NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on pirfenidone for treating idiopathic pulmonary fibrosis (review of TA282) [ID837]

Decision of the panel

Introduction

1. An Appeal Panel was convened on 1 December 2017 to consider an appeal against NICE's final appraisal determination, to the NHS, on pirfenidone for treating idiopathic pulmonary fibrosis.

2. The Appeal Panel consisted of:

• Professor Alan Silman	Chair
• Professor.Sheena Asthana	Non-Executive Director
• Dr Ashutosh Wechalekar	Health Services Representative
• Mr David Gillen	Industry Representative
• Mr John Morris	Lay Representative

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The panel considered appeals submitted by – Roche Products Limited (Roche) and British Thoracic Society (BTS)

5. Roche was represented by:

• Victoria Wakefield	Counsel, Brick Court Chambers
• Sarah Ellson	Partner, Fieldfisher LLP
• Kevin Jameson	Head of Franchise Access Leads, Roche
• Dr James Mawby	Country Medical Lead, Roche
• Dawn Lee	Health Economist, Bresmed

6. The appeal hearing was transcribed on behalf of Roche by:

• Sarah Edwards	Stenographer (TA Reed and Co)

7. British Thoracic Society was represented by:

• Dr Michael Gibbons	Consultant Respiratory Physician, Royal Devon and Exeter Hospital

- Dr Felix Woodhead — Consultant Respiratory Physician, Glenfield Hospital Leicester

8. Dr Michael Gibbons declared he had received fees for acting on advisory boards from Roche and from their competitors.

9. Dr Felix Woodhead declared he had received educational support from Roche and from their competitors and had acted on advisory boards.

10. In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel:

- Dr Amanda Adler — Chair, Technology Appraisal Committee B
- Mr Meindert Boysen — Programme Director – TA and HST
- Ms Sophie Cooper — Technical Analyst NICE
- Sir Andrew Dillon — Chief Executive, NICE

11. NICE's legal adviser – Mr Stephen Hocking, DAC Beachcroft LLP – was also present.

12. Under NICE's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

13. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

a) Failed to act fairly
b) Exceeded its powers.

Ground Two: The recommendation is unreasonable in the light of the evidence submitted to NICE.

14. The Vice Chair of NICE (Dr Rosie Benneyworth) in preliminary correspondence had confirmed that:

- Roche had potentially valid grounds of appeal as follows:
    - Grounds 1a – NICE had failed to act fairly
    - Ground 1b – NICE had exceeded its powers
    - Ground 2 – The recommendation is unreasonable in light of evidence submitted to NICE
- British Thoracic Society had potentially valid grounds of appeal as follows: Ground 2 – The recommendation is unreasonable in light of evidence submitted

to NICE

15. Idiopathic pulmonary fibrosis is a chronic, progressive lung disease in which scarring (fibrosis) occurs. The cause is unknown, but it is thought to be related to an abnormal immune response. Symptoms may include breathlessness and cough. Over time, people experience a decline in lung function, reduced quality of life, and death. There is currently no cure for the disease. The median survival for people with idiopathic pulmonary fibrosis in the UK from the time of diagnosis is approximately 3 years. People first diagnosed with mild-to-moderate disease live longer than people first diagnosed with severe disease.

16. The appraisal that is the subject of the current appeal provided advice to the NHS on the use of pirfenidone within its marketing authorisation for treating idiopathic pulmonary fibrosis.

17. Before the Appeal Panel inquired into the detailed complaints, the Appeal Panel agreed with the appellants the order of discussion of the appeal points. The appellants agreed to the order suggested by the Appeal Panel.

18. The Appeal Panel asked Dr Gibbons/Dr Woodhead to put a clinical context of idiopathic pulmonary fibrosis (IPF) and the drug under consideration.

19. Dr Gibbons, on behalf of the BTS, explained that IPF is a "dreadful" condition with ongoing clinical progression and all patients eventually died due to the condition (unless they died from some other cause first). The overall survival is poor at a median of 3-5 years from diagnosis and only 20% patients will be alive at 5 years from diagnosis. He emphasised that outcomes in IPF were not dissimilar to a number of cancers and that it should be thought of like a “cancer” from a clinical context. It is important to treat the disease early rather than late. Thirty eight percent of all patients presented with mild disease with a forced vital capacity (FVC) above 80%. That meant those 38% were currently not eligible for treatment. He could not imagine a situation where 38% of patients with cancer at an early stage of the disease would not be treated. These patients will all progress and they will all die and clinicians feel duty bound to treat them as aggressively and as early as possible. He also mentioned that there are trial data showing efficacy of pirfenidone in mild disease.

20. The Appeal Panel asked the appellants to present their views on the interpretation of the previous appeal decision in terms of what they felt it required to have happened.

21. Victoria Wakefield, on behalf of Roche, explained that Roche challenge that NICE took a specific view of the appeal decision and then directed itself that it (NICE)

was not bound by that Appeal Panel decision. She clarified that paragraph 45 in the previous Appeal Panel decision was the important point of the final appeal decision. Roche's view was that this paragraph was then not complied with. Specifically, she referred to the second sentence in that paragraph and suggested that the Guidance Executive disagreed with that sentence. Roche and the Guidance Executive interpreted that sentence to mean that subgroup analysis should *only* be considered if the drug was not cost effective in the whole population.

22. Victoria Wakefield, said that there was tension between paragraph 45 and paragraph 30-31 of the appeal decision. Roche had no problem with paragraph 30 as it was general. However, the discussion in paragraph 31 was in tension with paragraph 45, particularly the penultimate sentence of paragraph 31 which could mean that the Appraisal Committee could look at subgroups. She felt that paragraph 45 was the conclusion of the appeal and should prevail over paragraph 31, if the two were inconsistent. In the email from the Guidance Executive, they too considered that paragraph 45 and the decision letter overall must be interpreted as allowing the use of subgroups only if treatment in the whole population was cost ineffective. She argued that NICE then disagreed with that approach.

23. Dr Amanda Adler, Chair Technology Appraisal Committee B, responded that there was a tension in the paragraphs from the appeal decision. Paragraph 45 could be interpreted as if the word “only” was present. But this was inconsistent with how the Institute looked at clinical and cost effectiveness. If the drug was cost effective, looking at subgroups was still reasonable as there may be subgroups where it was not cost effective or there may be subgroups where it was indeed more cost effective than the whole population. The Appraisal Committee does not wish to be limited to subgroup analysis if or only if the drug was not cost effective in the whole population.

24. The Appeal Panel requested Mr Meindert Boysen clarify the NICE view.

25. Mr Meindert Boysen, Programme Director NICE TA, responded that the intention of the NICE paper for the Guidance Executive was to describe the totality of the appeal decision. He considered the letter to be inconsistent between points 30-31 and point 45. The role of the Guidance Executive was to decide what to do in response to an appeal. The paper for the Guidance Executive was to help them understand there were differences of opinion [on the use of subgroups]. The Appraisal Committees are themselves completely independent to take the final decisions.

26. Dr Amanda Adler, Chair Appraisal Committee B, added that there was no reason to treat pirfenidone any differently from any other drug. It would be unusual to look at subgroups if a treatment was cost effective overall, but not wrong. It is not

unusual to have one analysis for the overall population and then to use subgroups for analysis, but only look at subgroups if that makes clinical sense.

27. The Appeal Panel sought clarification of the Appraisal Committees' view in the recent FAD suggesting that the cost effectiveness was consistent regardless of a patient's FVC.

28. Dr Amanda Adler, Chair Appraisal Committee B, responded that in mild disease, in fact, there was suggestion of better outcomes with placebo in the data presented by Roche. The Committee gave the benefit of the doubt to the patient and decided that it was fair to say that the drug was equally effective across subgroups defined by FVC. That does not mean that therefore the cost effectiveness will be the same. If you have the same percentage effect but one group is at much higher risk, then the absolute value of the effect, which is what determines the cost effectiveness, would be different.

29. Dr Felix Woodhead, on behalf of BTS, disagreed with the conclusions of Dr Amanda Adler about the efficacy of pirfenidone in mild disease. He pointed out that the ASCEND study included patients with FVC of 50-90% with no pre-planned subgroup analysis, and was effective at that level. Subgroups were analysed but no difference in clinical efficacy was shown.

30. The Chair of the Appeal Panel moved the discussion to the issues of direction from Guidance Executive to the Appraisal Committee – "did the Guidance Executive ignore the panel's advice and was there predetermination?"

31. The Appeal Panel asked NICE and Appraisal Committee chair whether it was usual for the chair of Appraisal Committees to attend the Guidance Executive meeting.

32. Dr Amanda Adler, Chair Technology Appraisal Committee B, responded that this was not part of normal process for the chair of an Appraisal Committee to do this. The chair is not part of the Guidance Executive.

33. Victoria Wakefield, on behalf of Roche, went to the report sent to the Guidance Executive. She referred the Appeal Panel's attention to the 4th point in the report to the Guidance Executive – specifically – "We are concerned that his suggestion that the **only** reasonable approach to consideration of subgroups for cost effectiveness would be where (treatment in) the whole population is not cost effective, where economic theory (Sculpher MH 2008 referenced) and practice, clearly support a different approach". She submitted that this was illegitimate. She went on to repeat that paragraph 30-31 of the previous Appeal Panel decision do not override paragraph 45.

34. Victoria Wakefield, on behalf of Roche, continued on to address the point of predetermination of the Appraisal Committee by referring the Appeal Panel's attention to the paragraphs on top of page 3 of the report to the Guidance Executive and language such as "'*we'* will (re)draft the FAD". Rather than saying that they would look at the whole population to see if the drug is cost effective it sets out other reasons to go back to the original FAD. That is clear evidence of predetermination.

35. She then referred the Appeal Panel's attention to the minutes of the Guidance Executive meeting and read from the minutes. These contained a critique of the Appeal Panel's decision which she argued was illegitimate. It does not matter what NICE think of the decision. She further went on to say that the minutes essentially repeat the words from the Appeal Panel's decision paragraphs 31 (and not paragraph 45).

36. She then referred the Appeal Panel to the Appraisal Committee's slides. Slide 7 essentially rejects the previous Appeal Panel's decision paragraph 45. In response to a question she explained that the right of appeal is a statutory right. If NICE disagrees with the decision of an Appeal Panel, NICE can go to court and seek a judicial review of that decision just in the same manner as an appellant may do so. Unless NICE seeks a judicial review of the Appeal Panel decision, it is bound by the Appeal Panel decision.

37. Dr Amanda Adler, Chair Technology Appraisal Committee B, clarified that the previous appeal decision letter was vague and therefore it was fully reasonable for the Appraisal Committee to proceed in line with established ways of working to evaluate clinical and cost effectiveness, and that would include looking at subgroups.

38. Victoria Wakefield, on behalf of Roche, said that paragraph 45 of the previous appeal decision letter specifically prohibited this. She added that they had made an enquiry by email of Meindert Boysen who, in his reply, clearly said that NICE Guidance Executive asks itself whether it believes that the Appeal Panel decision accurately reflects the Methods Guide and, if it takes the view that it does not, it is free to depart from it. It is illegitimate for the Guidance Executive to ask itself, "Do I agree with the Appeal Panel decision? If I do not, I can disregard it". NICE cannot say, "Even though we lost the appeal, we are disregarding the Appeal Panel decision because we maintain our interpretation of (e.g.) the Methods Guide". That would render the whole purpose of the appeal redundant.

39. The Appeal Panel sought clarification from the NICE team on points raised about the role of the Guidance Executive and how the Guidance Executive review and present the results of an Appeal Panel to a NICE Appraisal Committee.

40. Sir Andrew Dillon, Chief Executive of NICE, clarified that the role of the Guidance Executive was to receive an appeal decision and then take appropriate action. They clarify to the Appraisal Committee the appeal decision. Long standing practice is for the appraisal team to present the outcome of an Appeal Panel decision with a commentary. In this case the Guidance Executive considered the entirety of the view and accurately set out the points raised in the appeal decision. There was nothing to suggest that the Guidance Executive considered that the previous Appeal Panel had "got it wrong". The Guidance Executive's job is to pass on the decisions of the Appeal Panel to the Appraisal Committee, which is what it did. There can be all sorts of views about the interpretation of NICE's methods, but this particular part of the process in producing advice to the NHS requires NICE to ask the Appraisal Committee to address the outcome of the Appeal Panel, which it evidently did.

41. Sir Andrew Dillon continued by saying, another role of the Guidance Executive is to ensure that all advisory committees operate consistently with the Methods Guide. It is not the role of the Guidance Executive to question the interpretation of the NICE Methods Guide adopted by an Appeal Panel. The role of the Guidance Executive is to pass on the requests of an Appeal Panel to an Appraisal Committee. The Guidance Executive may point out concerns about a request from an Appeal Panel. The only thing that is important is the instruction from the Appeal Panel which the Guidance Executive passed on to the Appraisal Committee.

42. Sir Andrew Dillon was asked to comment on committee slide 7 and responded that the Appraisal Committee were informed of the discussion of the Guidance Executive. But the Appraisal Committee then went on to do what the Appeal Panel had asked.

43. Dr Amanda Adler, Chair Technology Appraisal Committee, said this was all moot. The committee looked at the whole population first as the panel had suggested. When they found the drug was not cost effective for the whole population, the committee then went on to look at subgroups.

44. Sir Andrew Dillon, Chief Executive of NICE, said that NICE was very clear on the role of the Guidance Executive and need for consideration by the Guidance Executive. It was clear the Guidance Executive understood that it has to pass the appeal decision on to the Appraisal Committee.

45. The Chair of the Appeal Panel moved to discussion of the next agreed point which was the substance of the second FAD and the question of whether the Appraisal Committee took appropriate account of the previous Appeal Panel's decision and whether the conclusions of the committee are reasonable.

46. Victoria Wakefield, on behalf of Roche, contended that the third ground of challenge was the failure of the second FAD to recommend use in the 50-90% population when it did recommend use in the 50-80% population. This was not comparing groups with FVC of 50-80% and those with FVC 50-90% that would be statistically inappropriate. Instead different answers were given in relation to essentially similar populations.

47. The two populations (50-80% and 50-90%) have materially identical ICERs. The population of 50-90% has less uncertainly due to the data available from the ASCEND trial. She then went on to deal with each supposed point of distinction in turn. She pointed out that the ICERs with a two year and five year stopping rule for the populations are essentially the same. The uncertainly mentioned in the second FAD in paragraph 4.18 should apply equally to both the populations under consideration. The Appraisal Committee had considered a 5 year treatment effect horizon as their preferred assumption, but in the FAD the 2 year assumption appears. Finally, she wanted the clinical experts in BTS to comment on the severity of the 50-80% vs. 50-90% as well as the relevance of the trial data to UK clinical practice.

48. Dr Michael Gibbons, on behalf of BTS, clarified that 38% of the UK patient population with IPF had a FVC >80% by looking at the prevalence data in the UK BTS patient registry compared to the 16% of the patients had FVC of 80-90% in the trial data.

49. Dr James Mawby from Roche and Dr Felix Woodhead from BTS clarified that the UK had 5-6 trial centres but they could not give an exact patient number in each FVC category. However, the BTS registry data suggest that the UK patient population was broadly similar to the trial population.

50. Victoria Wakefield, on behalf of Roche, pointed the Appeal Panel's attention to slide 9 of the presentation made by the Appraisal Committee showing the population distribution considered and that there was no real mismatch between trial and UK patient populations. She then went on to discuss the uncertainties in the FAD – the data for 50-90% FVC were in fact more certain than 50-80% population.

51. The other consideration Victoria Wakefield raised was the Methods Guide discussing incomplete capture of all health-related issues. The FAD in section 4.18 suggests that the committee rejected these issues. This applies to both groups.

52. Victoria Wakefield then reminded the Appeal Panel about consideration of innovation as per the NICE Methods Guide. When pirfenidone was considered for the very first time in 2013, it was considered to be an innovative treatment for IPF.

She submitted that it still remains an innovative treatment and the only treatment for patients with IPF with FVC of 80-90%.

53. Victoria Wakefield continued that NICE had considered a body of evidence in 2013, reached a certain conclusion in respect of that evidence and it needed to maintain that interpretation of the evidence, unless something has changed in the interim, unless we know something that we did not know at the time. A decision maker cannot simply change its mind on a different day of the week.

54. Victoria Wakefield further stated that, having made that decision in respect of 50-80%, the logical consequences needed to be drawn from it. If pirfenidone is recommended for the group 50-80%, it should be recommended for the total population. Not to recommend it in that group is public law unreasonable. It is a decision that is robbed of any logic.

55. Dr Felix Woodhead, from BTS, clarified that the 2013 Technology Appraisal was based on the CAPACITY study. That study had persuaded the EMA to license the product but not the FDA. The evidence for efficacy was now significantly better with data from the ASCEND study, which had led to FDA approval. The evidence of efficacy in ASCEND is considerably better than CAPACITY. The 50-80% was a historical carry over from the 2013 Technology Appraisal. There was no material difference between the 50-80% vs. 50-90% on clinical grounds. Additionally, the ICERs were the same. He also mentioned the difficulty of explaining to a patient the lack of funding on a cost benefit basis. He argued that the 50-80% threshold was completely arbitrary, open to question about inequality and contrary to the NHS constitution on equity of health care benefits.

56. Dr Amanda Adler, Chair Technology Appraisal Committee B, replied that the appeal hearing was not a re-appraisal. She stated that the committee had indeed looked at the whole population and that one cannot compare the whole population to a subgroup. There was no difference in the subgroups anyway. One cannot compare averages in overlapping populations. She quoted the President of the Royal Statistical Society as having confirmed to her that, “it is wholly inappropriate to compare averages when one group is a subset of the other.” To conclude that two subsets are equal when comparing one of them to the total, rather than comparing them to each other, is fundamentally flawed and inconsistent with good statistical practice and yet we are hearing over and over the clinical effectiveness in the 50-80% group was not that different than the 50-90% group. She illustrated the point with a metaphor: if you knew the total weight of the rowers in an eight, and the total weight of the whole crew, and you wanted to know the weight of the cox, if you were to compare the average crew weight of the whole boat to the average weight of the rowers alone, you would not see much difference. To say therefore that the weight of the cox must be the same as the rowers is an illustration of why even if the 50-90% and the 50-80% cost effectiveness figures are similar

this does not mean that the 80-90% would therefore also be similar to either of those figures.

57. The committee had an option of taking a view that the drug was not cost effective and stopping the treatment for the entire patient population. Having taken into account that the NHS currently offers pirfenidone to patients with an FVC of 50-80%, and taking into account the best interests of patients, the committee chose not to take away access to the drug. The committee took a view that it was not cost effective in mild or moderate disease. The committee did not find the drug cost effective in the whole population, but it chose not to take away a treatment from patients with moderate disease because the NHS currently offers pirfenidone, so the NHS would have to disinvest and that is something that the committee chose not to do. Its decisions are not fully algorithmic, which is why NICE uses committees and not a computer to make decisions.

58. The Appeal Panel sought clarification on the issue of comparing overlapping subgroups dependant on the size of the overall groups and Dr Adler confirmed this was not something the committee would do.

59. The Appeal Panel challenged Dr Adler on whether the committee had taken a different approach to decision making for the 50-80% and the 80-90% groups, one being clinically based and the other purely statistical. Dr Adler said the considerations were fundamentally different; in one case you would be choosing to take away a treatment.

60. Dr Amanda Adler, confirmed that the human cost of the disease had been discussed specifically by having a lay committee member to present the details on the effects of IPF. She added that there were many clinicians on the committee and she herself in her capacity as a consultant treated such patients in her own practice. As to treatment effect the committee discussed a range of scenarios not focusing on a 2-year scenario as a preferred option. Sophie Cooper, NICE Technical analyst, said that the confusion may be because of the Guidance Executive report which is written in shorthand. It was the 5-year effect which was the committee's preferred assumption. The 2-year scenario was considered. The 8-year effect was looked at as mentioned in paragraph 4.14 but discounted for the reason given in the FAD. Dr Amanda Adler confirmed that 2 years was the committee's worst case and 5 years was the committee's best-case scenario.

61. The Appeal Panel raised the issue of possible predetermination.

62. Victoria Wakefield said that the problem in paragraph 45 only arises if, when the committee looks at the whole population, they find the treatment is cost effective. Due to erroneous decision making and predetermination, they held that the whole population was not cost effective, so they never got to the bit in the logical chain in

which paragraph 45 would bite. It was not seen whether, across a population for which pirfenidone was cost effective, the Committee would then go on to look for a non-cost-effective subgroup or not. She said that did not make the Guidance Executive's instructions lawful and it did not take those instructions out of the scope of this appeal, because each error fed into each other error. This gave rise to a situation in which a second FAD was produced in which the same result was reached as the first-time round, even though Roche won the first-time round. They then learned that their victory in fact was rejected behind the scenes by NICE, in which Roche learned that the Chair of the Committee in fact had written to the Guidance Executive saying, "We will make the same decision again and here are some reasons that we think might be good ones", and then Roche get a FAD in which they say that the decision making just does not add up at all. Any suggestion that the Appraisal Committee somehow managed to go about its business in the normal way and so any earlier error had no effect, was entirely wrong.

63. Dr Amanda Adler, Chair Technology Appraisal Committee B, denied this and said this was misrepresentation of the working of an Appraisal Committee. It was incorrect to state that a committee will not change its mind. The committee had a number of independent individuals and not a collective mind. The chair of the committee does not talk to the individuals before a committee meeting. The committee members value their independence. The fact that an Appraisal Committee reached the same conclusion does not mean predetermination since the committee has reviewed the same data with no new evidence presented. The Appraisal Committee has not seen the Guidance Executive documents. Those are internal to NICE.

64. Dr Adler confirmed that she had not attended the Guidance Executive meeting.

65. Sir Andrew Dillon, Chief Executive NICE, confirmed that the function of the Guidance Executive is to pass on the decision of an Appeal Panel to an Appraisal Committee. The minutes of the Guidance Executive are not passed on to the Appraisal Committee. He took strong issue with labelling the Guidance Executive decision as unlawful. It was a straightforward reading of the Appeal Panel's decision.

66. The Appeal Panel Chair asked the appellants if any other points were to be raised and had not yet been covered.

67. Victoria Wakefield, on behalf of Roche, confirmed these issues – that she was not working with overlapping groups, instead, she was saying that there were two groups with similar considerations and yet two different conclusions were reached. The argument was not about an 80-90% group. On the point of comparison of ICERs, she directed the Appeal Panel's attention to FAD point 4.17 and read out the last sentence. She responded to Sir Andrew that unlawful did not mean

wrongdoing but meant contrary to the legal structures underpinning NICE. She referred the Appeal Panel back to the FAD section 4.20 and said that it was an endorsement of the cost effectiveness of the drug in patients with FVC between 50-80%.

68. Dr Amanda Adler, Chair Technology Appraisal Committee B, summed up on behalf of the Appraisal Committee. Dr Gibbons presented a summary on behalf of the British Thoracic Society. Victoria Wakefield presented a final summation on behalf of Roche.

Appeal Panel's deliberations on specific appeal grounds and decision

Appeal by Roche

Appeal Ground 1a – NICE has failed to act fairly

Appeal Ground 1a.1 In determining that there was a relevant distinction between the subgroups of patients with a FVC between 50-80% (para 4.19 FAD) the committee acted contrary to policy and procedures without adequate reasons and unfairly.

69. The Appeal Panel considered the arguments presented by the appellants and the clarification given by the Appraisal Committee. Essentially the point was whether the distinction made by the Appraisal Committee in finding that treatment in the whole population was cost ineffective but that treatment in the 50-80% FVC population should be allowed was reached fairly, in accordance with policy or procedures, and with adequate reasoning.

70. Roche's approach was to take each of the reasons advanced in FAD 4.18 for considering pirfenidone cost ineffective in the total patient population, and to show that those factors were the same or not materially different in the subgroup.

71. The Appraisal Committee had taken issue with the validity of that approach. It argued that their approach was not purely "algorithmic" and that it had decided not to remove an existing treatment option.

72. At one level the Appeal Panel could understand Roche's concern. If the two groups 50-80% and 50-90% were looked at in isolation, and without knowledge of the current treatment situation, then the considerations did look similar. However, the Appraisal Committee had stated that for one group, they were considering offering a new treatment option, and for the other, removing an existing option. The panel felt that this reasoning was presented in the FAD at para 4.19 and could not be considered an *ex post facto* consideration. The panel felt that treating a decision to remove an existing treatment option more benevolently than a decision to recommend extending that option was relevant, fair, and not inconsistent with

policy. It was an adequate reason even if it stood alone for the difference in treatment. Appraisal Committees are expected to exercise their judgement and should not be discouraged from drawing a distinction of this sort.

73. **Appeal Ground 1a.1:** The Appeal Panel dismissed the appeal on this appeal point.

Appeal ground 1a.2: NICE directed itself to disregard the Appeal Panel's decision, which is fundamentally unfair and frustrates the right of the appeal.

Ground 1b – NICE has exceeded its powers

Appeal Ground 1b.1: The Guidance Executive and/or the Appraisal Committee acted outside their powers by disregarding the Appeal Panel's decision, thus frustrating the statutory appeal rights granted by regs 9 and 10 of the National Institute for Health and Care Excellence (Constitution and Functions) regulations 2013

74. The Appeal Panel considered these two points together in their deliberations, although it was mindful of the distinction between them.

75. The Appeal Panel agrees with the appellant that a valid appeal decision may not be "disregarded" and must be given effect.

76. For the purpose of this appeal only because both NICE and Roche appear to have understood the December 2016 appeal decision as allowing a consideration of subgroups in this appraisal *only if a prior consideration of the total population concluded that treatment in the total population was cost ineffective*. For the purpose of this appeal the Appeal Panel proceeded on the basis that that was the objective meaning of the previous Panel's decision. It expresses no more general view on the use of subgroups.

77. The appellant's arguments were directed largely to what NICE thought it could do, although it also asserted that NICE had in fact ignored the decision of the Appeal Panel. In the Appeal Panel's view, what the decision making committee did is more important than what they or others in NICE may have thought they could do. It does not rob the appeal process of value, and it is not unfair, if NICE or elements within NICE disagree with the reasoning of an Appeal Panel, any more than it robs a judgement of the Court of effect if the losing party complains outside Court that the judge "got it wrong". What matters, and what may found a successful subsequent appeal, is whether NICE in fact properly acted as the Appeal Panel directed.

78. Further, it is necessary to bear in mind a distinction between what an appeal decision letter requires to happen, and the reasoning explaining a decision. Not

every word in a decision letter is intended to dictate future action. The Appeal Panel considers its decision on whether a particular action has been (in this case) unfair to be definitive and to be followed (subject of course to the supervision of the Courts). It provides reasons for its decisions both so that the parties can understand why they have won or lost and, in the case of a successful appeal, so that the same error will not be repeated. The key point is that the error is not repeated, not that NICE must agree with the Appeal Panel as to why it was an error.

79. There are five key documents to consider:

- a report to the NICE Guidance Executive dated 10 January 2017
- The minutes of the Guidance Executive meeting also dated 20 January 2017
- slides 4-7 presented to the Appraisal Committee and dated 20 April 2017
- an email written by Mr Boysen, undated in the panel's papers but responding to a letter dated 11 May 2017
- The FAD itself

80. The Appeal Panel is concerned with whether the decision making body, in this case the Appraisal Committee, did or did not act as the December 2016 decision letter required. The actions of the Guidance Executive or Mr Boysen are not relevant save if they led to the Committee not acting as the decision letter required.

81. The action recorded in the Guidance Executive minutes (para 21) was correct and in accordance with the decision letter, and Mr Boysen's email, is of little relevance to understanding what the committee did at its meeting of 20 April 2017.

82. As to the report to the Guidance Executive, it is clear that its authors, one of whom was the Appraisal Committee chair, did not agree that the only reasonable approach to using subgroups was where treating the whole population was not cost effective. The authors appear to be unclear as to whether or not that was in fact what the Appeal Panel had said. This document is evidence of the state of mind of the chair of the Appraisal Committee in January 2017 but does not bear on the actions of the Appraisal Committee in April 2017.

83. The committee slides show that the slide author (the Appeal Panel infers this was the committee chair), perceived that there was a disagreement between the Guidance Executive and the Appeal Panel on the question of when subgroups could be looked at. Although the appellant focused on slide 7 the Appeal Panel feels it is necessary to look at what the committee were told in its totality. Slides 4-7 present a fair summary of the December 2016 appeal decision. The Appraisal Committee was correctly directed to consider the whole patient population. If they

had considered treatment in the whole patient population cost effective then the disagreement between the committee chair (at least) and the December 2016 decision letter could have had a bearing on their actions. However, this situation did not arise.

84. Finally, there is the FAD. This document is the best evidence for what the Appraisal Committee actually did. It is telling that the appellant was unable to point to any action or consideration recorded in the FAD that was contrary to what was required by the December 2016 decision letter. There were two requirements in paragraph 45 of that letter (1) for the committee to take all reasonable steps to demonstrate consideration of the [clinical] and cost-effectiveness of pirfenidone in the whole population and (2) to document clearly any assessment in subgroups. NICE and Roche understood that there was a third requirement or caveat (3) that subgroups could only be considered if the answer to (1) was that treatment was not cost effective in the whole population. Elements within NICE felt that it was possible to look at subgroups in situations outside (3). However, the FAD is in fact fully consistent with all three requirements. As noted above whether NICE or elements of NICE agreed with the requirements, or thought they were following them *ex gratia* rather than as a matter of obligation, or happened to have acted consistently with them only because the situation in which they would have departed from them did not arise is not relevant for this appeal.

85. This Appeal Panel cannot allow an appeal on the basis of a hypothetical scenario. The Appeal Panel does not agree with the appellant on this point. Unless and until there is an actual departure from what an Appeal Panel had required to happen, there can be no valid ground of appeal. Paragraph 45 was accepted by Roche as describing what they were entitled to as a result of their "victory" in the first appeal, and Roche had received exactly what paragraph 45 required. What might have happened if the Appraisal Committee had decided that treatment in the whole population was cost effective is hypothetical and the appeal process does not exist to allow the Appeal Panel to express opinions on hypotheticals.

86. **Appeal ground 1a.2 and 1b.1:** The Appeal Panel dismissed the appeal on these appeal points.

Appeal Ground 1a.3: The Appraisal Committee had a closed mind in respect of and/or had predetermined to a significant degree, the recommendation which it made

87. The Appeal Panel heard the arguments presented by the appellants, by the NICE Guidance Executive and the Chair of the Appraisal Committee. The Panel's approach to the question of predetermination is to ask whether it considers there is a real possibility that the committee did not approach the decision taken on 20 April 2017 with an open mind. In answering that question, the Panel has in mind both that the Appraisal Committee consists of a substantial number of professional

and responsible people, has no vested interest in the outcome of any particular appraisal, and meets largely in public, but also to the fact that predetermination or lack of an open mind may be unconscious as well as conscious and there is no need to show a wilful refusal to reconsider the question in an open minded way.

88. Clearly, the Appraisal Committee were already familiar with the evidence in the appraisal, as they had once formed a view on it. It would be unrealistic to expect them to be unaware of this history, or to act as if they were. They were obliged to approach the question afresh and be willing to reach a different conclusion. Thus, the Appeal Panel considered it to be important to examine whether the Appraisal Committee had predetermined the questions that were referred back to them. The December 2016 appeal decision did not require them to restart the appraisal de novo. They had to consider the whole population (this was a new decision), and they had to document any assessment of subgroups (which was not necessarily a new decision).

89. The Appeal Panel considers there are three documents that bear on this point:

- the report to the NICE Guidance Executive dated 10 January 2017
- the slides presented to the Appraisal Committee and dated 20 April 2017
- the FAD itself.

90. The Panel can understand why the Guidance Executive report would put the suspicious reader on enquiry as to predetermination. Some of the wording ("*We accept that the FAD could be clearer about the Committee's consideration of clinical and cost effectiveness of the whole population, as well as the subgroups, and we will (re) draft the FAD with the Panel's observations in mind after the Committee has next met", "We accept that the Committee could be clearer about its reasons for excluding the >80% subgroup from the recommendations"*) is indeed consistent with a failure to understand that the redetermination must be approached with an open mind. However, it is at least equally and if not more consistent with explaining that the Appraisal Committee (or rather its chair who was one of the authors of the report) understood the Appeal Panel's concerns about adequacy of reasoning and would take steps to ensure they were not repeated. The Panel concluded that this was loose drafting of a paper not intended to be subject to close textual analysis, rather than evidence of predetermination.

91. The Panel has also noted the statement "...*even with more clarity about* [the] *Committee's judgement on clinical effectiveness, the estimates of cost effectiveness for the subgroup will not change as the Committee accepted the same estimate of treatment effect for the* [two subgroups]". The panel did not consider this to be evidence of predetermination, but rather a reflection that if the data have not changed then the analysis of the data would not change. This

passage relates back to the Appeal Panel's requirement that consideration of subgroups be clearly documented, not that it be reconsidered.

92. The Appeal Panel also noted that the report to the Guidance Executive was not put before the Appraisal Committee and so as such cannot have influenced its deliberations. (It is mindful that an author of the report was the Committee chair and that she at least was aware of the report's content.)

93. As to the Committee slides, although they record a disagreement as to when subgroups may be considered, if anything the inclusion of that disagreement (which would only become relevant if the Committee had decided that treatment was cost effective in the whole population) tend to support rather than undermine the view that the Committee was approaching the decision with an open mind. If the slide's author had been confident that treatment in the whole population would be found to be cost ineffective there would have been no need to mention the difference in opinion, which was relevant only if there was a finding that treatment was cost effective. Read as a whole the complete presentation of the slides did not raise any concern in the Appeal Panel's mind that the Committee may have approached its task without an open mind.

94. Finally, although the Appeal Panel accepts that it would be an unusual decision document that contained clear evidence of predetermination, there is nothing in the FAD which raises a suspicion of predetermination.

95. Applying a real possibility test the Appeal Panel are, therefore, satisfied that the Appraisal Committee approached the matter with an open mind. The Appeal Panel, therefore, dismissed this point. However, the Appeal Panel recommend that on matters related to decisions from Appeal Panel's and in the interests of maximising confidence in NICE's processes there should be clearer separation between the Guidance Executive and Appraisal Committees. The Appeal Panel suggests that NICE should reconsider whether Appraisal Committee chairs or other Appraisal Committee members should continue to be involved in drafting reports on appeal decisions for the Guidance Executive.

96. **Appeal Ground 1a.3:** The Appeal Panel dismissed the appeal on this appeal point.

Ground 1b – NICE has exceeded its powers

Appeal Ground 1b.1: The Guidance Executive and/or the Appraisal Committee acted outside their powers by disregarding the Appeal Panel's decision, thus frustrating the statutory appeal rights granted by regs 9 and 10 of the National Institute for Health and Care Excellence (Constitution and Functions) regulations 2013

97. The Appeal Panel considered this point jointly with appeal point 1a.2 and it was dismissed above.

98. The appellant, British Thoracic Society, had no appeal under Ground 1a or 1b.

Appeal by Roche

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal point Ground 2.1: In determining that there was a relevant distinction between the subgroups of patients with a FVC between 50% and 80% and the total patient population (para 4.19) the committee drew a distinction with no rational basis.

99. The Appeal Panel considered the arguments presented by the appellants and the response by the Appraisal Committee. Part of this discussion has been reported in point 69. The Appeal Panel were satisfied that the Appraisal Committee had a clear understanding of what they were doing. The Appeal Panel understood that the Appraisal Committee were clear that pirfenidone was not cost effective in the whole population and hence they looked at subgroups. The Appeal Panel felt that the Appraisal Committee showed a humanity when it considered it important to preserve access to the drug which patients were already receiving (and which patients who currently have mild disease will expect to receive in due course) rather than rescind this recommendation based on a very strict application of their current analyses. In short, the distinction between maintaining a current use and extending that use to encompass a new population was a rational one and explained the difference in conclusion between the 50-80% subgroup and the 50-90% subgroup. This could not be said to be illogical, because a rational, relevant and genuine reason for distinguishing between the groups was identified. The outcome "added up" in light of the consideration identified.

100. In conclusion, the Appeal Panel were not convinced that the recommendations of the Appraisal Committee were unreasonable in light of the evidence presented.

101. **Appeal Ground 2.1:** The Appeal Panel dismissed the appeal on this appeal point.

Appeal by the British Thoracic Society

Appeal point Ground 2.1: The Appraisal Committee's refusal to consider the evidence of the efficacy of pirfenidone in IPF since the time of the original TA and the weakness of the health economic argument in choosing an FVC threshold of 80%

102. The Appeal Panel considered the arguments presented by the appellants and the clarification by the Appraisal Committee. The Appeal Panel was satisfied that the Appraisal Committee had indeed looked at all the available evidence. This has been clearly documented in the slides presented as well as the FAD. The Appeal Panel heard no new evidence of efficacy from the appellants beyond the trials already referred and discussed in detail in the Appraisal Committee's meeting.

103. In conclusion, the Appeal Panel were satisfied that the Appraisal Committee had considered the available evidence for pirfenidone in IPF. The Appeal Panel were also satisfied by the reasons and health economic arguments for the consideration of the various FVC thresholds including choosing of a FVC threshold of 80% by the Appraisal Committee.

104. **Appeal point Ground 2.1:** The Appeal Panel dismissed the appeal on this appeal point.

Conclusion and effect of the Appeal Panel's decision

105. The Appeal Panel dismissed the appeal against this appraisal on all grounds.

106. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.