NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

APPEAL HEARING

Advice on adalimumab, etanercept and infliximab for the treatment of Rheumatoid Arthritis

Decision of the Panel

April 2007

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Introduction

1. An Appeal Panel was convened on 4th April 2007 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis

2. The Appeal Panel consisted of Mr Mark Taylor (chair of the Panel), Mrs Jenny Griffiths (non-executive director of the Institute), Mr Peter Sanders (lay representative), Dr Angus Sim (industry representative), and Professor Robin Ferner (NHS representative).

3. The Panel considered appeals submitted by:

Abbot Laboratories Ltd
Arthritis and Musculoskeletal Alliance (ARMA)
National Rheumatoid Arthritis Society (NRAS)
Royal College of Nursing (RCN)
Schering-Plough Ltd
Wyeth Pharmaceuticals

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), Dr Carole Longson (Director, Centre for Health Technology Evaluation), Dr Darren Ashcroft, Zoe Garrett, and Janet Robertson.

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

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.

7. There are three grounds on which an appeal can be lodged:
The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process;
The Institute has prepared guidance that is perverse in light of the evidence submitted;
The Institute has exceeded its legal powers.

8. The chair of the Appeal Panel (Mr Mark Taylor), in preliminary correspondence, had confirmed that the appellants had potentially valid grounds of appeal as follows:

Abbott Laboratories Ltd: Grounds 1 and 2
Wyeth Pharmaceuticals: Grounds 1 and 2
Arthritis and Musculoskeletal Alliance: Ground 2
National Rheumatoid Arthritis Society: Ground 2
Royal College of Nursing: Ground 2
Schering-Plough Ltd: Ground 2

9. The three drugs considered in this Final Appraisal Determination, adalimumab, etanercept and infliximab, are antiTNF treatments. They inhibit the actions of tumour necrosis factor (TNF), a factor in the blood that causes inflammation in rheumatoid arthritis. Alternative agents for the treatment of rheumatoid arthritis, such as methotrexate and sulphasalazine, are termed Disease Modifying Anti Rheumatic Drugs (DMARDs), or standard disease-modifying agents.

Ground 1: The Institute has failed to act fairly and in accordance with its procedures

Schering-Plough Ltd

10. Schering-Plough did not wish to pursue their Appeal under ground 1, preferring to develop the argument under ground 2.

Wyeth Pharmaceuticals

11. Wyeth 4.1 Failure of the Assessment Group to use probabilistic sensitivity analysis, when this is recommended by the Guide to the Methods of Technology Appraisal (sections 5.9.3.1 and 5.9.3.2.)

12. Dr Longson, for the Appraisal Committee, explained that the Institute had both a Process Guide and a Methods Guide. The latter gives general principles, and helps to explain what methods may be appropriate, but does not in her view form a set of prescriptive instructions.

13. Ms Garrett briefly explained the Birmingham Rheumatoid Arthritis Model (BRAM) to the Panel. The model examined different potential sequences of treatment for patients with rheumatoid arthritis. A patient enters the model with a set of characteristics, and starts a treatment that continues until the characteristics diverge sufficiently for treatment to be changed. There is then an opportunity to give a subsequent treatment. The assessment group examined outcomes, judged by Health Assessment Questionnaire (HAQ) scores, for various possible treatment strategies, including antiTNF treatment first; after two standard disease-modifying agents; and last in the sequence.

14. Dr Longson explained that the assessment group had chosen to use patient simulation modelling, and that probabilistic sensitivity analysis was difficult with this approach; but manufacturers did provide probabilistic sensitivity analyses and those were considered by the Appraisal Committee. Professor Barnett, for the Appraisal Committee, explained that the assessment group had judged that probabilistic sensitivity analysis was not required. If the approach had been used

in this case, it would have been likely to generate a higher cost per quality-adjusted life year than the Appraisal Committee in fact used.

15. Mr Baxter, for Wyeth, stated that, had probabilistic sensitivity analysis been used, the Appraisal Committee would have been able to examine cost-effectiveness more completely, and reach more certain conclusions.

16. The Appeal Panel observed that the relevant ground of appeal is that "The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's **Guide to the Technology Appraisal Process** [emphasis added]**.**"

17. Any argument based on the Guide to the Methods of Technology Appraisal ("Methods Guide") faces formidable difficulties. First, the Appellant has to argue that the Methods Guide is prescriptive in whatever particular has not been followed. The Panel agreed with Dr Longson that the Methods Guide is not as a rule prescriptive, and so this will usually be a difficult point to establish. Second, as a failure to follow the Method Guide is not of itself a valid ground of appeal (even in a case where the Methods Guide is prescriptive) the appellant will also have to establish that the failure is procedurally unfair. It is possible to conceive of cases where this could be shown (where, for example, the appellant submits evidence generated or compiled in accordance with the recommendations of the Methods Guide and, unknown to the appellant, the Appraisal Committee discount that evidence on the grounds of its method of generation or compilation). However the Appeal Panel judges from past experience that it will be a rare case where this can be shown.

18. In the light of this judgment it may well be appropriate in the future for the Appeal Panel chairman to adopt a more robust approach to allegations of unfairness based on a failure to follow the Methods Guide at the initial scrutiny stage.

19. Accordingly the Panel decided that the assessment group was not obliged to undertake a probabilistic sensitivity analysis, and accepted that such an analysis would have been difficult or impossible with the patient simulation approach chosen on this occasion. The Appeal Panel also decided that some relevant information was available to the Appraisal Committee from the manufacturers' submissions. The omission of a probabilistic sensitivity analysis was not unfair.

20. The Appeal Panel therefore dismissed the appeal by Wyeth on the ground of unfairness.

Abbott Laboratories

21. (Abbott 3.1–3.5) The selection of effectiveness estimates was unfair and unreasonable.

22. Data on the relative effectiveness of treatments for rheumatoid arthritis have not been taken from a systematic review of the evidence, as required by the Guide to the Methods of Technology Appraisal.

23. BRAM uses data on HAQ multipliers to estimate the effectiveness of different treatments, but the Committee did not explain which data were used to make the estimates, nor which studies were excluded.

24. The results from the current BRAM differed substantially from those of a previous use of the model.

25. Mr Arundel McDougall, for Abbot Laboratories, stated that the Appraisal was unfair, because it relied on estimates of the efficacy of standard disease-modifying agents extracted from a systematic review, details of which were not provided.

The results appeared to differ from those used in another appraisal (of anakinra) based on the same data. The appraisal was also unfair because in the analysis that underpinned it there was no adjustment for the differences between populations. The 'speculative analysis' considered only treatment with adalimumab alone, and failed to consider treatment with adalimumab and methotrexate combined.

26. Professor Barnett assured the Appeal Panel that the Appraisal Committee well understood that drugs could have different effects on the disease at different stages, and when used at different points in a sequence of drugs.

27. Ms Garrett explained that the search strategy for the trials used in the assessment was explicitly listed [at Appendix 6 of the Assessment Report] and could be replicated.

28. Mr Alistair Curry, for Abbott, stated that the company had examined data from the British Society for Rheumatology Biologics Register (BSRBR).

29. Professor Barnett stated that the Appraisal Committee had considered the BSRBR data. There were no randomised controlled trials on which to base the estimates of relative effectiveness of different drugs at different stages in the disease. In consequence, the Appraisal Committee had to make a judgement about the relative values of standard disease-modifying agents at different stages of rheumatoid arthritis. Different studies of the efficacy of standard disease-modifying agents examined different populations.

30. Ms Garrett pointed out that there was no robust way to adjust estimates of efficacy for these differences in population. Abbott had themselves submitted a model that had no adjustment for population differences.

31. Dr Longson reminded the Appeal Panel that the Appraisal Committee had seen four other models, some very sophisticated, submitted in addition to the BRAM.

32. Professor Barnett reiterated that, under a series of assumptions that the Appraisal Committee considered reasonable, the use of one antiTNF treatment was close to the acceptable margin for cost-effectiveness. Any diminution of cost-effectiveness would fall outside the margin.

33. Mr Curry expressed concern that the data used to deduce HAQ multipliers were not correct.

34. The view of Professor Paul Emery, speaking for NRAS, was that patients with late disease differed from those with early disease, both because their condition was refractory to standard treatments and because TNF was not the main mediator of inflammation in late disease. This made estimates of efficacy in late disease based on early disease very unreliable.

35. Dr Christopher Deighton, for ARMA, argued that three-quarters of the patients treated with antiTNF therapy in the BSRBR cohort were not co-prescribed methotrexate. The values derived for the Incremental Cost Effectiveness Ratio (ICER) for use of a second antiTNF treatment were likely to be too high.

36. With regard to the 'speculative analysis,' Professor Barnett stated that this was not intended to represent a 'real-world' example, but only to show how adjustment might be made for the fact that the model mixed data from randomised controlled trials and from observational studies. The Appraisal Committee was clear that, in general, the combination of an antiTNF therapy with methotrexate was more effective than antiTNF therapy alone. The evidence did not allow exact figures for the efficacy of a second antiTNF therapy when used after a first antiTNF therapy had failed, but there was likely to be some diminution in efficacy.

37. Mr Curry accepted that there was likely to be some loss of efficacy when a second antiTNF therapy was used after a first antiTNF therapy has failed, and that it was reasonable to take this as 30%, as the assessment group had done.

38. Ms Garrett accepted that there was a great deal of uncertainty in estimates of the efficacy of standard disease-modifying agents in late disease.

39. Dr John Medich, for Abbott, stated that the values of HAQ multipliers used as inputs to the model were derived from the treatment arms of randomised trials in early rheumatoid arthritis, and were not appropriate.

40. Professor Barnett reiterated that there were no data on standard disease-modifying agents used after antiTNF therapy, and their efficacy was therefore a matter for speculation.

41. The Appeal Panel observed that the assessment report described the search strategies for several systematic reviews, including a review of the efficacy of standard disease-modifying agents. The company had had the opportunity to undertake the same reviews, based on the search strategy described. The Appraisal Committee had therefore conducted itself fairly.

42. The Appeal Panel could see no unfairness and therefore dismissed the appeal on this point.

43. The Appeal Panel also concluded that, in the absence of direct information from clinical studies, the approach taken by the Appraisal Committee with regard to the use of information on standard disease-modifying agents was not intrinsically unfair, and did not make the use of the BRAM unfair. The BRAM had, moreover, formed only part of the evidence before the Appraisal Committee.

44. The Appeal Panel therefore dismissed the appeal on this point that was brought on the grounds of unfairness.

Ground 2: The Institute has prepared guidance that is perverse in light of the evidence submitted

Abbott Laboratories

45. The Appeal Panel went on to consider whether the Appraisal Committee had reached a reasonable decision in respect of each of the points raised by Abbott (above). The Appeal Panel was aware that the Appraisal Committee could only base decisions on the evidence presented to it. The Appraisal Committee had evidence on the effectiveness of standard disease-modifying agents from a systematic review, and that was reasonable, albeit all parties agreed that the evidence available was not ideal for the question asked of the Appraisal Committee. The Appraisal Committee and the Final Appraisal Determination,which they issued, can not be criticised for that fact.

46. The Appraisal Committee had considered the problem of how to express the efficacy of disease-modifying agents at different stages of disease. The Appeal Panel noted that there were no robust data on the efficacy of standard disease-modifying agents used in late disease, or used after an antiTNF treatment had failed. It was, in itself, not unreasonable for the Appraisal Committee to conclude that, in the absence of better evidence, the values for the HAQ multipliers should not be adjusted. Abbott had not made such adjustments in the model they had submitted, and presumably therefore they too considered this reasonable.

47. Considered in isolation this approach was not perverse. However, the effect of this approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of a second antiTNF treatment.

48. The Appeal Panel noted the apparent disparity between the results for the efficacy of standard disease-modifying agents that the BRAM produced in its current version, and in a previous version used in the assessment of anakinra. The Appeal Panel noted that there were difficulties with the BRAM. However, the main conclusion drawn by the Appraisal Committee from the results that the model produced was that antiTNF treatment could be cost-effective. All the Appellants accepted this. The BRAM had been used in previous assessments, and the main conclusions drawn from its results had also been accepted then. The Panel decided that it was not necessarily unreasonable for the Appraisal Committee to accept the results from the current BRAM.

49. Considered in isolation this approach was not perverse. However, the effect of this approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of a second antiTNF treatment.

50. (ARMA Page 1 bullet points 1 and 2) The decision on the efficacy of a second antiTNF treatment was unreasonable, given the information from the BSRBR that the Appraisal Committee had seen.

51. (ARMA Page 2 bullet point 2) Changes in HAQ and cost-effectiveness estimates for second antiTNF treatment and standard disease-modifying anti-rheumatic drugs.

52. Dr Deighton told the Appeal Panel that antiTNF treatment had made an enormous difference to patients with rheumatoid arthritis. ARMA considered that the Appraisal Committee had reached an unreasonable conclusion. The Alliance had little confidence in the effects of standard disease-modifying agents in patients who have failed to benefit from antiTNF treatment. When a second antiTNF

treatment was used after a first had failed to work, ARMA believed that the ICER for second use was similar to first use, and the adjustment made by the assessment group to the efficacy of a second antiTNF was greater than warranted; in any event, there was significant uncertainty over this. The Alliance also found it unreasonable to restrict the use of a second antiTNF treatment to those who had suffered an adverse reaction to the first antiTNF treatment, even though there was no information that suggested the efficacy of the second antiTNF treatment would be different to use of a first antiTNF. There were differences of opinion as to the effectiveness of standard disease-modifying agents, and some believed they would have no effect at all if used after two standard disease-modifying agents and an antiTNF treatment had failed, as the Final Appraisal Determination proposed. If the belief were correct, the ICER would be more favourable.

53. Professor Emery supported the view that standard disease-modifying agents would have 'almost no effect' in this circumstance.

54. Professor Barnett emphasized that, in the absence of published evidence, the possible efficacy of standard disease-modifying agents was a matter of judgment. The Appraisal Committee had heard various views from clinicians, and had to decide among them.

55. The Appeal Panel considered whether the Appraisal Committee had been unreasonable in its judgment of the efficacy of standard disease-modifying agents. It had evidently considered how to approach the problem in the absence of robust evidence. Considered in isolation the approach taken was not perverse. However, the effect of this approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of a second antiTNF treatment.

56. (ARMA Page 3 Bullet point 1) The Appraisal Committee's preference for the BRAM was unreasonable, when four other models calculated substantially lower ICERs.

57. Dr Deighton stated that there was considerable uncertainty over the use of BRAM, which produced higher ICERs than any of the other four models, including the model submitted by ARMA.

58. Mrs Ailsa Bosworth, for the NRAS, explained to the Appeal Panel her own experience of severe rheumatoid arthritis that was held in check by a third antiTNF treatment when the first and second antiTNF treatments she had received had been unsatisfactory. Patients felt better on antiTNF treatment, but the HAQ score failed to capture some of the benefits, especially in late disease. She also explained the much wider costs of rheumatoid arthritis to society, although she accepted that the Appraisal Committee, in accordance with NICE's remit from the Department of Health, had to make a judgment on the costs to the National Health Service and Personal Social Services.

59. Professor Emery supported Dr Butler in stating that treatment of early rheumatoid arthritis with antiTNF treatment could achieve remission, and supported Mrs Bosworth in her view that there were difficulties with the HAQ score.

60. Professor Barnett and Ms Garrett described how the Appraisal Committee had discussed in detail the use of HAQ scores and other measures to derive estimates of quality of life, and agreed that the HAQ score had a number of disadvantages. These were discussed in paragraph 4.3.2 of the Final Appraisal Determination. Professor Barnett agreed that in using the HAQ score, the assessment group had made the 'least bad choice.'

61. The Appeal Panel considered whether the use of HAQ scores as derived was unreasonable, and concluded that it was not. However, the HAQ scores in late

rheumatoid arthritis were difficult to interpret, principally because the scale was non-linear and the prospects for an improvement in score after joint damage had occurred were reduced. Considered in isolation the approach taken was not perverse. However, the effect of this approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of a second antiTNF treatment.

62. (A**RMA Page 3 Bullet point 3) The decision not to recommend treatment with a second TNF-alpha inhibitor, even though the cost-effectiveness was only slightly diminished and still within an acceptable range, was unreasonable, given the data from registers and given that randomised controlled trials were unlikely.**

63. Dr Deighton accepted that the estimates of cost-effectiveness derived from the ARMA model lay within the range that the assessment group had estimated from the BRAM, although the estimates from the BRAM itself were more uncertain.

64. Professor Barnett explained that the cost-effectiveness of the first antiTNF treatment used was close to the margin of acceptability, and that was true only when certain favourable assumptions – for example, that the HAQ score did not increase during antiTNF treatment; and that treatment was permitted for up to six months – were incorporated into the BRAM. Without those assumptions, even first use was outside the normally accepted range. The Appraisal Committee accepted that the use of a second antiTNF treatment could in theory be cost-effective, but that could not be proven. There was no good evidence as to the efficacy of a second antiTNF. In the light of evidence before it, the Appraisal Committee had concluded that any diminution in efficacy between first and second use would take the cost-effectiveness of second use outside the acceptable range.

65. Dr Robin Butler, for ARMA, explained that the appellant's submission, based on data from the BSRBR, showed ICERs within an acceptable range, even though the patients in that cohort were likely to benefit less from treatment, having had rheumatoid arthritis for over ten years on average, and having been treated with six standard disease-modifying agents on average.

66. Dr Deighton told the Appeal Panel that it was appropriate to adjust for the reduced efficacy of a second antiTNF treatment, but that in the model provided by ARMA, the intervention remained cost-effective, even with this adjustment.

67. The Appeal Panel accepted that the Appraisal Committee was entitled to consider whether, on the basis of the evidence before it, the cost-effectiveness of a second antiTNF treatment was outside the acceptable range, and to conclude that it was. Considered in isolation the approach taken was not perverse. However, the effect of this approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of a second antiTNF treatment.

Royal College of Nursing

68. (RCN Point 1. Economic Model) the BRAM was defective, and its use was unreasonable. It produced results that differed substantially from the other models submitted. It used the HAQ score, which will be flawed when applied to patients with late disease. The disparity between the ICERs determined by different models was unexplained. Treatment effects and costs for patients returning to sub-optimal disease-modifying anti-rheumatic drugs once one antiTNF treatment has failed may be understated. The earlier treatment is instigated, the greater the likely benefit, but the BSRBR data come from patients treated late in the disease.

69. Mrs Susan Oliver, for the RCN, described the dramatic changes that had taken place in care of patients with rheumatoid arthritis, who were now largely treated

as outpatients where in the past they had required hospital admission. She expressed concern that the BRAM failed to take these and other savings fully into account.

70. Trials of antiTNF treatment in early rheumatoid arthritis would, she hoped, show that joint damage was reduced and cost of joint replacement, which was approximately £5000 per joint, avoided.

71. Mrs Oliver also explained that the economic analyses apparently omitted other factors, such as the cost of treating cardiovascular disease in patients with active rheumatoid arthritis, although Professor Barnett questioned whether this was relevant in discussing the cost-effectiveness of antiTNF treatment, which was not known to improve outcomes in cardiovascular disease in patients with rheumatoid arthritis.

72. Mrs Oliver accepted that, while the RCN was critical of the models used, it had not provided data for an economic model, or a further economic analysis, for the Appraisal Committee to consider.

73. Professor Barnett assured the Appeal Panel that relevant costs likely to be incurred by patients with late stage disease had been included in the BRAM, and that adjustments for these costs, and for other factors, had reduced the incremental cost effectiveness from about £100,000 per quality-adjusted life year to a value the Appraisal Committee had finally agreed as just acceptable for first use of antiTNF treatment.

74. Dr Ashcroft, for the Appraisal Committee, stated that the cost of joint replacement was accounted for in the £860 per year per one point reduction (improvement) in HAQ score had been included in the model.

75. The Appeal Panel noted that section 4.3.9 of the Final Appraisal Determination states: '*The Committee was persuaded that the inclusion of benefits related to reduction in hospitalisations and longer-term requirements for joint replacement, although based on as yet unproven assumptions, was important in the economic modelling and an important factor to be taken into account in the costs associated with the treatment of rheumatoid arthritis. The Committee was however persuaded that this had been accounted for in the revisions to the Assessment Group model, and that this was not a key driver of the differences in cost effectiveness between the various models reviewed.*'

76. The Appeal Panel was clear that allowance for Health Service costs had been made in the economic models, and agreed that the Appraisal Committee had been reasonable in accepting the assessment group's judgment on this.

77. The Appeal Panel therefore dismissed the appeal from the RCN on that point.

78. With regard to the wider reservations that the RCN had on the use of the BRAM in determining the value of a second antiTNF treatment, the Appeal Panel restated its view that it was not unreasonable for the Appraisal Committee to accept the results from the current version of the BRAM. Considered in isolation the approach taken was not perverse. However, the effect of this approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of an antiTNF treatment.

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79. (RCN Point 2) Switching between anti-TNF treatments was effective, and it was unreasonable to decide against their use.

80. In the College's judgment, Mrs Oliver told the Appeal Panel, 75% of patients would benefit from a second antiTNF treatment if they had failed to respond to a

first **a**ntiTNF treatment. Such treatment brought other benefits, such as a reduction in the dosage of corticosteroids and non-steroidal anti-inflammatory drugs used.

81. In the light of previous discussion, the Appeal Panel concluded that the Appraisal Committee had not been perverse in considering whether, on the basis of the evidence before it, the cost-effectiveness of a second antiTNF treatment was outside the acceptable range, and to conclude that it was. Considered in isolation the approach taken was not perverse. However, the effect of this approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of a second antiTNF treatment.

82. (RCN Point 3) If switching therapy is not supported, nurses and practitioners will face a serious ethical dilemma in guiding patients about their optimum treatment options.

83. Mrs Oliver stated that asking that patients return to using standard disease-modifying agents when one antiTNF treatment had failed was tantamount to asking them to accept palliative care. She also expressed concern that nurses would have to explain to patients that treatments that she and her colleagues considered beneficial might be denied to them as a result of the Appraisal Committee's determination.

84. The Appeal Panel recognized that any constraint on clinical practice could require health care professionals to explain that options had been curtailed. It was the place of the Institute to weigh the potential benefits of treatments against their costs, and the Appraisal Committee had undertaken that task.

85. The Appeal Panel therefore dismissed the RCN's appeal on this point.

Schering-Plough

86. (Schering-Plough 2.1) The Final Appraisal Determination fails to recognise that infliximab represents the least expensive treatment option for patients with rheumatoid arthritis.

87. Dr Brian Muller, for Schering-Plough, said that the company believed infliximab to be the cheapest antiTNF treatment. It also believed that infliximab would be cost-effective if used as a second antiTNF treatment.

88. Dr Muller accepted that there were patients in whom infliximab would not be the cheapest drug.

89. Professor Barnett agreed that the Appraisal Committee had recommended which antiTNF treatment to use on grounds of cost-effectiveness in the case of psoriatic arthropathy, but in that case, with higher doses of infliximab than would be given in RA, the cost of the alternative agent was substantially less. In this case, efficacy was similar, and costs were similar and would depend in part on local circumstances. The Appraisal Committee also wished to allow some freedom to exercise clinical choice among preparations that were administered in different ways.

90. The Appeal Panel recognised that the evidence indicated that the antiTNF treatments were of similar efficacy. The Final Appraisal Determination had not been perverse in stating at paragraph 1.8 that the cheapest agent should generally be used. The appeal by Schering-Plough on this point was dismissed.

91. (Schering-Plough 2.2-2.3) The cost-comparison proposed by the Appraisal Committee in the Final Appraisal Determination is methodologically incorrect. The Final Appraisal Determination recommendations are based on an assumed average weight of 70 kg for patients receiving infliximab and a related assumption that 3 vials are required per infusion.

92. Dr Muller stated that the dose of infliximab depended on the weight of the patient. The Appraisal Committee had accepted an estimate of the cost of infliximab, based on a patient weighing 70 kilograms. This was equivalent to using 3 vials per patient. When the company had considered the weights of a cohort of over 3000 real patients, and calculated from the weights the number of whole vials required, this came to an average of 2.7 vials, not 3 as assumed in the information before the Appraisal Committee.

93. Mr Alan Kane, for Schering-Plough, expressed the view that, even without vial sharing ('vial optimisation'), this meant that the costs of infliximab considered by the Appraisal Committee were 10% higher than the true costs. If vial sharing were taken into account, the disparity would be greater. One hospital had saved £250 000 in one year by introducing vial sharing.

94. Mr Kane accepted that the calculated usage, based on the observed weights was not the same as the observed usage of infliximab in the cohort.

95. Schering-Plough had presented data showing the usage in patients who were part of the BSRBR. These indicated that doses higher than the recommended dose were commonly used. Mr Morris advised that the data should be interpreted cautiously, because it was possible that in some centres values represented doses dispensed and in other centres doses administered.

96. Dr Ashcroft confirmed that the Appraisal Committee had considered the question of vial sharing.

97. Professor Peter Taylor, for Schering-Plough, accepted that vial sharing was not always possible, especially in units with relatively few patients. In some units it was the practice to use the nearest number of whole vials, rather than the exact dose calculated from the patient's weight.

98. The Appeal Panel considered whether the approach used in the BRAM, and described in paragraph 3.3.3 of the Final Appraisal Determination might have been perverse. It concluded that the company's evidence on the true costs of infliximab was not compelling, and that the Appraisal Committee had not been perverse in modelling an average usage of three vials.

99. (Schering-Plough 2.4) In failing to state which is the least expensive treatment option, the Final Appraisal Determination is inconsistent.

100. The Appeal Panel recognized that the Institute had recommended which product to use in the treatment of psoriatic arthropathy, but were persuaded by Professor Barnett's view that there was a clear difference in cost of agents in that condition. This was not true of the antiTNF treatments used in doses appropriate for rheumatoid arthritis, where treatments were of similar efficacy and cost, and where patient factors might be important in choice of agent.

101. The Appeal Panel therefore dismissed Schering-Plough's appeal on this point.

102. (Schering-Plough 2.5) A second TNF-alpha inhibitor will not necessarily be associated with a lower treatment effect compared to a first TNF-alpha inhibitor.

103. Mr James Morris, for Schering-Plough, expressed the view that the data from the BSRBR register could not reasonably have been interpreted to conclude that a second antiTNF treatment was substantially less effective than the first.

104. Professor Barnett stated that the Appraisal Committee would have welcomed more robust evidence, but in this case such evidence was absent. The Appraisal Committee therefore had three choices: to recommend that a drug be used; to recommend that it should not be used; or to permit its use only in clinical

trials. In this case, there was a possibility that the use of a second antiTNF treatment could be cost effective, but the evidence was thin, and therefore in his view it was not perverse for the Appraisal Committee to recommend against the use of a second antiTNF treatment.

105. Dr Longson said that the Appraisal Committee was obliged to reach a clear decision, even though the evidence might be limited in some regards.

106. Mr Morris stated that the company had no additional data that would have helped the Appraisal Committee to make this decision.

107. Professor Taylor explained that a patient who required a second antiTNF treatment did so because of an adverse reaction to the first treatment, or because the first treatment failed to have an initial effect, or because the effect of the first treatment had diminished after a time. The loss of response occurred when patients formed antibodies against the agent, and since agents differed in structure, a response to a second agent was very likely in this circumstance. The Appraisal Committee had accepted that patients who had experienced an adverse effect from one antiTNF treatment could be treated with a second agent.

108. The Appeal Panel, having heard from ARMA and the RCN that it was reasonable to assume some reduction in efficacy of a second antiTNF treatment compared with a first antiTNF treatment, found that the Appraisal Committee had been reasonable to make this assumption on the evidence before them.

109. The Appeal Panel therefore dismissed the appeal by Schering-Plough on this point.

110. **Schering-Plough 2.6 Cost-effectiveness estimates that support the Committee's recommendations are based upon implausible modelling assumptions.**

111. Professor Taylor also stated that it was likely that models based on HAQ scores would underestimate the significance of antiTNF treatment in preventing long-term joint destruction, an effect that was reflected in radiographic scores, and which was not apparent with standard disease-modifying agents.

112. The Appeal Panel considered whether the Appraisal Committee's treatment of the possible efficacy of a second anti-TNF was perverse. It accepted that the evidence base on this issue was far from complete, and that the Committee's approach was not in itself perverse. However, the effect of this approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of a second antiTNF treatment.

Wyeth

113. (Wyeth 1.3) The Appraisal Committee failed to consider the cost effectiveness of the use of TNF α inhibitors as second line therapy.

114. Dr Vignesh Rajah, for Wyeth, contended that the Appraisal Committee had been unfair in failing to consider whether etanercept was cost-effective when used after the failure of one standard disease-modifying agent. In the company's view, the drug was acceptably cost-effective whether used initially or after the failure of two disease-modifying agents, and the cost-effectiveness of use after the failure of one standard disease-modifying agent could therefore be assumed to be intermediate between the two cases. The Appraisal Committee had failed to consider this.

115. Professor Barnett stated again that the Appraisal Committee had held the view that, from the evidence before it, any use of antiTNF therapy would be outside the range of acceptable cost-effectiveness unless a series of favourable

assumptions – such as zero worsening of HAQ score while on treatment – was made. Cost-effectiveness was marginal, even on the most optimistic evaluation. Therefore, any detailed evaluation of a circumstance that was almost certainly less cost-effective was unnecessary: the Appraisal Committee could reasonably judge the cost-effectiveness of such use to be outside the acceptable range. On balance, patients were best served by treatment with two standard disease-modifying agents before antiTNF treatment. Such treatment, he reminded the Appeal Panel, carried important risks, including increased risk of reactivation of tuberculosis, malignancy, and unknown future harms. He considered that clinical evidence also on balance supported the desirability of patients being treated with two DMARDS before trying an antiTNF treatment.

116. Dr Rajah stated that the options in this circumstance were very limited, and that the assessment group had used measures of the effectiveness of standard disease-modifying agents that were fundamentally flawed, because they were taken from one arm of a set of randomised clinical trials. The Decision Support Unit, in its advice to the Appraisal Committee, had specifically drawn attention to this. There was no published evidence to guide a decision on the effectiveness of standard disease-modifying agents after failure of antiTNF treatment, but the 'speculative analysis' that considered their effectiveness to be reduced by 50% did bring the cost-effectiveness within an acceptable range.

117. With respect to the use of poor data, the Appeal Panel accepted that the Appraisal Committee considered all the data presented to it, and that the Committee had considered how best to deal with the paucity of relevant data, and had made a reasonable decision.

118. The Appeal Panel therefore dismissed Wyeth's appeal on this point.

119. (Wyeth 1.4) Undue weight appears to have been given to clinical opinion of the effectiveness of alternative comparator disease-modifying antirheumatic drugs.

120. Mr Garth Baxter, for Wyeth, stated that after failure of two standard disease-modifying agents and one antiTNF treatment, the changes in HAQ score were uncertain, and that the reasonable judgment was to allow the use of a second antiTNF therapy.

121. Professor Barnett questioned the appropriateness of the data from the BSRBR, since this did not represent a randomised controlled trial. Sensitivity analyses had been preformed by the assessment group, and the Appraisal Committee accepted that these covered the range of likely possibilities.

122. Dr Longson reminded the Appeal Panel that appropriate comparative data were not available, so that the Appraisal Committee had to make a judgment about the likely effectiveness. They did what they could with the information available. There was no probabilistic sensitivity analysis, as previously discussed. While it was possible that the standard disease-modifying agents would have no effect after two disease-modifying agents and an antiTNF treatment had failed, that was not something the Appraisal Committee had explored.

123. The Appeal Panel considered whether the Appraisal Committee's treatment of the possible efficacy of standard disease-modifying agents was perverse. It accepted that the evidence base on this issue was far from complete, and that the Committee's approach was not in itself perverse. However, the effect of this approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of a second antiTNF treatment.

124. (Wyeth 1.5) The Appraisal Committee failed to recommend etanercept as a second-line therapy.

125. The Appeal Panel was satisfied that the Appraisal Committee had considered use of an antiTNF treatment before other treatments, and after two standard disease-modifying agents. These were the clinically relevant considerations. It was not unreasonable for the Appraisal Committee to omit any detailed consideration of the potential use of antiTNF treatment as second-line therapy

126. The Appeal Panel therefore dismissed Wyeth's appeal on this point.

127. (Wyeth 2.1) The Appraisal Committee apparently based its decision on a comparison of first and second use of antiTNF treatments when it should have compared second use with standard disease-modifying agents.

128. The cost-effectiveness of a second antiTNF treatment had implicitly been compared with the cost-effectiveness of a first antiTNF treatment. Professor Barnett had explained that the Appraisal Committee's judgment was made on the basis that the cost-effectiveness of the first antiTNF treatment was at the margin, so any less effective treatment was outside the acceptable range. The Appeal Panel accepted that, in the absence of good information on the value of standard disease-modifying agents after a first antiTNF treatment had failed, it was difficult to make the comparison. They also accepted that, in practice, many patients who received a second antiTNF treatment would receive it in addition to a standard disease-modifying agent, not as an alternative.

129. The Appeal Panel understood that the cost-effectiveness of the second antiTNF treatment might be compared with the cost-effectiveness of the first one, and the correct comparators were not available to the Committee. The Committee's approach was not in itself perverse. However, the effect of this

approach, in the context of other approaches taken by the Appraisal Committee to the evidence before it, had been to lead to a perverse conclusion regarding the use of a second antiTNF treatment.

130. (Wyeth 2.2) Inputs into the cost effectiveness model were inconsistent.

131. In the view of the Appeal Panel, it was reasonable for the Appraisal Committee to consider that the BSRBR was not the most appropriate source of data for judging the efficacy of standard disease-modifying agents.

132. The Appeal Panel therefore dismissed Wyeth's appeal on this point.

133. (Wyeth 3.1) There was a failure to recommend the most cost-effective drug.

134. The Appeal Panel decided that the Appraisal Committee had reasonably concluded that the antiTNF treatments were of similar efficacy. Cost-effectiveness then reduced to choosing the least expensive agent, as recommended in the Final Appraisal Determination. The Appeal Panel again endorsed the wording of paragraph 1.8 of the Final Appraisal Determination as entirely reasonable.

135. The Appeal Panel dismissed Wyeth's appeal on this point.

Appeal Panel overall finding regarding ground 2 appeal points

136. While the Appeal Panel found that the Appraisal Committee had not acted unreasonably in any single judgment, it had to combine a series of judgments in reaching its decisions on the use of a second antiTNF agent. The series of judgments included those on the use of the BRAM, the inconsistencies between the results from the BRAM in this and an earlier assessment, the use of HAQ scores as the basis for measuring efficacy, the efficacy of standard disease-modifying agents in different circumstances, the extent to which clinical trial data reflected real-life data, the value of register data in the absence of data from

randomised clinical trials, the true cost of a drug whose dosing is based on weight, the range over which sensitivity analyses should be conducted, and the form of those sensitivity analyses. The sum effect of all the judgments made by the Appraisal Committee on the data presented to it was to make a decision that was unreasonable with regard to the use of a second antiTNF treatment in patients who had failed to respond to a first antiTNF treatment.

137. The Panel considered the fact that, in at least some cases, there was little or no good information to enable the Committee to inform its judgement on some of these issues. It was not the Panel's view that this fact either precluded the Committee issuing guidance at all, or that it required that the guidance reach any particular conclusion. This decision should not be considered to support any such view. Where the Panel considers that the Committee fell into error was in two regards: first, in not quantifying in more detail the effect of certain key uncertainties (in particular the efficacy of standard disease-modifying agents in late disease, and the efficacy of a second antiTNF after a first has failed); and secondly, in not considering the cumulative effect of all of the uncertainties inherent in the data. In combination, and only in combination, the effect was that the Committee's judgement as regards the use of a second antiTNF was perverse.

Ground 3: The Institute has exceeded its legal powers.

138. None of the Appellants wished to pursue an appeal point under this ground.

Conclusion and effect of the Appeal Panel's decision

139. The Appeal Panel rejected all appeals under Ground 1. The Panel also rejected the individual appeals under Ground 2. The Panel upheld the appeals under ground 2 to the extent that they had led to an unreasonable decision with

regard to the use of a second antiTNF treatment where the there had been no response to a first antiTNF treatment.

140. The Appeal Panel's decision is that the guidance must be reconsidered by the Appraisal Committee. The Appeal Panel suggests that the Appraisal Committee reassess the evidence for the cost-effectiveness of a second antiTNF treatment with an extended sensitivity analysis that considers a wider possible range of effectiveness for standard disease-modifying agents when used after antiTNF therapy, a wider possible range of doses for infliximab, and a more complete examination of the minimum effectiveness that would be required of a second antiTNF treatment for it be marginally cost-effective.

141. If the Appraisal Committee should then decline to recommend the use of a second antiTNF treatment in the NHS for patients who have failed to respond to a first antiTNF treatment, the Panel suggests that it explain more fully its reasons for failing to recommend such treatment if there may be a reasonable possibility, on the evidence before the Committee, that the incremental cost effectiveness ratios are within the range that it previously considered to be an effective use of NHS resources. It should also consider explaining more fully why it chose to accept estimates from the BRAM, in preference to the estimates from any of the other four models submitted to it. The factors listed above give guidance as to the issues to be addressed when considering this.

142. However the Panel wishes to state clearly that it is not for it to direct the Committee as to the content of its guidance after reconsideration. It is open to the Committee to reaffirm its earlier guidance, or to change it, as it thinks fit.

143. There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel and the Institute's decision to issue the Guidance may be challenged by an interested party through an application to the High Court for permission to apply for judicial

review. Any such application must be made promptly and in any event within three months of this Decision or the issuing of the Guidance.

Signed: Dated:

Mark Taylor

Chair of the Appeal Panel