panel consider that it was exceeding the Institute's powers to issue guidance that recommended use that was less extensive than a product's marketing authorisation.

Finally, the panel did not accept that the guidance had created a subset of patients and that this was outside the scope of the appraisal. This was really a restatement of the first point raised under this heading. If a comparison of two objective evaluations produces a favoured treatment and a less favoured (but still acceptable) treatment, then any patients who cannot have the favoured treatment (for example because of contraindications) could be described as a "subset" of patients. But here this is a legitimate outcome at the end of an appraisal process which did not begin with subsets, rather than the illegitimate creation of arbitrary subsets at the beginning of the appraisal process.

The panel therefore rejected the argument that the Institute would exceed its legal powers by promoting the use of one treatment, over another, on grounds of cost or clinical effectiveness.

The Appeal Panel dismissed the appeal on this point.

4.2 Serono alleged that the FAD contained fundamental mistakes of fact which vitiated the guidance. These included: the creation and reliance of a subset of patients who “fail to respond to etanercept ”; the use of an inappropriate baseline to measure patient’ response to treatment with etanercept ; and flawed assumptions about etanercept re-treatment rates and QALYs lost due to relapse.

The Appeal Panel, noting Professor Barnett’s comments in paragraph 2.2 (above) did not consider that the appellant had demonstrated any fundamental mistakes of fact in the FAD.

The Appeal Panel dismissed the appeal on this point.

5. Conclusion

4.1 The appeal panel has upheld this appeal on ground 1 (paragraph 2.1 and 2.5, above) but dismissed the appeal on all other grounds.

4.2 The panel requests that the Appraisal Committee review the FAD in the light of its findings. In addition, and in order for the guidance to be more accessible to its intended audience, the panel also invites the Appraisal Committee to address the comments in paragraphs 2.2, 2.3, 3.2, 3.5, 3.6, 3.8, 3.11, 3.12, and 3.13 (above). The Committee should publish a revised FAD (or, at its discretion, a revised ACD) in due course.